

TITLE PAGE

Division: Worldwide Development

Information Type: Protocol Amendment

Title:

201832: A Randomised, Double-Blind, Double-Dummy, Crossover Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once Daily Versus Fluticasone Propionate 250 mcg Twice Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction

Compound Number: GW685698+GW642444

Development Phase: IV

Effective Date: 25-MAY-2016

Protocol Amendment Number: 3

Author (s): PPD

Copyright 2016 the GlaxoSmithKline group of companies. All rights reserved.
Unauthorised copying or use of this information is prohibited.

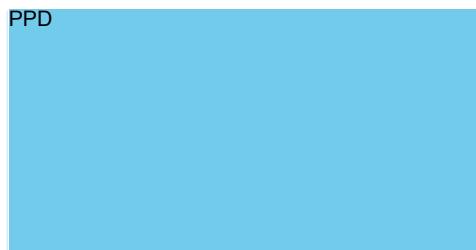
Revision Chronology

GlaxoSmithKline Document Number	Date	Version
2015N231308_00	2015-JUL-06	Original
2015N231308_01	2015-AUG-25	Amendment No. 1
<p>This protocol amendment was created to include an additional exercise challenge procedure at 23 hours after the first dose of double-blinded study medication in each Treatment Period. The purpose is to demonstrate that inhaled Fluticasone Furoate/Vilanterol (FF/VI)100/25 mcg provides improved bronchoprotection against exercise-induced bronchoconstriction (EIB) compared with Fluticasone Propionate (FP) 250 mcg after 23 hours of treatment with blinded medication. In addition, it will allow for an evaluation of the presence and extent of tachyphylaxis. Separately, the study title was revised to indicate the study is a 'randomised' study with a 'crossover' design. Other minor corrections and edits were also made.</p>		
2015N231308_02	2015-DEC-16	Amendment No. 2
<p>This protocol is being amended to increase the screen failure rate to 20% (from 10%) and the run-in failure rate to 70% (from 55%). This takes into consideration the challenge of enrolling EIB subjects with Symptomatic Allergic Rhinitis (SAR) at screening and also the challenge for subjects to demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of the exercise challenge at Visit 2; after taking fluticasone propionate for approximately four weeks during the run-in period. The amendment also allows subjects with symptomatic allergic rhinitis at screening to be treated with intranasal corticosteroids for up to four weeks, followed by a repeat screening visit to determine eligibility prior to entry into the study. Subjects with symptomatic allergic rhinitis during the study may be treated with intranasal corticosteroids at a constant dose for the duration of the study.</p> <p>The time window for the repeat exercise challenge has been extended from 24-48 hours to up to one week; taking into consideration the challenge for subjects to return within 48 hours for a repeat procedure.</p> <p>The ACT questionnaire has been replaced by the ACQ-5 questionnaire given the mismatch between treatment periods of two weeks and the recall period of 4 weeks for the ACT.</p> <p>Tobacco/marijuana use and pregnancy (which were omitted in error in the original protocol) have been added as exclusion criteria.</p> <p>The secondary endpoint for time to recovery has been changed to a binary endpoint defining recovery as those subjects who have a 30 minute post-exercise FEV₁ measurement that is no more than 5% lower than their pre-exercise FEV₁. In addition, the statistical testing hierarchy has been changed to prioritise the maximal percentage FEV₁ reduction (primary endpoint) and binary recovery endpoints following the 12 hour post-</p>		

dose exercise challenge. Other minor corrections and edits have been made.		
2015N231308_03	2016-MAY-25	Amendment No. 3
<p>This amendment has been written to adjust text to better reflect the intention of the protocol with regard to visit timing:</p> <p>Visit 2 (currently Day 1) redefined as Day 0 and Visit 3 (currently Day 2) redefined as Day 1.</p> <p>Visit window around day 29 removed and footnote added.</p> <p>Text regarding timing of visits clarified to ensure that the intention of the protocol is clearly reflected</p> <p>Other changes were made as follows:</p> <p>Subject number will be assigned at Pre-Screening following informed consent rather than at Visit 1</p> <p>Nucala™ added as an example prohibited medication</p> <p>Rescue medication supply strategy has been removed and the reader referred to the SRM</p> <p>Confirmation that post exercise vital signs will be immediately post exercise, not after 5 minutes of rest.</p>		

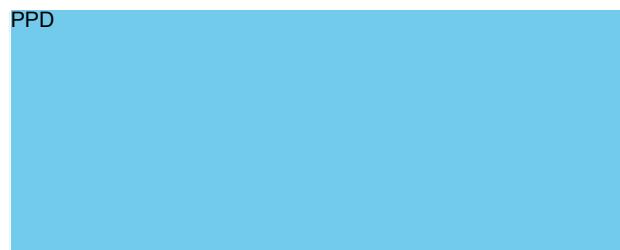
SPONSOR SIGNATORY

PPD



8/25/2016
Date

PPD



MEDICAL MONITOR/SPONSOR INFORMATION PAGE

Medical Monitor/SAE Contact Information:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Fax Number	Site Address
Primary Medical Monitor	PPD PPD	PPD PPD	PPD PPD	Not Applicable	Stockley Park West, 1-3 Ironbridge Road, Uxbridge, Middlesex, UB11 1BT, United Kingdom
Secondary Medical Monitor	PPD PPD	PPD PPD	PPD PPD	PPD PPD	5 Moore Drive, PO Box 13398, RTP, NC 27709-3398, United States
SAE contact information	Medical monitor as above				

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
 980 Great West Road
 Brentford
 Middlesex, TW8 9GS
 UK

In some countries, the clinical trial sponsor may be the local GlaxoSmithKline Affiliate Company (or designee). If applicable, the details of the alternative Sponsor and contact person in the territory will be provided to the relevant regulatory authority as part of the clinical trial application.

Regulatory Agency Identifying Number(s): IND number for FF/VI (077855), IND number for FP (IND 044090).

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 201832

I confirm agreement to conduct the study in compliance with the protocol, as amended by this protocol amendment.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:	
Investigator Address:	
Investigator Phone Number:	
Investigator Signature	Date

TABLE OF CONTENTS

	PAGE
1. PROTOCOL SYNOPSIS FOR STUDY 201832.....	11
2. INTRODUCTION.....	16
2.1. Background	16
2.2. Study Rationale	16
2.3. Brief Background	16
3. OBJECTIVE	17
3.1. Primary Objective	17
4. ENDPOINTS	17
4.1. Primary Endpoint	17
4.2. Secondary Endpoints.....	17
4.3. Other Endpoints.....	17
4.4. Safety Endpoints.....	18
5. STUDY DESIGN	18
5.1. Overall Design	18
5.2. Treatment Arms and Duration.....	20
5.3. Type and Number of Subjects.....	21
5.4. Design Justification.....	21
5.5. Dose Justification.....	21
5.6. Benefit: Risk Assessment	22
5.6.1. Risk Assessment	23
5.6.2. Risk assessment for FP 250mcg	30
5.6.3. Benefit Assessment	30
5.6.4. Overall Benefit: Risk Conclusion	30
6. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA	31
6.1. Screening Criteria.....	31
6.1.1. Inclusion Criteria	31
6.1.2. Exclusion Criteria	32
6.2. Randomization Criteria	34
6.2.1. Inclusion Criteria	34
6.2.2. Exclusion Criteria	35
6.3. Screening/Baseline/Run-in Failures	35
6.4. Withdrawal/Stopping Criteria.....	36
6.4.1. Study Specific Withdrawal Criteria	36
6.4.2. Reasons for Study Withdrawal	37
6.4.3. Lost to Follow up (Non-Attendance).....	38
6.4.4. Early Withdrawal Visit	38
6.5. Subject and Study Completion.....	39
7. STUDY TREATMENT	39
7.1. Investigational Product and Other Study Treatment.....	39
7.2. Treatment Assignment.....	41
7.2.1. Assignment of Subject Number.....	41
7.2.2. Assignment of Treatment Number	41

7.3.	Blinding.....	42
7.4.	Packaging and Labeling.....	42
7.5.	Preparation/Handling/Storage/Accountability	42
7.6.	Investigational Product Malfunction.....	43
7.7.	Compliance with Study Treatment Administration	43
7.8.	Treatment of Study Treatment Overdose.....	43
7.9.	Treatment after the End of the Study	44
7.10.	Concomitant Medications and Non-Drug Therapies	44
7.10.1.	Permitted Medications and Non-Drug Therapies.....	44
7.10.1.1.	Permitted Asthma Medications	44
7.10.1.2.	Permitted Non-Asthma Medications	44
7.10.2.	Prohibited Medications and Non-Drug Therapies.....	45
7.10.2.1.	Prohibited Non-Asthma Medications.....	46
8.	STUDY ASSESSMENTS AND PROCEDURES	46
8.1.	Time and Events Table	47
8.2.	Critical Baseline Assessments	50
8.3.	Efficacy	50
8.3.1.	Spirometry	50
8.3.1.1.	Target FEV ₁ Calculations	51
8.3.2.	Exercise Challenge Testing	51
8.3.2.1.	Worsening of Asthma during Exercise Challenge	52
8.3.3.	Key Study Assessments	52
8.3.3.1.	Visit 1 (Screening)	52
8.3.3.2.	Visit 2 (Randomization)	52
8.3.3.3.	Visit 3 and Visit 6 (23 hours Post First Dose Exercise Challenge)	53
8.3.3.4.	Visit 4 and Visit 7 (Blinded Treatment Exercise Challenges)	54
8.3.3.5.	Visit 5	54
8.3.4.	Physical Activity Monitor	54
8.3.5.	Asthma Control Questionnaire-5 (ACQ-5).....	55
8.4.	Safety	55
8.4.1.	Adverse Events (AE) and Serious Adverse Events (SAEs).....	56
8.4.1.1.	Time period and Frequency for collecting AE and SAE information.....	56
8.4.1.2.	Method of Detecting AEs and SAEs	56
8.4.1.3.	Follow-up of AEs and SAEs.....	57
8.4.1.4.	Cardiovascular and Death Events	57
8.4.1.5.	Regulatory Reporting Requirements for SAEs.....	57
8.4.2.	Asthma Exacerbations	58
8.4.3.	Pregnancy	58
8.4.4.	Physical Exams	58
8.4.5.	Vital Signs.....	58
8.4.6.	Electrocardiogram (ECG).....	59
8.5.	Genetics	59
9.	DATA MANAGEMENT	59
10.	STATISTICAL CONSIDERATIONS AND DATA ANALYSES	60
10.1.	Hypotheses.....	60

10.2.	Study Design Considerations.....	61
10.2.1.	Sample Size Assumptions	61
10.2.2.	Sample Size Sensitivity.....	62
10.2.3.	Sample Size Re-estimation.....	62
10.3.	Data Analysis Considerations	63
10.3.1.	Analysis Populations.....	63
10.3.2.	Analysis Data Sets.....	63
10.3.3.	Treatment Comparisons	63
10.3.3.1.	Primary Comparisons of Interest	63
10.3.3.2.	Other Comparisons of Interest.....	63
10.3.4.	Interim Analysis	64
10.4.	Key Elements of Analysis Plan	64
10.4.1.	Efficacy Analyses.....	64
10.4.1.1.	Primary Analysis.....	64
10.4.1.2.	Secondary Analyses.....	65
10.4.1.2.1.	Other Efficacy Analyses.....	65
10.4.2.	Safety Analyses	66
10.4.2.1.	Extent of Exposure	66
10.4.2.2.	Adverse Events (AEs)	66
10.4.2.3.	Exacerbations.....	66
10.4.3.	Pharmacogenetic Analyses	66
11.	STUDY GOVERNANCE CONSIDERATIONS	66
11.1.	Posting of Information on Publicly Available Clinical Trial Registers.....	66
11.2.	Regulatory and Ethical Considerations, Including the Informed Consent Process	66
11.3.	Quality Control (Study Monitoring)	67
11.4.	Quality Assurance.....	68
11.5.	Study and Site Closure	68
11.6.	Records Retention	68
11.7.	Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication	69
12.	REFERENCES.....	70
13.	APPENDICES	72
13.1.	Appendix 1 – Abbreviations and Trademarks.....	72
13.2.	Appendix 2: Liver Chemistry Stopping and Increased Monitoring Algorithm	74
13.3.	Appendix 3: Liver Safety Required Actions and Follow up Assessments	76
13.4.	Appendix 4: Genetic Research	80
13.5.	Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events.....	83
13.5.1.	Definition of Adverse Events	83
13.5.2.	Definition of Serious Adverse Events	84
13.5.3.	Definition of Cardiovascular Events	86
13.5.4.	Recording of AEs and SAEs	86
13.5.5.	Evaluating AEs and SAEs.....	87
13.5.6.	Reporting of SAEs to GSK.....	88

13.6.	Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information	90
13.6.1.	Collection of Pregnancy Information	90
13.7.	Appendix 7 - Country Specific Requirements.....	92
13.8.	Appendix 8 – Protocol Changes.....	93
13.8.1.	Protocol Amendment 01	93
13.8.2.	Protocol Amendment 02	116
13.8.3.	Protocol Amendment 03 (25-MAY-2016) from Protocol Amendment 02 (16-DEC-2015)	162

1. PROTOCOL SYNOPSIS FOR STUDY 201832

Rationale

For many patients with symptomatic asthma, physical exertion is often a precipitating factor. Although varying in methodology and criteria, early studies showed that as many as 90% of asthmatic patients have bronchoconstriction after exercise. In subjects with symptoms of persistent asthma, exercise and other forms of physical activity represent only one of many triggers that lead to worsening symptoms.

Chronic treatment with inhaled corticosteroids (ICS) has been shown to reduce the severity of asthma associated with exercise. However, some patients continue to demonstrate asthma symptoms and a decrease in lung function during exercise even while receiving ICS. In patients with persistent asthma, improvements in protection from exercise-induced bronchoconstriction (EIB) with ICS/long-acting beta₂-agonist (LABA) combination product Fluticasone propionate (FP)/salmeterol (ADVAIR™) have been demonstrated. However, differences between FP/salmeterol and FP monotherapy have not consistently been observed. In a study that evaluated the effect of FP/salmeterol compared with FP over the 12 hour dosing interval, a large percentage of subjects in both the FP/salmeterol (18%) and FP (36% and 33% at Day 1 and Week 4, respectively) treatment arms failed to complete the second exercise challenge test 8.5 hours after dosing, suggesting loss of protection against EIB towards the end of the 12 hour dosing interval.

FF/VI (Fluticasone furoate/Vilanterol), a new ICS/LABA combination treatment, is dosed once daily and has demonstrated significant bronchodilation over 24 hours. The purpose of this study is to determine if the once-daily administration of FF/VI demonstrates improved protection from EIB over ICS alone (FP) over the 24-hour dosing interval.

Objectives

Primary Objective

To evaluate the protective effect of fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once-daily compared with fluticasone propionate (FP) 250 mcg twice-daily against exercise-induced bronchoconstriction in adolescent and adult subjects aged 12 to 50 with persistent asthma

Primary Endpoint

- Maximal percent decrease from pre-exercise FEV₁ (Forced Expiratory Volume in One Second) following exercise challenge at 12 hours post evening dose at the end of the 2-week treatment period

Secondary Endpoints

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Proportion of subjects with a 30 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Weighted mean for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12-hours and 23 hours post evening dose (weighted mean 0-60 min) at the end of the 2-week treatment period

Other Endpoints

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from treatment period baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Mean change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score at the end of the 2-week treatment period.
- Percentage of subjects controlled, defined as an ACQ-5 score ≤0.75, at the end of the 2-week treatment period.
- Percentage of subjects achieving an improvement of ≥0.5 or greater in ACQ-5 score at the end of the 2-week treatment.
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, Metabolic Equivalent of Tasks (METs), sleep duration)
- Proportion of subjects with a 5 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period. Repeat for the 10,15,45 and 60 minute time points.

Safety Endpoints

- Adverse events

Overall Design

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will participate in up to eight study visits (Visit 0 to Visit 7) over the course of the study and a follow up phone call approximately a week after Visit 7. Visits 1, 2, 3, 5 and 6 are evening visits that will be conducted between 5PM and 11PM. Visit 4 and Visit 7 are also evening visits that will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will be required to attend three clinic visits during this 24-hour period.

Standardized exercise challenge testing (using a treadmill) will be conducted at Visit 2 for eligibility determination, Visit 3 and Visit 6 (after 23 hours of the first treatment dose in each Treatment Period); and at 12 and 23 hours post evening dose at Visits 4 and 7.

Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 5, and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. At Visit 2, subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to $< 20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures **once** within a week of the original procedure. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.

A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent, demography and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate.

At Visit 1, subjects meeting eligibility criteria and will enter a 4 week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD). Subjects with symptomatic allergic rhinitis at Visit 1 (screening) may be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Only **one** repeat screening visit will be performed following treatment with intranasal corticosteroids. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded. Eligible subjects will enter the run-in period. Subjects who are asymptomatic at screening, who become symptomatic during the study will remain in the study and may be treated with intranasal corticosteroids at a constant dose for the duration of the study.

Albuterol/salbutamol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs including pulse rate and systolic and diastolic blood pressure will be obtained at each clinic visit, including any Early Withdrawal visit. At all time points where both vital signs and spirometry are performed, vital signs will be done before the spirometry measurement. At visits where the exercise challenge is performed, vitals will be measured before (prior to the pre-exercise spirometry) and after the exercise challenge.

Asthma control will be assessed using the ACQ-5 at Visits 2, 4, 5 and 7.

Physical activity levels will be monitored to assess activity outside the clinic with the use of a physical activity monitor (SenseWear Armband accelerometer) worn for 7 days prior to Visit 2 (baseline), for 7 days prior to Visit 4 (during the last week of Treatment Period 1), for 7 days prior to Visit 5, and for 7 days prior to Visit 7 (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate.

A follow up phone call will be conducted approximately 7 days after Visit 7.

Treatment Arms and Duration

Two treatment arms will be employed for the study:

- FF/VI 100/25 mcg QD via ELLIPTA + Placebo BD via Diskus
- FP 250 mcg BD via Diskus + Placebo QD via ELLIPTA

As this is a 2-period cross-over study, all randomized subjects will receive both treatments in the study, either in Treatment Period 1 or Treatment Period 2. Also, each subject will receive a Diskus and ELLIPTA inhaler in Treatment Period 1 and Treatment Period 2.

Subjects will complete a 4-week single blind run-in on FP 250 mcg BID, followed by 2-week double-blind Treatment Period 1 on randomized treatment, a 2-week single blind washout period on FP 250 mcg BID, 2-week double-blind Treatment Period 2 receiving the alternative treatment, and follow-up contact approximately 7-days after completing Treatment Period 2. The total duration of study participation is approximately 11 weeks; and up to 15 weeks for subjects with SAR at screening who may need to be treated with intranasal corticosteroids followed by a repeat screening visit.

Type and Number of Subjects

Approximately 275 subjects with persistent asthma with evidence of EIB and current use of a low- to moderate-dose inhaled corticosteroid (ICS) will be screened in order to randomize 66 subjects, assuming a 20% screen failure rate and 70% run-in failure rate. This is to achieve 56 evaluable subjects completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. This calculation assumes a 15% withdrawal rate during the study.

Analysis

The primary treatment comparison will be between the FF/VI combination and FP and will be performed using the intent-to-treat (ITT) Population. Demonstration of efficacy for the treatments will be based on a hypothesis testing approach whereby the null hypothesis is that there is no difference between the population treatment groups and the alternative hypothesis is that there is a difference between the population treatment groups.

The primary endpoint will be defined as the maximal percent decrease from pre-exercise FEV₁ at 12 hours post-evening dose at the end of the 2-week treatment period. Pre-exercise FEV₁ will be defined as the FEV₁ value collected prior to the exercise challenge test at 12 hours post-dose. Maximal percent decrease will be defined as the percent change from the pre-exercise FEV₁ value to the minimum FEV₁ collected within one hour following exercise challenge at 12 hours post-dose. Mean post-exercise minimum FEV₁ measurements and mean maximal percent decrease from pre-exercise values will be summarized with descriptive statistics by treatment group. A linear mixed model will be fitted that includes the following covariates: treatment, subject-level mean of the FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the FEV₁ period baselines), gender, age and treatment period as fixed effects, and a random intercept for each subject.

A 2-sided 5% probability associated with incorrectly rejecting the null hypothesis (significance level) is considered acceptable for this study. In order to account for multiplicity, the primary hypothesis test on the primary endpoint for the ITT population will act as a gatekeeper for all other hypothesis tests using the secondary endpoints, where these tests will proceed in a pre-defined order. If a given statistical test fails to reject the null hypothesis of no population treatment group difference at the significance level of 0.05, then all tests lower down the hierarchy will be interpreted as descriptive only.

2. INTRODUCTION

2.1. Background

For many patients with symptomatic asthma, physical exertion is often a precipitating factor. Although varying in methodology and criteria, early studies showed that as many as 90% of asthmatic patients have bronchoconstriction after exercise [McFadden, 1994; Poppius, 1970]. In subjects with symptoms of persistent asthma, exercise and other forms of physical activity represent only one of many triggers that lead to worsening symptoms.

Chronic treatment with inhaled corticosteroids (ICS) has been shown to reduce the severity of asthma associated with exercise. However, some patients continue to demonstrate asthma symptoms and a decrease in lung function during exercise even while receiving ICS. The addition of a long-acting beta₂-agonist (LABA) to ICS has been considered as a possible treatment in these cases. International guidelines such as those issued by the Global Initiative for Asthma (GINA) [GINA, 2015] and the National Heart Lung and Blood Institute (NHLBI) [NIH, 2007] advocate the use of inhaled LABA in combination with ICS as maintenance therapy in asthma for subjects who remain symptomatic on low- to mid-dose ICS.

2.2. Study Rationale

In patients with persistent asthma, improvements in protection from exercise-induced bronchoconstriction (EIB) with ICS/LABA combination product Fluticasone propionate (FP)/salmeterol (Advair™) have been demonstrated [Murray, 2011; Pearlman, 2009; Weiler, 2005]. However, differences between FP/salmeterol and FP monotherapy have not consistently been observed [Murray, 2011; Weiler, 2005]. In a study that evaluated the effect of FP/salmeterol compared to FP over the 12 hour dosing interval [Weiler, 2005], a large percentage of subjects in both the FP/salmeterol (18%) and FP (36% and 33% at Day 1 and Week 4, respectively) treatment arms failed to complete the second exercise challenge test 8.5 hours after dosing, suggesting loss of protection against EIB towards the end of the 12 hour dosing interval.

FF/VI, a new ICS/LABA combination treatment, is administered once daily and has demonstrated significant bronchodilation over 24 hours. The purpose of this study is to determine if the once-daily administration of FF/VI demonstrates improved protection from EIB over ICS alone (FP) over the entire 24-hour dosing interval.

2.3. Brief Background

Fluticasone furoate (FF) is a novel glucocorticoid approved in the US for use as a once-daily inhaled treatment for asthma.

Vilanterol (VI) is an orally inhaled LABA. The inhaled fixed-dose combination of once-daily VI and FF is approved in the US for the maintenance treatment of asthma in adults aged 18 and older, and in the European Union and other regions in adults and adolescents ≥ 12 years of age. The FF/VI 100/25 mcg combination is being developed globally as a

once-daily therapy for the long-term maintenance treatment of asthma in adults and children ≥ 5 years of age. The inhaled fixed-dose combination of FF and VI is administered via the Ellipta™ Dry Powder Inhaler (DPI).

Information on the physical, chemical, and pharmaceutical properties of FF alone, VI (GW642444) alone, and FF/VI in combination may be found in the respective Investigator Brochures (IB).

3. OBJECTIVE

3.1. Primary Objective

To evaluate the protective effect of fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once-daily compared with fluticasone propionate (FP) 250 mcg twice-daily against exercise-induced bronchoconstriction in adolescent and adult subjects aged 12 to 50 with persistent asthma.

4. ENDPOINTS

4.1. Primary Endpoint

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post evening dose at the end of the 2-week treatment period

4.2. Secondary Endpoints

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Proportion of subjects with a 30 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Weighted mean for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose (weighted mean 0-60 min) at the end of the 2-week treatment period

4.3. Other Endpoints

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period) of:
 - <10%,
 - $\geq 10\%$ to <20%,
 - $\geq 20\%$

- Maximal percent decrease from treatment period baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period.
- Mean change from baseline in Asthma Control Questionnaire -5 (ACQ-5) score at the end of the 2-week treatment period.
- Percentage of subjects controlled, defined as an ACQ-5 score ≤ 0.75 , at the end of the 2-week treatment period.
- Percentage of subjects achieving an improvement of ≥ 0.5 or greater in ACQ-5 score at the end of the 2-week treatment.
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, Metabolic Equivalent of Tasks (METs), sleep duration).
- Proportion of subjects with a 5 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period. Repeat for the 10, 15, 45 and 60 minute time points.

4.4. Safety Endpoints

- Adverse events

5. STUDY DESIGN

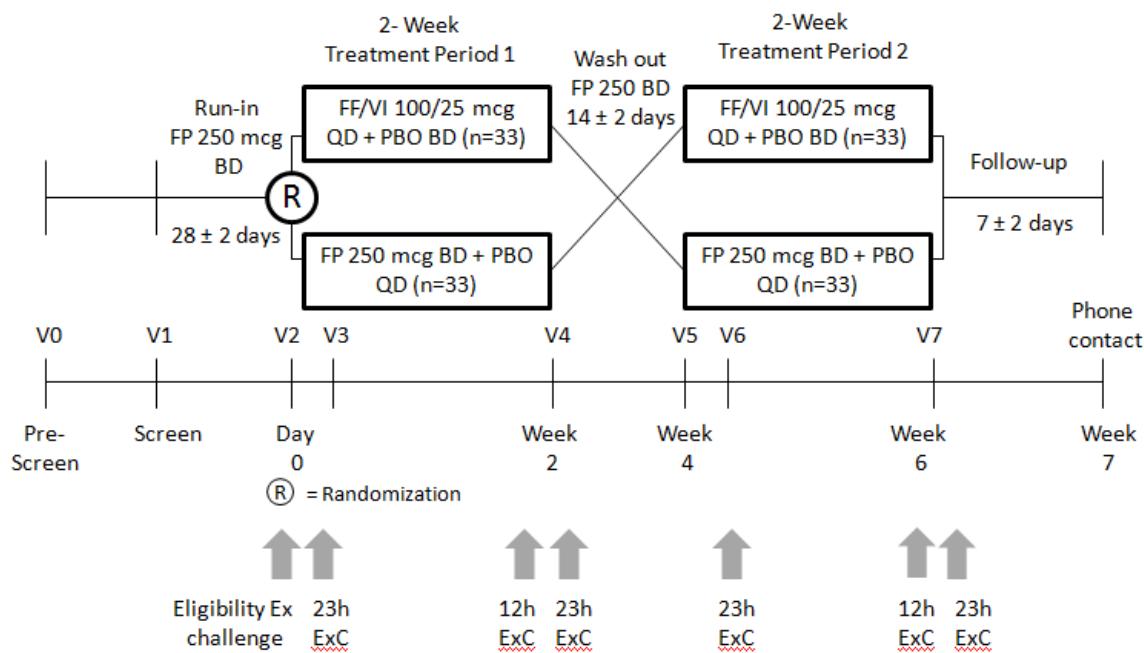
5.1. Overall Design

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will participate in up to eight study visits (Visit 0 to Visit 7) over the course of the study and a follow up phone call approximately a week after Visit 7. Visits 1, 2, 3, 5 and 6 are evening visits that will be conducted between 5PM and 11PM. Visit 4 and Visit 7 are also evening visits that will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will be required to attend three clinic visits during this 24-hour period.

Standardized exercise challenge testing (using a treadmill) will be conducted at Visit 2 for eligibility determination, Visit 3 and Visit 6 (after 23 hours of the first dose in each Treatment Period); and at 12 and 23 hours post evening dose at Visits 4 and 7.

Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 5 and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. At Visit 2, subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to $< 20\%$ may continue taking their daily run-in medication and repeat the eligibility

exercise challenge and associated procedures **once** within a week of the original procedure. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.



A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent (ICF), demography and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate.

At Visit 1, subjects meeting eligibility criteria will enter a 4-week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD). Subjects with symptomatic allergic rhinitis at Visit 1 (screening) may be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Only **one** repeat screening visit will be performed following treatment with intranasal corticosteroids. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded. Eligible subjects will enter the run-in period. Subjects who are asymptomatic at screening, who become symptomatic during the study will remain in the study and may be treated with intranasal corticosteroids at a constant dose for the duration of the study.

Albuterol/salbutamol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs including pulse rate and systolic and diastolic blood pressure will be obtained at each clinic visit, including any Early Withdrawal visit. At all time points where both vital signs and spirometry are performed, vital signs will be done before the spirometry measurement. At visits where the exercise challenge is performed, vitals will be measured before (prior to the pre-exercise spirometry) and after the exercise challenge.

Asthma control will be assessed using the ACQ-5 at Visits 2, 4, 5 and 7.

Physical activity levels will be monitored to assess activity outside the clinic [Mitchell, 2014] using a physical activity monitor (SenseWear Armband accelerometer) worn for 7 days prior to Visit 2 (baseline), for 7 days prior to Visit 4 (during the last week of Treatment Period 1), for 7 days prior to Visit 5, and for 7 days prior to Visit 7 (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate. See Study Reference Manual (SRM) for additional details.

A follow up phone call will be conducted approximately 7 days after Visit 7.

Re-screening of subjects is not allowed in this study with the exception of subjects with symptomatic allergic rhinitis at screening who may have a repeat screening visit after treatment with intranasal corticosteroids.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion, as asthma treatments including ICS/LABA combination products are available worldwide.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

5.2. Treatment Arms and Duration

Two treatment arms will be employed for the study:

- FF/VI 100/25 mcg QD via ELLIPTA + Placebo BD via Diskus
- FP 250 mcg BD via Diskus + Placebo QD via ELLIPTA

As this is a 2-period cross-over study, all randomized subjects will receive both treatments in the study either in Treatment Period 1 or Treatment Period 2. Also, each subject will receive a Diskus and ELLIPTA inhaler in Treatment Period 1 and Treatment Period 2.

Subjects will complete a 4-week single blind run-in on FP 250 mcg twice daily, followed by 2-week double-blind Treatment Period 1 on randomized treatment, a 2-week single blind washout period on FP 250 mcg twice daily, 2-week double-blind Treatment Period 2 receiving the alternative treatment, and follow-up contact approximately 7-days after completing Treatment Period 2. The total duration of study participation is approximately

11 weeks; and up to 15 weeks for subjects with SAR at screening who may need to be treated with intranasal corticosteroids followed by repeat screening visit.

5.3. Type and Number of Subjects

Subjects must have been diagnosed with persistent asthma with evidence of EIB and have been using a low- to moderate-dose ICS as a part of their asthma maintenance treatment. Assuming a 20% screen failure rate and 70% run-in failure rate, approximately 275 subjects will be screened in order to randomize 66 subjects in this study and ultimately achieve 56 evaluable subjects who have completed both the exercise challenges and spirometric evaluations at the end of both treatment periods. This calculation assumes a 15% withdrawal rate during the study.

5.4. Design Justification

The study design is based on the practice parameters for assessing EIB developed by the Joint Task Force on Practice Parameters for Allergy and Immunology [[Weiler, 2010](#)], American Thoracic society clinical practice guideline [[Parsons, 2013](#)], EMA (European Medicines Agency) Note on Guidance on Clinical Investigation of Medicinal Products for Treatment of Asthma [[EMA, 2013](#)] and FDA Draft Guidance for the Development of Drugs for Exercise-Induced Bronchospasm [[FDA Guidance for Industry, 2002](#)].

A randomized, double-blind, double dummy, cross-over design is a well-validated means to assess the efficacy and safety of two treatment groups. A cross-over design was chosen to reduce the impact of confounding variables, and allow for between and within group comparisons. The expectation that mild to moderate patients with EIB would already be using an ICS necessitated standardization of baseline ICS therapy and eliminates the need for use of a placebo comparator. Considering a 4-week run-in period on FP, two weeks of treatment with FF/VI followed by exercise challenge is considered adequate to observe a treatment effect for this within-subject comparison. A two-week washout period is adequate to wash out the LABA, VI, prior to Treatment Period 2.

FP was chosen as the “gold standard” ICS active comparator as its ability to prevent EIB has been previously characterized and FF is not currently commercially available outside of the US.

The primary endpoint of maximal percent decrease from pre-exercise baseline FEV₁ is a well-established measure of EIB and is consistent with agency guidance and established practice parameters. Exercise challenge testing at 12, and 23 hours post-dose at the end of each Treatment Period will allow for assessment of the duration of protective effect for the interventions.

5.5. Dose Justification

The inhaled FF/VI 100/25 mcg dose combination corresponds to the dose approved in the US (adults) and EU (adults and adolescents) for the treatment of asthma corresponding to low to moderate ICS/LABA asthma therapy. FF100 is deemed a low/mid strength ICS.

5.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with FF (GW685698)/VI (GW642444) can be found in the corresponding Investigator's Brochure and in the RELVAR/BREO™ ELLIPTA Prescribing Information for countries in which FF/VI is approved for marketing. For the FP section, information is taken from the label of FLOVENT ACCUHALER/DISKUS.

The following section outlines the risk assessment and mitigation strategy for this protocol:

5.6.1. Risk Assessment

For FF/VI the following risks and the mitigation strategy as applicable to asthma patients were taken from the summary of safety concerns in the European Union – Risk Management Plan (EU-RMP). For FF/VI the data/rationale for the risk were derived from the 2014 Investigator's Brochure, from an integrated analysis of key RELVAR studies (Integrated Summary of Safety for Fluticasone Furoate/Vilanterol v02 DBL 31 Jan 2014), from the RMP version 6.2 and in the RELVAR/BREO ELLIPTA Prescribing Information for countries in which FF/VI is approved for marketing.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [FF/VI]		
Pneumonia in patients with asthma	<p>The incidence of pneumonia in patients with asthma was uncommon. The incidence (adjusted for exposure) seen with FF/VI 100/25 microgram strength (8.5/1000 patient years) was similar to placebo (9.3/1000 patient years). No risk factors were identified.</p> <p>In an analysis performed on the 18 key studies in subjects with asthma pneumonia was reported by 0.5% (13 of 2369) of subjects who received FF/VI 100/25 subjects and 0.2% (2 of 1070) of subjects who received placebo.^a</p>	<p>The risk of pneumonia in asthma patients is very low and is consistent with the risk of other ICS. Subjects are not at an increased risk in this study, since they enter the study stable on an existing ICS treatment. Subjects are alerted to the potential risk of pneumonia in the informed consent. Investigators are informed of the risk in Section 1.2.3 (Asthma Clinical Studies) and Section 5.3.3 (Safety in Asthma Clinical Studies) of the IB. Subjects with concurrent respiratory disease are excluded from the study.</p>
Asthma related intubations and deaths	<p>This is a class effect of LABA in asthma. This has not been observed for FF/VI.</p> <p>An FDA meta-analysis of LABA vs. no LABA (60,954 patients in 110 trials) by age group on a composite endpoint of asthma-related deaths, intubations, and hospitalizations (asthma</p>	<p>Subjects with a history of life-threatening asthma are excluded from the study.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>composite index) showed a statistically significant difference among age groups. The composite event incidence difference for all ages was 6.3 events per 1000 patient-years (95% confidence interval [CI]: 2.2-10.3) with LABAs compared with no LABA use. Among the 15,192 patients with concurrent ICS use, the incidence difference was 0.4 events per 1000 patient-years (95% CI: -3.8 to 4.6). The authors noted a trend of greater excess risk with LABA among the younger age groups [McMahon, 2011].</p>	
Serious cardiovascular events	<p>In an analysis performed on the 18 key studies in subjects with asthma, eight serious cardiovascular events have been reported in patients exposed to FF/VI. Seven events in FF/VI 100/25 and one event in FF/VI 200/25. This represents an incidence less than 1% in the asthmatic patients exposed to FF/VI.^a</p> <p>The events reported include atrial fibrillation, acute coronary syndrome, coronary artery disease, hypertension, myocardial ischemia, tachyarrhythmia and tachycardia.</p>	<p>Subjects with existing serious cardiovascular disease and/or abnormal ECG findings are excluded from the study. Investigators are made aware of the potential class effects of LABAs and are advised to exercise caution for subjects with existing serious cardiovascular disease (Section 6.3 [Warnings and Precautions] of the IB).</p>
Hypersensitivity	<p>No FF/VI drug related hypersensitivity was noted in clinical trials.</p> <p>Spontaneous reports of hypersensitivity reactions have been reported in post-marketing</p>	<p>Subjects will be informed about the risk of hypersensitivity in the informed consent. Subjects will be advised to seek medical treatment if any signs of hypersensitivity occur.</p> <p>Subjects with milk protein allergy or known</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	<p>data for FF/VI. A possible causal association cannot be ruled out based on the temporal association between drug administration and hypersensitivity events including anaphylactic reaction, angioedema, urticaria, pruritis and rash.</p>	<p>hypersensitivity to FF, VI, the classes ICS or beta-agonist or any ingredient of the IP preparation will be excluded from participating in the study. Investigators are informed of the risk in Section 6.2 (Contraindications) of the IB.</p>
<p>Decreased bone mineral density and associated fractures</p>	<p>Risk of fracture has been associated with oral corticosteroids. It is unclear if inhaled corticosteroids carry the same risk.</p> <p>There were few events associated with bone disorders or fractures reported during the asthma development program. These events tended to be those associated with trauma.</p> <p>Currently the risk of reduced bone mineral density has not been observed in the asthma population [Jones, 2002]. In addition specific assessments in adolescents with asthma have not demonstrated an effect on bone mineral density, when controlled for growth [König, 1993; Turpeinen, 2010].</p> <p>In an analysis performed on the 18 key studies in subjects with asthma bone fractures were reported by <1% (16 of 2369) of subjects who received FF/VI 100/25.^a</p>	<p>Subjects will be informed about the risk of decreased bone mineral density and bone fractures in the informed consent. Investigators are made aware of the potential for this ICS class effect. Subjects will be advised to seek medical treatment if any signs of decreased bone mineral density or fractures occur.</p>

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Adrenal Suppression	<p>This is considered a class effect of ICS. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic-pituitaryadrenal axis (HPA) at the 100/25 strength. This includes a formal HPA study (HZA106851), using 24-hour serum cortisol measurements, and multiple studies with chronic obstructive pulmonary disorder (COPD) and asthma subjects which monitored urinary cortisol.</p>	<p>Subjects will be informed about the risk of adrenal suppression in the informed consent. Investigators are made aware of the potential for this class effect in Section 6.3 (Warnings and Precautions) of the IB. If systematic symptoms appear, investigators should implement an appropriate treatment while observing the subject's' asthma symptoms.</p>
Corticosteroid associated eye disorders	<p>This is considered a class effect of ICS. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI, FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed.</p>	<p>Subjects will be informed about the risk of corticosteroid associated eye disorders in the informed consent. Subjects will be advised to seek medical treatment if any signs of eye disorder occur. Investigators are made aware of the potential for this class effect in Section 5.3.3.7 (Ophthalmic Effects) of the IB.</p>
Study Design and Procedures		
Exercise-induced bronchoconstriction following exercise challenge testing	This study specifically recruits a study population which demonstrates a minimal level of exercise-	Exercise challenges may be stopped at any time during the assessment for worsening asthma. (Guidelines for treatment are provided in the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	induced bronchoconstriction ($\geq 20\%$ decrease from their pre-exercise FEV ₁). However, more severe bronchoconstriction is possible following exercise challenge testing.	<p>study reference manual [SRM].)</p> <p>If a subject's FEV₁ decreases to $\geq 40\%$ from their pre-exercise FEV₁ following exercise challenge, he/she must receive rescue therapy. If he/she requires rescue therapy with anything other than MDI (Metered Dose Inhaler) or nebulized albuterol/salbutamol or ipratropium (secondarily) following the exercise challenge assessment, he/she will not be allowed to continue in the study.</p> <p>Subjects will be monitored until their FEV₁ reaches $\geq 95\%$ of their pre-exercise FEV₁. Rescue Albuterol/salbutamol may be given during recovery.</p>
Cardiovascular stress resulting from exercise	Rigorous exercise can lead to heart attack, stroke and even death.	Subjects with existing serious cardiovascular disease and abnormal ECG findings are excluded from the study. Investigators are made aware of the potential class effects of LABAs and are advised to exercise caution for subjects with existing serious cardiovascular disease (Section 6.3 [Warnings and Precautions] of the IB).
Musculoskeletal injury resulting from exercise challenge testing	Musculoskeletal injury is a risk of exercise on a treadmill.	The exercise challenge will begin gradually to allow the subject to warm up over 2 minutes, and end with a gradual stop.
Falls or other injuries resulting from exercise	Exercise challenge testing will be conducted on a	Front and side handrails will be in place in order to prevent a fall. Subjects will be instructed to

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
challenge testing	treadmill, with an air mask and heart rate monitor. Subjects unfamiliar with treadmill usage or with wearing equipment while on the treadmill could become unbalanced and fall.	refrain from holding on to the support railings during the challenge. At least one staff member will be behind and within reach of the subject throughout the challenge. It is recommended that 3 staff members should facilitate the challenge procedures.
Unknown risks to an embryo, fetus (unborn baby) or nursing infant	There are no studies with FF/VI or the individual components (FF and VI) in pregnant women.	<p>As specified in the protocol:</p> <ul style="list-style-type: none"> • Women who are pregnant, lactating or are planning on becoming pregnant during the study are not eligible to participate in this study. • Female subjects must be postmenopausal or using a highly effective method for avoidance of pregnancy while in this study. • If a female subject becomes pregnant during the study, she should let the study doctor know immediately. The study medication will be stopped. • For women of child-bearing potential, a urine pregnancy test will be performed at Screening (Visit 1). For enrolled subjects, a urine pregnancy test will be performed at Screening, randomization, Visit 4 and at home at the Follow-Up contact. The result will be reported to the site study staff during the

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		Follow-Up Phone Contact.
Asthma symptoms may worsen during the study	<p>As specified in the protocol:</p> <ul style="list-style-type: none"> • The use of certain asthma medications is excluded prior to and during the study. • After Visit 1, the use of rescue medication (albuterol/salbutamol) must be withheld for at least 6 hours prior to and during each clinic visit. • Patients will be placed on an ICS alone treatment during the run-in period and possibly during the treatment period. 	<p>The informed consent advises the subject to:</p> <ul style="list-style-type: none"> • Talk to the study doctor about the excluded medications before deciding and consenting to participate in the study. • Use the rescue medication (albuterol/salbutamol) if asthma symptoms worsen. • Notify the study doctor or staff if his/her asthma symptoms worsen or do not get better after using the rescue medication. • Go immediately to the emergency department/seek medical attention if the symptoms are severe.
Shortness of breath, coughing, lightheadedness or fainting, and/or chest tightness during the spirometry measurements	None.	As specified in the informed consent form for this study, if any of these symptoms should happen to the subject, he/she will receive medical treatment.

a. RELVAR studies summarized include FFA109684, FFA109685, FFA109687, B2C109575, HZA106827, HZA106829, HZA113091, HZA113714, HZA113719, HZA116863, HZA106837, HZA106839, HZA106851, FFA112059, FFA114496, FFA115283, FFA115285, B2C112060.

5.6.2. Risk assessment for FP 250mcg

FLOVENT/FLIXOTIDE is a marketed drug that contains the ICS fluticasone propionate (FP 250 mcg). A similar profile of undesirable effects as reported for ICS may occur with FP. Since FLOVENT/FLIXOTIDE contains an ICS (FP), the risk mitigation strategies for FF (ICS) as mentioned in Section [5.6.1](#) will be applicable.

Please refer to the authorized product label for further information about the risks of using FP. In this study, FP will be used in line with the recommendations provided in the product label.

5.6.3. Benefit Assessment

Combined treatment with ICS and LABA has been shown to be more effective than the individual components in asthma, leading to the development of fixed dose combination inhalers. The use of ICS/LABA combinations is now well established in international treatment guidelines for moderate to severe persistent asthma patients for whom treatment with ICS alone is not sufficient.

In patients with persistent asthma, improvements in protection from EIB with ICS/LABA combination product FP/salmeterol (Advair) have been demonstrated [[Murray, 2011](#); [Pearlman, 2009](#); [Weiler, 2005](#)]. Once-daily FF/VI 100/25 mcg is hypothesized to provide protection from EIB throughout the dosing period.

FP 250 mcg is a commercially available product for the treatment of persistent asthma and has a recognized safety profile.

5.6.4. Overall Benefit: Risk Conclusion

GlaxoSmithKline (GSK) has assessed this study for any potential risks that a subject may experience. The investigational product (IP) FF/VI has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported by the results of previously performed clinical studies with the products in healthy volunteers and subjects with Asthma and COPD. The ICS (FP) described above will be used at a dose and frequency that is approved for the treatment of Asthma and has an acceptable safety profile for use. This conclusion is supported by the results of previously performed clinical studies and post-marketing experience (see local label).

Adverse effects that could be associated with the use of FF/VI and FP will be closely monitored. A safety criterion outlining details for subject withdrawal is included in the protocol (Section [6.4](#), Withdrawal Criteria). A thorough summary and evaluation of the available pre-clinical data can be found in the IB. Routine safety analysis of this study will be conducted by the company.

Taking into account the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with FF/VI and FP are justified by the anticipated benefits that may be afforded to patients with asthma.

6. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

Specific information regarding warnings, precautions, contraindications, adverse events, and other pertinent information on the GSK investigational product or other study treatment that may impact subject eligibility is provided in the product label or IB/IB supplement(s).

Deviations from inclusion and exclusion criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability or subject safety. Therefore, adherence to the criteria as specified in the protocol is essential.

6.1. Screening Criteria

6.1.1. Inclusion Criteria

A subject will be eligible for inclusion in this study only if all of the following criteria apply:

1. **Informed consent:** Subjects must give their signed and dated written informed consent to participate prior to commencing any study related activities.
2. **Age Range:** 12 to 50 years of age, inclusive, at Visit 1 (Screening).
3. **Diagnosis:** A diagnosis of asthma, as defined by the National Institutes of Health [NIH, 2007], for at least 12 weeks prior to Visit 1.
4. **Asthma Severity:** Subjects must have a pre-bronchodilator FEV₁ of $\geq 70\%$ of the predicted normal value. Predicted values will be based upon Global Lung Function Initiative (GLI) [Quanjer, 2012] equations for spirometry reference values.
5. **Evidence of EIB:** Subjects must answer “Yes” to at least 2 of the following 3 questions reflecting on the previous 12 months:
 - Are you short of breath during exercise or other physical exertion?
 - Do you wheeze after exercise or other physical exertion?
 - Do you cough after exercise or other physical exertion?
6. **Concurrent Anti-Asthma Therapy:** Subjects must be taking low- to moderate-dose inhaled steroids for 12 weeks prior to Visit 1 in order to participate with no change in dose for the 4 weeks prior to Visit 1. Example dosages considered appropriate for study participation are outlined in the SRM.
7. **Gender:** Subjects may be male or an eligible female.

A female is eligible to enter and participate in the study if she is of:

Non-child bearing potential (i.e., physiologically incapable of becoming pregnant, including any female who is post-menopausal or surgically sterile). Surgically sterile females are defined as those with a documented hysterectomy

and/or bilateral oophorectomy or tubal ligation. Post-menopausal females are defined as being amenorrhoeic for greater than 1 year with an appropriate clinical profile, e.g., age appropriate, > 45 years, in the absence of hormone replacement therapy.

OR

Child bearing potential, has a negative pregnancy test at screening, and agrees to acceptable contraceptive methods approved in their local country, when used consistently and correctly (i.e., in accordance with the approved product label and the instructions of the physician for the duration of the study – screening to follow-up contact). See [Appendix 5](#).

8. **Albuterol/salbutamol Use:** All subjects must be able to replace their current short-acting beta₂-agonist (SABA) with albuterol/salbutamol, to be used only on an as-needed basis for the duration of the study. Each subject must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to performing spirometric evaluations.
9. **Physical Capacity:** Each subject must be physically able to perform the exercise challenges on a treadmill when bronchodilators have been withheld.

6.1.2. Exclusion Criteria

A subject will not be eligible for inclusion in this study if any of the following criteria apply:

1. **Intermittent Asthma, Seasonal Asthma, or Exercise-Induced Bronchoconstriction Only:** Subjects with only intermittent or seasonal asthma or only exercise-induced asthma are excluded from participation in this study.
2. **History of Life-threatening Asthma:** Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnia, respiratory arrest or hypoxic seizures within the last 10 years.
3. **Asthma Exacerbation:** Any asthma exacerbation requiring oral corticosteroids within 12 weeks of Visit 1 or that resulted in an overnight hospitalization requiring additional treatment for asthma within 6 months prior to Visit 1.
4. **Symptomatic Allergic Rhinitis:** Subjects with symptomatic allergic rhinitis at Visit 1 may be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded.
5. **12-Lead Electrocardiogram (ECG):** A subject is not eligible if he/she has an abnormal, clinically significant ECG as determined by the investigator at the Screening Visit.
6. **Pregnancy:** Women who are pregnant or lactating or are planning on becoming pregnant during the study.

7. **Respiratory Infection:** Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of Visit 1 and led to a change in asthma management or, in the opinion of the investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
8. **Concurrent Respiratory Disease:** A subject must not have current evidence of:
 - a. Atelectasis
 - b. Bronchopulmonary dysplasia
 - c. Chronic bronchitis
 - d. Chronic obstructive pulmonary disease (current or past diagnosis including asthma/COPD overlap)
 - e. Pneumonia
 - f. Pneumothorax
 - g. Interstitial lung disease
 - h. Or any evidence of concurrent respiratory disease other than asthma
9. **Other Concurrent Diseases/Abnormalities:** A subject must not have 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 efficacy results if the condition/disease exacerbated during the study.

The list of additional excluded conditions/diseases includes, but is not limited to, the following:

Table 1 Excluded Conditions/Diseases

Addison's disease	hypertension ¹ (uncontrolled)
aortic aneurysm (clinically significant)	immunologic compromise
cardiac arrhythmia (clinically significant)	malignancy ² (current)
congestive heart failure	peptic ulcer (recent or poorly controlled)
coronary heart disease (clinically significant)	renal disease
Cushing's disease	stroke within 3 months of Visit 1
diabetes mellitus (uncontrolled)	thyroid disorder (uncontrolled)
drug or alcohol abuse (recent history)	tuberculosis (current or untreated ³)
hematological disease	

1. Two or more measurements with systolic pressure >160mmHg or diastolic pressure >100mmHg
2. A history of malignancy is acceptable only if subject has been in remission for one year prior to Visit 1 (remission = no current evidence of malignancy and no treatment for the malignancy in the 12 months prior to Visit 1)
3. Subjects with a history of tuberculosis infection who have completed an appropriate course of antituberculosis treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease.

10. **Investigational Medications:** A subject must not have used any investigational drug within 30 days prior to Visit 1 or within five half-lives ($t^{1/2}$) of the prior investigational study, whichever is longer of the two periods.
11. **Allergies:**
 - a) **Drug Allergy:** Any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy, or excipients used with FF/VI 100/25 or FP 250 (i.e., drug, lactose or magnesium stearate).
 - b) **Milk Protein Allergy:** History of severe milk protein allergy.
 - c) **Latex Allergy:** History of allergy or sensitivity to latex that in the opinion of the investigator contraindicates the subject's participation in the study.
12. **Concomitant Medication:** Administration of prescription or non-prescription medication that would significantly affect the course of asthma, or interact with study drug (see Prohibited Medication Section [7.10](#) for a list of prohibited medications and washout times required prior to Visit 1).
13. **Immunosuppressive Medications:** A subject must not be using or require the use of immunosuppressive medications during the study.
14. **Compliance:** A subject will not be eligible if he/she or his/her parent or legal guardian has any infirmity, disability, disease, or geographical location which seems likely (in the opinion of the investigator) to impair compliance with any aspect of this study protocol
15. **Tobacco/Marijuana Use:** Current tobacco smoker or has a smoking history of ≥ 10 pack-years (20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g., cigarettes, cigars, electronic cigarettes, or pipe tobacco).
16. **Affiliation with Investigator's Site:** A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub investigator, study coordinator or an employee of the participating investigator.

6.2. Randomization Criteria

At the end of the run-in period, a subject will be eligible for Randomization to double-blinded study treatment if he/she meets all the following criteria at Visit 2.

6.2.1. Inclusion Criteria

1. **Physical Capacity:** All subjects must be physically able to perform the exercise challenges on a treadmill with specific consideration of any health changes since Visit 1.
2. **FEV₁ Target:** Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge. Subjects who achieve a decrease in FEV₁ of 15% to <20% may continue taking

their daily run-in medication and repeat the eligibility exercise challenge and associated procedures **once** within a week of the original procedure.

6.2.2. Exclusion Criteria

1. **Pregnancy:** Positive urine pregnancy test at Visit 2.
2. **Asthma Medication Changes:** Changes in asthma medication after Visit 1 (excluding albuterol/salbutamol inhalation aerosol provided at Visit 1) are not permitted.
3. **Prohibited Medication:** Use of any prohibited medications (Section [7.10.2](#)) during the run-in period or at Visit 2.
4. **Respiratory Infections:** Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
5. **Asthma Exacerbation:** Evidence of a severe exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department (ED) visit due to asthma that required systemic corticosteroids between Visits 1 and 2.

6.3. Screening/Baseline/Run-in Failures

In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure reason details, Eligibility Criteria, and any Serious Adverse Events.

A subject who is assigned a subject number, has signed the informed consent, and has completed at least one study procedure, but does not enter the run-in period of the study is considered a 'screen failure'.

A subject who completes the screening visit and is dispensed FP 250 mcg, albuterol/salbutamol for rescue use, and a medical conditions diary card is considered to have entered the run-in period. A subject who has entered the run-in period, but is not randomized to study treatment medication, is classified as a 'run-in failure'.

At a minimum, the following information will be collected for subjects who fail screening or run-in:

1. Demographic information for race, age and gender
2. Reason for screen/run-in failure (screen/run-in failure eCRF page, inclusion/exclusion criteria eCRF page, and randomization criteria eCRF page [if applicable])

3. SAE information
4. Investigator signature page

Re-screening of subjects is not allowed in this study with the exception of subjects with symptomatic allergic rhinitis at screening who may have a repeat screening visit after treatment with intranasal corticosteroids.

6.4. Withdrawal/Stopping Criteria

A subject may withdraw from study treatment at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioural or administrative reasons. Once withdrawn from the investigational product a subject will be considered withdrawn from the study. Subjects who are withdrawn from the study may be replaced at the discretion of the Sponsor. The primary reason for withdrawal will be recorded in the eCRF.

6.4.1. Study Specific Withdrawal Criteria

A Subject will be withdrawn from the study if any of the following withdrawal criteria are met:

1. **Liver Chemistry:** Meets any of the protocol-defined liver chemistry stopping criteria (see [Appendix 2](#)).

Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

If the liver chemistry stopping criteria are met by any subject participating in this study, treatment restart or rechallenge is not permitted.

2. Severe Asthma Exacerbation

Subjects who experience a severe asthma exacerbation at any time during the study must be withdrawn from the study. A severe exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or Emergency Department visit due to asthma that required systemic corticosteroids during the study.

3. Worsening of Asthma requiring additional treatment

Subjects requiring rescue therapy with anything other than MDI or nebulized albuterol/salbutamol or ipratropium (secondarily) following the exercise challenge assessment should be withdrawn.

NOTE: If a subject's FEV₁ decreases to $\geq 40\%$ from their pre-exercise FEV₁ following exercise challenge, he/she must receive rescue therapy. If he/she requires rescue therapy with anything other than MDI or nebulized

albuterol/salbutamol or ipratropium (secondarily) following the exercise challenge assessment, he/she is not allowed to continue in the study

Subjects who experience asthma worsening outside of the exercise challenges which, in the opinion of the investigator, requires additional asthma treatment other than study medication or study supplied albuterol/salbutamol should be withdrawn.

4. **Pregnancy:** Positive urine pregnancy test
5. **ECG:** Discontinuation is required if any of the following ECG criteria are met during the study:
 - QTcF>500 msec or uncorrected QT>600 msec
 - Change from baseline: QTcF> 60msec

For patients with underlying **bundle branch block**, follow the discontinuation criteria listed below:

Baseline QTc with Bundle Branch Block	Discontinuation QTc with Bundle Branch Block
< 450 msec	> 500 msec
450 – 480 msec	≥ 530 msec

- The *same* QT correction formula *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the subject has been enrolled.

For example, if a subject is eligible for the protocol based on QTcB, then QTcB must be used for discontinuation of this individual subject as well.

Once the QT correction formula has been chosen for a subject's eligibility, the *same formula* must continue to be used for that subject *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.

The QTc should be based on single or averaged QTc values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.

Details on performing ECG assessments can be found in Section [8.4.6](#).

6.4.2. Reasons for Study Withdrawal

The primary reason for Study Withdrawal will be recorded in the eCRF and any data collected up until the point of withdrawal will be used in the data analyses.

General reasons for withdrawal may include:

1. Adverse event
2. Withdrew consent
3. Lost to follow-up
4. Protocol deviation impacting safety
5. Lack of efficacy
6. Subject reached protocol-defined withdrawal criteria
 - Liver function
 - Asthma Exacerbation
 - Asthma Worsening
 - Pregnancy
 - ECG
7. Non-compliance
8. Injury during the exercise challenge
9. Study closed/terminated

6.4.3. Lost to Follow up (Non-Attendance)

The following actions must be taken in relation to a subject who fails to attend the clinic for a required study visit:

- The site must attempt to contact the subject and re-schedule the missed visit as soon as possible.
- The site must counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- In cases where the subject is deemed ‘lost to follow up’, the investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and if necessary a certified letter to the subject’s last known mailing address or local equivalent methods). These contact attempts should be documented in the subject’s medical record.
- Should the subject continue to be unreachable, only then will he/she be considered to have withdrawn from the study with a primary reason of “Lost to Follow-up”.

6.4.4. Early Withdrawal Visit

Subjects may withdraw or be withdrawn from the study for any reason. If withdrawal occurs, the investigator must make every effort to have the subject return to the clinic as soon as possible after the subject stopped study medication for an Early Withdrawal (EW) Visit (ideally within 24 hours). At withdrawal, all study medications and other

study-related materials should be returned to the site by the subject (Time and Events Table [Table 3](#)). In the event a subject withdraws at, or during, a scheduled visit, an Early Withdrawal Visit is not required. However, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead. A follow-up phone contact should be made 7 days (\pm 2 days) after the Early Withdrawal Visit.

Following completion of these procedures, the subject will be discharged from the study. Upon completion of the Early Withdrawal Visit, each subject may resume any asthma medications deemed appropriate by the investigator for the management of the subject.

In the event that a subject is withdrawn from the study due to an adverse event, the investigator must attempt to follow the subject until the adverse event has either resolved or has become clinically insignificant.

6.5. Subject and Study Completion

A completed subject is one who has completed all phases of the study including the follow-up phone contact.

The end of the study is defined as the last subject's last contact.

7. STUDY TREATMENT

7.1. Investigational Product and Other Study Treatment

The term 'study treatment' is used throughout the protocol to describe any combination of products received by the subject as per the protocol design. Study treatment may therefore refer to the individual study treatments or the combination of those study treatments.

Albuterol/salbutamol will be given to all subjects to use throughout the study to treat acute asthma symptoms as needed per product label. Only study-supplied albuterol/salbutamol should be used for rescue during the study. Rescue usage will be recorded once daily in the subject's paper diary. **Do not record albuterol/salbutamol use in the eCRF.**

Albuterol/salbutamol inhalation aerosol will be supplied as detailed in the SRM.

	Study Treatment			
Product name:	Fluticasone Furoate/ Vilanterol 100/25 mcg	Fluticasone Propionate 250 mcg	Placebo ELLIPTA	Placebo DISKUS/ ACCUHALER
Formulation:	First strip: FF 100 mcg blended with lactose Second strip: VI 25 mcg blended with lactose and magnesium stearate	FP 250 mcg blended with lactose.	First strip: lactose Second strip: blend of lactose and magnesium stearate	Lactose
Dosage form:	ELLIPTA – 30 doses per device	DISKUS/ ACCUHALER – 60 doses per device	ELLIPTA – 30 doses per device	DISKUS/ ACCUHALER – 60 doses per device
Unit dose strength(s)/Dosage level(s):	100/25 mcg per actuation	250 mcg per actuation	NA	NA
Route of Administration	Inhaled	Inhaled	Inhaled	Inhaled
Dosing instructions:	Once daily in the evening	Twice daily; once in the morning and once in the evening	Once daily in the evening	Twice daily; once in the morning and once in the evening

FF= fluticasone furoate; VI = vilanterol; FP = fluticasone propionate; mcg = micrograms; NA = not applicable

7.2. Treatment Assignment

Subjects will be assigned in a 1:1 ratio to the following treatment sequences ([Table 2](#)) in accordance with the randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software:

Table 2 Treatment Assignment

Treatment Sequence	Treatment Period 1	Washout	Treatment Period 2
1	FF/VI 100/25 mcg QD via Ellipta + Placebo BD via Diskus	FP 250 mcg BD	FP 250 mcg BD via Diskus + Placebo QD via Ellipta
2	FP 250 mcg BD via Diskus + Placebo QD via Ellipta	FP 250 mcg BD	FF/VI 100/25 mcg once daily (QD) via Ellipta + Placebo BD via Diskus

7.2.1. Assignment of Subject Number

At the Pre-screen Visit, a unique **Subject Number** (CRF number) will be assigned to any subject who has given informed consent. The unique Subject Number will be used to identify individual subjects during the course of the study.

All subjects that have a repeat screening visit following treatment for symptomatic allergic rhinitis will continue to use the same subject number assigned at the original screening visit.

7.2.2. Assignment of Treatment Number

Subjects meeting the randomization eligibility criteria at Visit 2 will be randomized to a treatment group through an Interactive Response Technology (IRT). The IRT will confirm the subject's CRF number (Subject Number) and provide two additional numbers:

- A **randomization** number will be assigned from a randomization schedule generated by Clinical Statistics, prior to the start of the study, using validated internal software. **Once assigned, this number must not be reassigned to any other subject in the study.**
- Two **treatment pack** numbers will be provided that identifies the single blinded study medication (Diskus) and double-blind study medication (ELLIPTA and Diskus) that should be dispensed to the subject from the investigator's inventory

7.3. Blinding

Subjects will be single blinded to the study medication given in the run-in and washout periods. Investigators and site staff will be unblinded to the run-in and washout medication.

The treatment periods will be double-blind, double-dummy study and the following will apply:

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the eCRF
- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with a Serious Adverse Event (SAE). If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

7.4. Packaging and Labeling

The contents of the label will be in accordance with all applicable regulatory requirements.

7.5. Preparation/Handling/Storage/Accountability

No special preparation of study treatment is required. Eligible subjects will be taught proper use of the Diskus inhaler and administer their first dose of inhaled FP 250 mcg at Visit 1. Randomized subjects will be taught proper use of the ELLIPTA inhaler at Visit 2 and administer their first doses from each inhaler (active and placebo) at the visit.

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored

(manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the SRM.
- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document 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.

7.6. Investigational Product Malfunction

Any investigational product inhaler that fails to function properly must be identified to GSK personnel for return to GSK for testing. Details of the failure will be documented in the eCRF. The subject should return the inhaler to the clinic as soon as possible to avoid missing any doses. The site will then contact GSK's internal IVRS (also known as the Registration and Medication Ordering System [RAMOS] NG) and obtain a new treatment pack number for this subject and dispense a new study medication kit from the site's investigational product supply, as instructed per the IVRS.

7.7. Compliance with Study Treatment Administration

Subject compliance with study medication will be assessed at all visits (including at Early Withdrawal) via review of the dose counters on the ELLIPTA and DISKUS inhalers. This information will be recorded in the eCRF. Subjects who are not compliant with run-in medication administration or study drug administration should be counselled on appropriate dosing of study drug and this counselling should be noted in the source documentation. Subjects who demonstrate <80% compliance may be withdrawn from the study upon consultation with the Sponsor.

7.8. Treatment of Study Treatment Overdose

For this study, an overdose will be defined as the subject receiving any amount of investigational product greater than the maximum dose permitted by the protocol, which results in clinical signs or symptoms.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose the investigator [or treating physician] should use their discretion as to whether other treatment is warranted and contact the Medical Monitor. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject.

7.9. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study as other treatment options are available for persistent asthma. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment. At the end of Visit 7, investigators should prescribe asthma medication appropriate to the severity of the subject's asthma in accordance with asthma guidelines [GINA, 2015; NIH, 2007]. **Do not record asthma medications started on or after the final clinic visit in the eCRF.**

7.10. Concomitant Medications and Non-Drug Therapies

The names, doses, and regimens of the asthma medications taken during the 12 weeks prior to Visit 1 must be recorded in the Concomitant Medications section in the eCRF.

All concomitant medications taken during the study will be recorded in the eCRF. The minimum requirement is for the reporting of the drug name and dates of administration. Study provided albuterol/salbutamol should NOT be recorded in the eCRF.

Asthma medications taken after the final clinic visit will not be recorded in the eCRF.

7.10.1. Permitted Medications and Non-Drug Therapies

7.10.1.1. Permitted Asthma Medications

1. **Short-acting β_2 -Agonist:** Subjects will receive albuterol/salbutamol inhalation aerosol at Visit 1 for rescue use throughout the run-in, washout and treatment periods. Subjects should be able to withhold albuterol/salbutamol at least 6 hours prior to spirometry at each visit.
2. **Anticholinergic Rescue:** Ipratropium is permitted as a secondary treatment for rescue purposes at the exercise challenges. All other anticholinergic use is prohibited during the study.

7.10.1.2. Permitted Non-Asthma Medications

The following non-asthma medications are permitted. This list is not all inclusive. For any questions contact the Medical Monitor.

- **Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers:** **Administer with caution** as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.
- **Strong cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin): Use with caution.** May cause systemic corticosteroid and cardiovascular effects.
- **Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs):** **Administer with extreme caution** as they may potentiate the effects of beta-agonists on the vascular system.
- **Diuretics:** **Caution** is advised in the co-administration of beta-agonists with non potassium-sparing diuretics.
- **Decongestants:** Subjects may take decongestants during the study except during the 24 hours prior to ECG measurements.
- **Antihistamines:** Short-acting and long-acting antihistamines are allowed to control symptoms of allergic disorders, however **are not permitted the week prior to exercise testing.** In addition, antihistamine eye drops are allowed during the study. **Subjects should be reminded to avoid taking any antihistamines a week before each exercise challenge procedure.**
- **Intranasal corticosteroids:** Subjects may take intranasal corticosteroids to control symptoms of allergic disorders as long as the dose remains constant for the duration of the study.
- **Topical corticosteroids:** Subjects may use topical corticosteroids ($\leq 1\%$ hydrocortisone) for dermatological diseases.
- Influenza and/or pneumonia vaccination.
- All medications for other disorders as long as the dose remains constant wherever possible and their use is not expected to affect the subjects' lung function or safety assessments.

7.10.2. Prohibited Medications and Non-Drug Therapies

The following asthma medications are prohibited during the conduct of the study or within the specified time frame:

Within 12 weeks of Visit 1 and during the study:

- Systemic (oral, parenteral or depot) corticosteroids
- Anti-IgE (e.g. Xolair, NucalaTM)

Within 2 weeks of Visit 1 and during the study:

- Theophyllines
- Oral long-acting beta₂-agonists (LABA) (e.g., bambuterol)

Within 1 week of Visit 1 and during the study:

- Anti-leukotrienes including suppressors of leukotriene production and antagonists

1 Day Prior to Visit 1 and during the study:

- Inhaled long-acting beta₂-agonists
- Anticholinergics

Use of anticholinergics are not permitted except for the use of ipratropium for rescue (secondary to albuterol/salbutamol) at exercise challenges, if required.

- Ketotifen
- Nedocromil sodium
- Sodium cromoglycate

7.10.2.1. Prohibited Non-Asthma Medications

A subject may not use any other prescription or non-prescription medication which may affect the course of asthma or interact with sympathomimetic amines beginning at the respective time points defined below and during the remainder of the study.

- **Immunosuppressive medications:** A subject must not be using or require the use of immunosuppressive medications during the study.
- **Prior use of study medication/other investigational drugs:** Subjects who have received an investigational drug within 30 days of entry into this study (Screening), or within 5 drug half-lives of the investigational drug, whichever is longer.

A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Protocol waivers or exemptions are not allowed with the exception of immediate safety concerns. Therefore, adherence to the study design requirements, including those specified in the Time and Events Table, are essential and required for study conduct.

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table [Table 3](#).

8.1. Time and Events Table

Table 3 Time and Events Table

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12, 14}	5 ¹²	6	7 ^{12, 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	0	1 ¹⁸	14 (-2/+2) days	28 (-2/+2) days	29 ¹⁸	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X									
Genetics Consent	X ¹									
Subject Demography	X									
Medical History (including CV)		X								
Disease (Asthma) History		X								
Medication History	X	X								
Smoking history/status		X								
Inclusion/Exclusion Criteria		X								
Evidence of EIB		X								
Efficacy Assessments										
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ^{3, 17}	X ⁴	X ⁵		X ⁴	X ⁵		
Post-Challenge Serial FEV ₁ Measurements			X ³	X ⁶	X ⁶		X ⁶	X ⁶		
Asthma Control Questionnaire-5			X		X	X		X	X	
Dispense SenseWear ¹⁵ accelerometer		X								
Collect SenseWear accelerometer								X	X	
Safety Assessments										
Concomitant Medication	X	X	X	X	X	X	X	X	X	X ⁷

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12, 14}	5 ¹²	6	7 ^{12, 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	0	1 ¹⁸	14 (-2/+2) days	28 (-2/+2) days	29 ¹⁸	42 (-2/+2) days		47 to 51 days
Physical Examination		X								
Vital Signs		X	X ⁸	X ⁸	X ⁸	X	X ⁸	X ⁸	X	
12-lead ECG		X								
Adverse Event Assessment	X ⁹	X ⁹	X	X	X	X	X	X	X	X
Issue Medical Conditions Diary Card		X	X		X	X				
Review Medical Conditions Diary Card			X ¹⁰	X	X ¹⁰	X ¹⁰	X	X ¹⁰	X	
Laboratory Assessments										
Genetics Saliva Sample			X ¹							
Urine Pregnancy Test		X	X			X			X	X ¹³
Investigational Product										
Dispense Fluticasone Propionate		X			X					
Collect Fluticasone Propionate			X			X				
Dispense Rescue ¹⁶ Albuterol/salbutamol		X	X	X	X	X	X			
Collect Rescue Albuterol/salbutamol			X		X	X		X		
Dispense IP			X ¹¹			X				
Assess study drug compliance			X	X	X	X	X	X	X	
Collect IP					X			X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and forced vital capacity (FVC) testing), conducted immediately pre-exercise (and after vital signs), if applicable. Subject should have withheld albuterol/salbutamol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge.
4. Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 95% of baseline FEV₁ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before (prior to the pre-exercise spirometry) and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.
14. Visit 4 and Visit 7 will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will return to the clinic at 12 hours (± 1 hour) and 23 hours (± 1 hour) (after the evening dose of study medication from the evening visit) for an exercise challenge procedure.
15. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.
16. Collect and re-dispense rescue as needed from Visit 1
17. Subjects who achieve a decrease in FEV₁ of 15% to $< 20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures **once** within a week of the original procedure.
18. Visit 3 must be performed on the day immediately following Visit 2. Visit 6 must be performed on the day immediately following Visit 5.

8.2. Critical Baseline Assessments

During the pre-screening visit (Visit 0); each subject will have the following information collected:

1. Demographic history (including gender, ethnic origin and date of birth)
2. Concomitant medication review
3. Adverse event assessment

The following data will be captured at Visit 1:

1. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section [6.1](#)
2. Smoking history
3. Asthma history (including duration of asthma)
4. Evidence of EIB questions
5. Asthma and non-asthma concurrent medications
6. Concurrent medical conditions
7. Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.
8. Reason for screen failure (if applicable)
9. Screening lung function
10. Vital signs (including height and weight)
11. Serious Adverse Events related to study participation

8.3. Efficacy

8.3.1. Spirometry

Subjects should abstain from drinking beverages with high caffeine content such as tea or coffee for 4 hours prior to the spirometry procedure.

FEV₁ should be measured using spirometry equipment that meets or exceeds the minimal recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [[Miller](#), 2005]. All sites will use standardized spirometry equipment provided by an external vendor. Full FEV₁ and FVC will be conducted at Visit 1, and pre-dose at Visit 5, and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7.

For full FEV₁ and FVC testing at Screening and at randomisation (Visit 2), at least two valid and two repeatable (with no more than 8) efforts should be obtained using ATS/ERS guidelines. For all other visits where full FEV₁ and FVC testing is performed (prior to each exercise test at visits 3, 4, 6 and 7), at least two valid efforts should be

obtained. At each time point, the largest FEV₁ and FVC should be recorded, even if they do not come from the same effort.

Serial FEV₁ measurements only (not FVC) will be conducted serially as described in Time and Events Table [Table 3](#) following each exercise challenge at Visits 2, 3, 4, 6 and 7.

Subjects must have a FEV₁ of at least 70% of their predicted normal value to be eligible to take part in the study at Visit 1.

After Visit 1, subjects will always be required to withhold their albuterol/salbutamol for at least 6 hours before each clinic visit.

Subjects must not administer study drug prior to coming to the clinic on study visit days.

8.3.1.1. Target FEV₁ Calculations

Three target FEV₁ values will be calculated from the pre-exercise FEV₁ to determine subject eligibility and for monitoring the safety of the subject prior to exercise challenge testing:

1. The FEV₁ value that represents a $\geq 20\%$ decrease in FEV₁, which is the eligibility criterion.
2. The FEV₁ value that represents a $\geq 40\%$ decrease in FEV₁, which will serve as an alert for severe bronchoconstriction and need for administering rescue treatment.
3. The FEV₁ value that represents a $\geq 95\%$ recovery of the FEV₁ result.

Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed (See Section [8.3.2.1](#)).

8.3.2. Exercise Challenge Testing

The exercise challenge test is a stepped challenge on a treadmill at a speed and incline that will allow the subject's heart rate to reach between 80% to 95% of their maximum heart rate. All exercise challenges will be performed on a treadmill. During the exercise challenge, subjects will breathe medical grade dry air at ambient temperature from a reservoir using a two-way non-rebreathing valve.

Subjects will exercise sufficiently to attain a heart rate between 80 to 95% of their predicted maximum within 4 minutes and maintain this heart rate with exercise for an additional 6 minutes for a total of 10 minutes of exercise. The challenge will be followed immediately by serial spirometry (FEV₁ efforts only) at 6 time points over 60 minutes (5, 10, 15, 30, 45 and 60 minutes post-exercise). The information gained from the eligibility challenge(s) regarding incline and speed will be used to obtain the target heart rate in the subsequent exercise challenges.

Exercise challenges should not be performed within 24 hours of exercise in cold air. Subjects should abstain from drinking beverages with high caffeine content such as tea or coffee for 4 hours prior to the exercise challenge.

Additional instructions on exercise challenge testing can be found in the SRM.

8.3.2.1. Worsening of Asthma during Exercise Challenge

Exercise challenges may be stopped at any time during the assessment for worsening asthma. Guidelines for treatment are provided in the SRM.

If a subject's FEV₁ decreases to $\geq 40\%$ from their pre-exercise FEV₁ following exercise challenge, he/she must receive rescue therapy. If he/she requires rescue therapy with anything other than MDI or nebulized albuterol/salbutamol or ipratropium (secondarily) following the exercise challenge assessment, he/she is not allowed to continue in the study (see Section 6.4.1).

The subject should not leave the clinic until FEV₁ returns to within 95% of the baseline FEV₁ target recovery value or the subject is judged medically stable by the investigator to leave the clinic.

8.3.3. Key Study Assessments

Information regarding spirometry, exercise testing, and study medication dosing at Visits will be conducted as described below. All other assessments will also be conducted as shown in Time and Events Table [Table 3](#).

8.3.3.1. Visit 1 (Screening)

Spirometry will be performed at Visit 1 between 5:00 PM and 11:00 PM, ideally at the end of the subjects ICS dosing interval. Full FEV₁ and FVC testing will be conducted. At least two valid and two repeatable spirometry efforts should be obtained. Subjects must have a best pre-bronchodilator FEV₁ of $\geq 70\%$ of their predicted normal value to be eligible to take part in the study.

8.3.3.2. Visit 2 (Randomization)

Treatment period 1 baseline FEV₁: Visit 2 begins between 5 PM and 11 PM and should begin at approximately the same time as Visit 1 (± 1 hour). Spirometry will be performed at Visit 2 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours (± 1 hour) after dosing with run-in medication (FP 250 mcg). At least two valid and two repeatable spirometry efforts should be obtained before the first exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Eligibility Exercise Challenge: After the pre-exercise baseline FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the eligibility exercise challenge, serial spirometry (FEV₁) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

To qualify for randomization, subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to $< 20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge **once** within a week. In the event where a repeat visit is required for the exercise challenge, spirometry and vital signs measurements will be performed pre- and post- exercise challenge as detailed in [Table 3](#). In addition, ACQ-5 and a review of concomitant medication and adverse events will be performed at the repeat visit.

Dosing: Eligible subjects will administer their evening dose of double-blinded study medication following the eligibility exercise challenge/serial spirometry. Evening dosing should occur between 5 PM and 11PM.

8.3.3.3. Visit 3 and Visit 6 (23 hours Post First Dose Exercise Challenge)

Visit 3 and Visit 6 begins between 5 PM and 11 PM and should begin at approximately the same time as Visit 1 (± 1 hour). These visits should begin prior to the subject's evening dose on that visit day.

Pre-exercise FEV₁: Spirometry will be performed at Visits 3 and 6 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 23 hours (± 1 hour) after the first dose in each treatment period. At least two valid spirometry efforts should be obtained before the exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section [8.3.1.1](#)) should be determined based on the pre-exercise FEV₁.

Exercise Challenge: After the pre-exercise FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the eligibility exercise challenge at each visit, serial spirometry (FEV₁) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

Medication Dosing: At the end of Visits 3 and 6, the evening dose of study treatment medication should be administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

8.3.3.4. Visit 4 and Visit 7 (Blinded Treatment Exercise Challenges)

Visit 4 and Visit 7 begin between 5 PM and 11 PM and are conducted over approximately 24 hours. Subjects will be required to attend three clinic visits during each 24-hour period for Visit 4 and Visit 7. The evening visit should begin at approximately the same time as Visit 1 (± 1 hour).

Dosing: At the beginning of Visit 4 and Visit 7, subjects will administer their evening doses of double-blinded study medication in the clinic and the time of dosing will be recorded. In addition to administering the evening dose, vital signs will be measured and a review of concomitant medication and AEs performed.

Subjects will return to the clinic 12 (± 1) hours and 23 (± 1) hours after evening dosing for exercise challenge testing.

Pre-exercise FEV₁: At least two valid spirometry efforts with full FEV₁ and FVC maneuvers should be obtained just prior to each exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Exercise challenge testing: Exercise challenge testing will occur at 12 (± 1) hours and 23 (± 1) hours after administering the evening dose. (The 12-hour exercise challenge and spirometry measurements should occur prior to dosing of the study medication).

Post-exercise Serial Spirometry: Following the eligibility exercise challenge at each visit, serial spirometry (FEV₁) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

Washout Medication Dosing: At the end of Visit 4, the washout medication should be dispensed and first evening dose administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

8.3.3.5. Visit 5

Treatment period 2 baseline FEV₁: Spirometry will be performed at Visit 5 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours (± 1 hour) after dosing with the washout medication. At least two valid spirometry efforts should be obtained.

Dosing: Subjects will administer their evening doses of double-blinded study medication following the spirometry.

8.3.4. Physical Activity Monitor

Subjects should refrain from significant changes in their exercise level (e.g., joining a gym), except as instructed by the investigator, for the duration of the study.

A clinically validated physical activity monitor (accelerometer) will be used to measure specific levels of physical activity. There will be 4 assessment periods, including an initial baseline assessment in order to provide a reliable estimate of habitual physical activity. The physical activity monitor will be worn by the study subjects during the weeks prior to Visit 2, Visit 4, Visit 5 and Visit 7. Further details will be provided in the SRM.

Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.

Physical activity monitors will be shipped from each study site directly to GSK for analysis and interpretation or to an independent vendor, contracted by GSK, blinded to treatment assignment, who will be responsible for transmitting the data to GSK.

8.3.5. Asthma Control Questionnaire-5 (ACQ-5)

The ACQ-5 will be completed at the beginning of all study visits where the form is completed.

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of subject' asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the subject. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breathe, wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/limitation) scale.

The subject should be given a quiet area in which to complete the questionnaire. The investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous week. The subject should be reassured that there are no right or wrong answers. The investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

It is recommended that the ACQ-5 be administered at the same time during each visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACQ-5.

8.4. Safety

Safety will be assessed, as indicated in the Time and Events Table [Table 3](#), by monitoring of AEs, a physical examination at screening, and vital signs (systolic and diastolic blood pressure and heart rate [pulse] at each visit. A screening 12-ECG will be conducted.

In cases of suspected pneumonia, a confirmatory chest x-ray should be conducted within 48 hours.

Planned time points for all safety assessments are listed in the Time and Events Table (Time and Events [Table 3](#)).

8.4.1. Adverse Events (AE) and Serious Adverse Events (SAEs)

The definitions of an AE or SAE can be found in [Appendix 5](#).

The investigator and their designees are responsible for detecting, documenting and reporting events that meet the definition of an AE or SAE.

8.4.1.1. Time period and Frequency for collecting AE and SAE information

- AEs and SAEs will be collected from the start of Study Treatment (the start of the run-in period) until the follow-up contact (see Section [8.4.1.3](#)), at the time points specified in the Time and Events Table [Table 3](#)).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the eCRF.
- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in [Appendix 5](#).
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. 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 study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in [Appendix 5](#).

8.4.1.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the subject is the preferred method to inquire about AE occurrence. Appropriate questions include:

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”

- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”

8.4.1.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 5.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 6.4). Further information on follow-up procedures is given in [Appendix 5](#).

8.4.1.4. Cardiovascular and Death Events

For any cardiovascular events detailed in [Appendix 5](#) and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV CRFs are presented as queries in response to reporting of certain CV Medical Dictionary for Regulatory Activities (MedDRA) terms. The CV information should be recorded in the specific cardiovascular section of the CRF within one week of receipt of a CV Event data query prompting its completion.

The Death CRF is provided immediately after the occurrence or outcome of death is reported. Initial and follow-up reports regarding death must be completed within one week of when the death is reported.

8.4.1.5. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to GSK of SAEs and non-serious AEs related to study treatment (even for non- interventional post-marketing studies) is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a product under clinical investigation are met.

GSK has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. GSK will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and GSK policy and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from GSK will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.4.2. Asthma Exacerbations

Severe asthma exacerbations should not be recorded as an AE unless they meet the definition of an SAE (Section 13.5.2). For the purposes of this study, severe asthma exacerbations will be collected and recorded on the exacerbations log in the eCRF. The treatment details must also be recorded in the eCRF.

The time period for collection of severe asthma exacerbations will begin from the time of randomization (first receipt of investigational product) and will end after the 7-day follow-up period has been completed.

8.4.3. Pregnancy

- Details of all pregnancies in female subjects will be collected from the time the informed consent is signed (Visit 1) and until the follow up contact.
- Any pregnancy that occurs during study participation must be reported using a clinical trial pregnancy form.
- If a pregnancy is reported then the investigator should inform GSK within 2 weeks of learning of the pregnancy and should follow the procedures outlined in Section 13.6.1.
- Any SAE occurring in association with a pregnancy, brought to the investigator's attention after the subject has completed the study and considered by the investigator as possibly related to the study treatment, must be promptly reported to GSK.

8.4.4. Physical Exams

- A detailed physical examination including, but not limited to an evaluation of the lungs and cardiovascular system, will be conducted at Visit 1. Investigators should pay special attention to clinical signs related to previous serious illnesses
- Licensed practitioners who are listed on the Form 1572 are permitted to perform the physical examination. A licensed physician on the Form 1572 must sign off on the physical examinations completed by non-physicians. The results will be recorded in the subject's clinic notes. Whenever possible, the same person should perform the examination.
- If during routine clinical examination of the subject there is evidence of oral candidiasis infection, a culture can be taken and appropriate therapy should be instituted at the discretion of the Investigator.

8.4.5. Vital Signs

- Vital signs including pulse rate and systolic and diastolic blood pressure will be obtained at each clinic visit, including any Early Withdrawal visit.
- Vital signs will be obtained after subjects have rested for approximately 5 minutes in a semi-supine position, except in the case of the post exercise test vital signs which will be performed immediately following the end of the exercise test.

- At all time points where both vital signs and spirometry are performed, vital signs will be done before the spriometry measurement.
- At visits where the exercise challenge is performed, vitals will be measured before (prior to the pre-exercise spirometry) and after the exercise challenge.
- Heart rate will be measured during each exercise challenge.
- If there are any clinically significant abnormalities noted, further examinations must be performed until the abnormality is resolved.

8.4.6. *Electrocardiogram (ECG)*

- A 12-lead ECG will be performed and interpreted by the investigator or his/her suitably qualified designee at Visit 1. The ECG will be recorded after 5 minutes rest; after vital signs and prior to performing spirometry.
- Investigators will use a site ECG machine and perform a manual reading of the ECG parameters to determine whether a subject meets the eligibility criteria for enrolment in the study at screening (Visit 1).
- The ECG interpretation including the paper trace will be maintained at the site within the source documentation.

8.5. *Genetics*

Information regarding genetic research is included in [Appendix 4](#).

9. *DATA MANAGEMENT*

- For this study, subject data will be entered into GSK defined CRFs, transmitted electronically to GSK or designee and combined with data provided from other sources in a validated data system.
- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- CRFs (including queries and audit trails) will be retained by GSK, and copies will be sent to the investigator to maintain as the investigator copy. Subject initials and full date of birth will not be collected or transmitted to GSK according to GSK policy.
- For this study subject data will be collected using GSK defined case report forms and combined with data provided from other sources in a validated data system.

- Management of clinical data will be performed in accordance with applicable GSK standards and data cleaning procedures to ensure the integrity of the data, e.g., removing errors and inconsistencies in the data.
- Adverse events and concomitant medications terms will be coded using MedDRA (Medical Dictionary for Regulatory Activities) and an internal validated medication dictionary, GSKDrug.
- Original CRFs will be retained by GSK, while the investigator will retain a copy. Subject initials will not be collected or transmitted to GSK according to GSK policy.

10. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

10.1. Hypotheses

The primary endpoint is the maximal percent decrease in FEV₁ following exercise challenge at 12-hours post-dose at the end of the 2-week treatment period.

The treatment comparison is the FF/VI combination versus FP. Demonstration of efficacy for this treatment comparison will be based on a hypothesis testing approach whereby the null hypothesis is that there is no difference between treatment groups and the alternative hypothesis is that there is a difference between treatment groups.

A 2-sided 5% probability associated with incorrectly rejecting the null hypothesis (significance level) is considered acceptable for this study. In order to account for multiplicity, this primary hypothesis test on the primary endpoint for the ITT (Intent-to-Treat) population will act as a gatekeeper for all other hypothesis tests using the secondary endpoints, where these tests will proceed in a pre-defined order.

If the primary hypothesis on the primary endpoint for the ITT population is rejected then the following hierarchy of tests will be performed using the ITT population;

1. Test at the 5% level the null hypothesis that the true odds ratio between the two treatment groups of recovering to within 5% of pre-exercise FEV₁ at the 30 minute post-exercise time point following the exercise challenge at 12 hours post evening dose is equal to one.
2. Test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease in FEV₁ from pre-exercise at 23 hrs post-dose at the end of the 2-week treatment period is zero.
3. Test at the 5% level the null hypothesis that the true odds ratio between the two treatment groups of recovering to within 5% of pre-exercise FEV₁ at the 30 minute post-exercise time point following the exercise challenge at 23 hours post evening dose is equal to one.
4. If 3 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in weighted mean 0-60

minutes for percentage decrease in FEV₁ from pre-exercise FEV₁ at 12 hrs post-dose at the end of the 2-week treatment period is zero.

5. If 4 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in weighted mean 0-60 minutes for percentage decrease in FEV₁ from pre-exercise FEV₁ at 23 hrs post-dose at the end of the 2-week treatment period is zero.

If either the primary null hypothesis or any of the above null hypotheses are not rejected, then although all of the subsequent hypothesis tests will be performed, each test result, and the associated p-value will be used for descriptive purposes only.

10.2. Study Design Considerations

10.2.1. Sample Size Assumptions

For the primary efficacy endpoint of maximal percent decrease in FEV₁ following exercise challenge at 12 hours post-dose at the end of the 2-week treatment period, given an assumed 20% screen failure rate, a 70% run-in failure rate, and a 15% withdrawal rate post-randomisation, a total of approximately 275 subjects will be screened. Given these assumed failure and withdrawal rates we expect 220 subjects will enter the run-in period, of which 66 subjects will be randomized, of which 56 subjects will be evaluable, that is completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. With 56 evaluable subjects this study has approximately 90% power assuming a true population difference of 5% in maximal percent decrease in FEV₁ between the two treatment groups. This assumes a within-subject standard deviation (SD) of 8% where significance is declared at the two-sided 5% significance level.

Subjects will be centrally randomized to one of the two treatment sequences shown below in [Table 4](#) in a 1:1 ratio:

Table 4 Treatment Sequencing

Allocation ratio	Sequence	Period 1	Period 2
1	1	FF/VI 100/25 mcg QD via Ellipta + Placebo BD via Diskus	FP 250 mcg BD via Diskus + Placebo QD via Ellipta
1	2	FP 250 mcg BD via Diskus + Placebo QD via Ellipta	FF/VI 100/25 mcg QD via Ellipta + Placebo BD via Diskus

10.2.2. Sample Size Sensitivity

To demonstrate the sensitivity of the sample size calculation for this study, [Table 5](#) shows the effect that different within-subject standard deviations would have on the power of the study.

Table 5 Power as a function of within-subject SD

Within-subject Standard Deviation (%)	Power for the primary endpoint (%)
5	>99.9
6	99.1
7	96.0
8	90.1
9	82.3
10	73.9
11	65.7

Table 6 Sample size as a function of within-subject SD

Within-subject Standard Deviation (%)	Number of evaluable subjects
5	24
6	33
7	44
8	56
9	71
10	87
11	104

Both [Table 5](#) and [Table 6](#) assume a true population difference of 5% between the two treatment groups.

10.2.3. Sample Size Re-estimation

Blinded sample size re-estimation will be conducted when approximately 50% of the subjects have completed their second exercise challenge. In order to assess the accuracy of the sample size assumption for the within-subject SD, the linear mixed model for the primary analysis will be fitted to this blinded interim data, but with a dummy variable to denote treatment group membership. If this suggests the original assumptions behind the sample size were incorrect, an adjustment may be made to the planned number of subjects to be recruited.

10.3. Data Analysis Considerations

10.3.1. Analysis Populations

Three subject populations will be identified.

Total Population: This population will comprise of all subjects screened and for whom a record exists on the study database and will be used for the tabulation and listing of reasons for withdrawal before randomization.

Intent-to-Treat (ITT) Population: The ITT Population will comprise all subjects randomized to treatment and who received at least one dose of trial medication. Randomized subjects will be assumed to have received trial medication unless definitive evidence to the contrary exists. This will constitute the primary population for all analyses of efficacy measures and safety measures. Outcomes will be reported according to the randomized treatment allocation.

Per Protocol (PP) Population: The PP Population will consist of all subjects in the ITT Population who do not have full protocol deviations. Protocol deviations can either be full or partial. Subjects with only partial deviations will be considered part of the PP population but their data will be excluded from the date of their deviation until either the end of the study or the end of the treatment period in which the deviation occurred. The decision to exclude a subject, or part of their data, from the PP Population will be made prior to breaking the blind. Protocol deviations that will lead to full or partial exclusion from the PP population will be detailed in the Reporting and Analysis Plan (RAP). This population will be used for confirmatory analyses of the primary efficacy endpoint only.

10.3.2. Analysis Data Sets

Details of the derived data in analysis datasets to be created will be given in the RAP.

10.3.3. Treatment Comparisons

10.3.3.1. Primary Comparisons of Interest

The primary treatment comparison is the comparison of group means for the FF/VI combination and FP for the primary endpoint of maximal percent decrease in FEV₁ from pre-exercise at 12 hrs post-evening dose at the end of the 2-week treatment period. This comparison is to be performed using the ITT Population.

10.3.3.2. Other Comparisons of Interest

The primary treatment comparison of FF/VI combination versus FP for the primary endpoint will also be performed for the PP population.

In addition FF/VI combination will be compared to FP for the secondary and other efficacy endpoints.

10.3.4. Interim Analysis

No interim analysis is planned.

10.4. Key Elements of Analysis Plan

Where possible, data from subjects who withdraw prematurely from the study will be included in any analyses. Specific details for inclusion will be detailed in the RAP but, in general, if a subject has completed a treatment period, including both exercise challenges and FEV₁ evaluations, then the data for that period will be included in the analysis.

Specifically if a subject has completed the first exercise challenge at 12 hours post-dose, as well as the FEV₁ evaluations after this challenge, but has not completed the second exercise challenge at 23 hours post-dose, then the data for the 12 hour post-dose time point will be included, but will not be carried forward to replace the missing 23 hour time point.

Any tests for interactions will be 2-sided at the 10% level of significance. In all cases, if any assumptions of the proposed methods of analyses are not met, alternative methods of analyses will be used.

The baseline FEV₁ for all endpoints will be the pre-treatment FEV₁ value obtained at the start of each Treatment Period (Visit 2 or Visit 5).

10.4.1. Efficacy Analyses

All efficacy data will be summarized using means, standard deviations, medians and ranges for continuous variables and frequencies and percentages for categorical variables.

10.4.1.1. Primary Analysis

The primary efficacy end point is maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post-dose following two weeks of treatment. Maximal percent decrease will be defined as the percent change from pre-exercise FEV₁ to the minimum FEV₁ collected within one hour following exercise challenge at 12 hours post-dose. Pre-exercise FEV₁ will be defined as the FEV₁ value collected prior to the exercise challenge test at 12 hours post-dose.

The primary analysis is a comparison of the estimated means of the two treatment groups in maximal percent decrease in FEV₁ from pre-exercise at 12 hrs post-dose using a LMM to adjust for covariate effects. The LMM will include the following covariates: treatment, subject-level mean of the pre-treatment FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the pre-treatment FEV₁ period baselines), gender, age, treatment period and smoking history as fixed effects, and a random intercept for each subject.

Details will be provided in the RAP of alternative analyses methods to be used in the event that distributional assumptions do not hold (e.g. if the distribution appears to be heavily skewed).

Mean post-exercise minimum FEV₁ measurements and mean maximal percent decrease from pre-exercise FEV₁ will be summarized with descriptive statistics by treatment group. Summaries and analyses for the primary endpoint will be provided for both the ITT and PP populations.

10.4.1.2. Secondary Analyses

Summaries and analyses for secondary endpoints will be provided for the ITT population.

Maximal percent decrease from pre-exercise FEV₁ following exercise challenge (at 23 hours post-dose at the end of the 2-week treatment period):

This endpoint will be summarized and analyzed as for the primary endpoint of maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post-dose.

Proportion of subjects with a 30 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period

This endpoint will be analysed using a logistic regression model separately for the 12 and 23 hour challenges using the covariates baseline FEV₁, treatment group, gender, age, and smoking history.

Weighted mean 0-60 minutes for percentage decrease from pre-exercise FEV₁ after exercise (at 12 hours and 23 hours post-dose at the end of the 2-week treatment period):

A comparison will be made of the estimated means of the two treatment groups in for weighted mean 0-60 minutes of the percentage decrease in FEV₁ from pre-exercise at 12 and 23 hrs post-dose using a LMM to adjust for covariate effects. The LMM will include the following covariates: treatment, subject-level mean of the pre-treatment FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the pre-treatment FEV₁ period baselines), gender, age, treatment period and smoking history as fixed effects, and a random intercept for each subject.

10.4.1.2.1. Other Efficacy Analyses

Other measures of efficacy include the evaluation of a categorical treatment response evaluating the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁<10%, a decrease $\geq 10\%$ to <20%, or a decrease $\geq 20\%$, and an evaluation of maximal percent decrease from treatment period baseline in FEV₁ (period baseline) following exercise challenge (at 12 hours and 23 hours post-dose). Additional endpoints

include evaluation of physical activity monitoring the ACQ-5 score, and the proportion of subjects with a 5 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period (repeat for the 10, 15, 45 and 60 minute time points).

10.4.2. Safety Analyses

Safety will be assessed with clinical adverse events and asthma exacerbations.

10.4.2.1. Extent of Exposure

The extent of exposure to study drug will be summarized by treatment group.

10.4.2.2. Adverse Events (AEs)

Frequency of adverse events will be tabulated by treatment group as the number of subjects with events occurring during the treatment period. Drug-related adverse events will be tabulated in the same manner. Subject listings will include all reported adverse events, all adverse events rated as serious and all adverse events leading to study discontinuation.

10.4.2.3. Exacerbations

The frequency of subjects experiencing an asthma exacerbation during the treatment period will be tabulated by treatment group. A subject listing will include all reported exacerbations.

10.4.3. Pharmacogenetic Analyses

See [Appendix 4](#) for details about the PGx Analysis Plan.

11. STUDY GOVERNANCE CONSIDERATIONS

11.1. Posting of Information on Publicly Available Clinical Trial Registers

Study information from this protocol will be posted on publicly available clinical trial registers before enrollment of subjects begins.

11.2. Regulatory and Ethical Considerations, Including the Informed Consent Process

Prior to initiation of a site, GSK will obtain favourable opinion/approval from the appropriate regulatory agency to conduct the study in accordance with ICH Good Clinical Practice (GCP) and applicable country-specific regulatory requirements.

The study will be conducted in accordance with all applicable regulatory requirements, and with GSK policy.

The study will also be conducted in accordance with ICH Good Clinical Practice (GCP), all applicable subject privacy requirements, and the guiding principles of the current version of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.
- Signed informed consent must be obtained for each subject prior to participation in the study
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

11.3. Quality Control (Study Monitoring)

- In accordance with applicable regulations including GCP, and GSK procedures, GSK monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and GSK requirements.
- When reviewing data collection procedures, the discussion will also include identification, agreement and documentation of data items for which CRF will serve as the source document.

GSK will monitor the study and site activity 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 other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents

11.4. Quality Assurance

- To ensure compliance with GCP and all applicable regulatory requirements, GSK may conduct a quality assurance assessment and/or audit of the site records, and the regulatory agencies may conduct a regulatory inspection at any time during or after completion of the study.
- In the event of an assessment, audit or inspection, the investigator (and institution) must agree to grant the advisor(s), auditor(s) and inspector(s) direct access to all relevant documents and to allocate their time and the time of their staff to discuss the conduct of the study, any findings/relevant issues and to implement any corrective and/or preventative actions to address any findings/issues identified.

11.5. Study and Site Closure

- Upon completion or premature discontinuation of the study, the GSK monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations including GCP, and GSK Standard Operating Procedures.
- GSK reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For multicenter studies, this can occur at one or more or at all sites.
- If GSK determines such action is needed, GSK will discuss the reasons for taking such action with the investigator or the head of the medical institution (where applicable). When feasible, GSK will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action.
- If the study is suspended or prematurely discontinued for safety reasons, GSK will promptly inform all investigators, heads of the medical institutions (where applicable) and/or institution(s) conducting the study. GSK will also promptly inform the relevant regulatory authorities of the suspension or premature discontinuation of the study and the reason(s) for the action.
- If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IRB/IEC promptly and provide the reason for the suspension or premature discontinuation.

11.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.

- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site 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 ensure 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, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

11.7. Provision of Study Results to Investigators, Posting of Information on Publicly Available Clinical Trials Registers and Publication

Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.

GSK will also provide the investigator with the full summary of the study results. The investigator is encouraged to share the summary results with the study subjects, as appropriate.

GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.

The procedures and timing for public disclosure of the results summary and for development of a manuscript for publication will be in accordance with GSK Policy.

A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

12. REFERENCES

European Medicines Agency (EMA). Note for guidance on clinical investigation of medicinal products for treatment of asthma. 27Jun2013. CHMP/EWP/2922/01 Rev.1.

FDA Guidance for Industry: Exercise Induced Bronchospasm (EIB)—Development of Drugs to Prevent EIB, February 2002.

Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. GINA, www.ginasthma.org; 2015.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007: 24. Table 3-2.

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, 2009; EMA/CPMP/ICH/286/1995

Jones A, Fay JK, Burr ML, Stone M, Hood K, Roberts G. Inhaled Corticosteroids Effects on Bone Metabolism in Asthma and Mild Chronic Obstructive Pulmonary Disease. *Cochrane Database of Systemic Reviews*. 2002;1:1-21.

Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the Asthma Quality of Life Questionnaire (standardised) in patients 12 years and older. *Health and Quality of Life Outcomes*. 2005; 3:58.

König P, Hillmana L, Cervantesa C, Levine C, Maloney C, Douglass B, et al. Bone Metabolism in Children with Asthma Treated with Inhaled Beclomethasone Dipropionate. *The Journal of Paediatrics*. 1993;122:219-226.

McFadden ER, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330:1362-1367.

McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics*. 2011;Nov;128(5):e1147-54.

Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi F, Coates A, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.

Mitchell KE, Johnson-Warrington V, Apps LD, Bankart LS, Williams JE, Rees K, et al. A Self-Management Programme for COPD: a Randomised Controlled Trial. *Eur Respir J*. 2014;44:1538-1547.

Murray JJ, Waitkus-Edwards KR, Yancey SW. Evaluation of Fluticasone Propionate and Fluticasone Propionate/Salmeterol Combination on Exercise in Pediatric and Adolescent Patients with Asthma. *Open Resp Med J*, 2011, 5, 11-18.

National Institutes of Health (NIH). *Guidelines for the Diagnosis and Management of Asthma - Expert Panel Report 3* 2007. U.S. Department of Health and Human Services, Bethesda, MD; 2007. NIH Publication No. 07-4051.

Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, Hull JH, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016–1027.

Pearlman D, Qaqundah P, Matz J, Yancey SJ, Stempel DA, Ortega HG. Fluticasone Propionate/Salmeterol and Exercise-Induced Asthma in Children With Persistent Asthma. *Pediatric Pulm* 2009;44:429–435.

Poppius H, Muittari A, Kreus KE, Korhonen O, Vilhanen A. Exercise Asthma and Disodium Cromoglycate. *Br Med J* 1970;4:337-339.

Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Enright P, et al. on behalf of the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations. *Eur Respir J*, 2012; 40: 1324–1343.

Turpeinen M, Pelkonen AS, Nikander K, Sorva R, Selroos O, Juntunen-Backman K, et al. . Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki Early Intervention Childhood Asthma study. *Paediatric Research*. 2010;68(2):169-173.

Weiler J, Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Ann Allerg Asthma Immunol* 2010;105 (6 Supp): S1-S47.

Weiler J, Nathan RA, Rupp NT, Kalberg CJ; Emmett A, Dorinsky PM. Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann. Allergy Asthma Immunol.* 2005;94:65-72.

13. APPENDICES

13.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire-5
AE	Adverse Event
COPD	chronic obstructive pulmonary disorder
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EIB	Exercise-induced bronchoconstriction
EMA	European Medicines Agency
ERS	European Respiratory Society
eCRF	Electronic Case Report Form
FEV ₁	Forced Expiratory Volume in One Second
FF	Fluticasone furoate
FP	Fluticasone propionate
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
HPA	Hypothalamic-pituitaryadrenal axis
IB	Investigator Brochure
ICF	Informed Consent Form
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IP	Investigational product
INR	International normalized ratio
IRB	Independent Review Board
IRT	Interactive Response Technology
ITT	Intent-to-Treat
LABA	Long Acting Beta-Agonist
mcg	Microgram
MDI	Metered Dose Inhaler
mL	Milliliter
MET	Metabolic Equivalent of Tasks
MSDS	Material Safety Data Sheet
NHLBI	National Heart Lung and Blood Institute
PK	Pharmacokinetic
PP	Per Protocol
RAP	Reporting and Analysis Plan
RNA	Ribonucleic acid

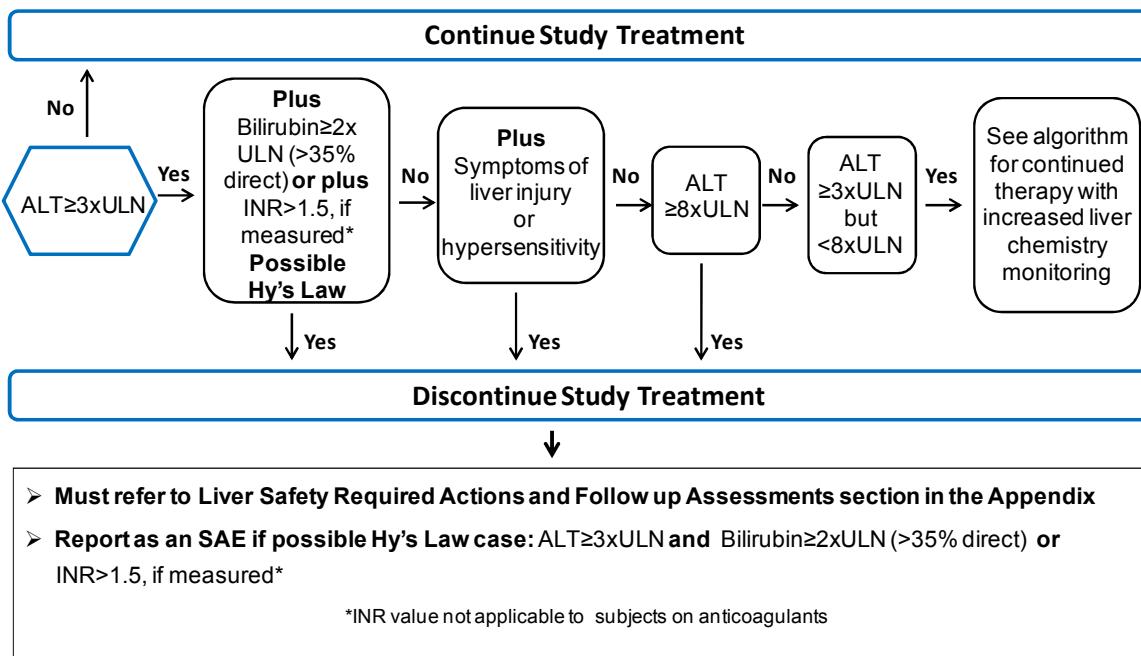
SABA	Short-acting beta-agonist
SAE	Serious Adverse Event
SAR	Symptomatic Allergic Rhinitis
SRM	Study Reference Manual
ULN	Upper Limit of Normal
VI	Vilanterol Trifénate (GW642444)

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
ADVAIR	
DISKUS	
ELLIPTA	
NUCALA	
RELVAR/BREO	SenseWear Armband

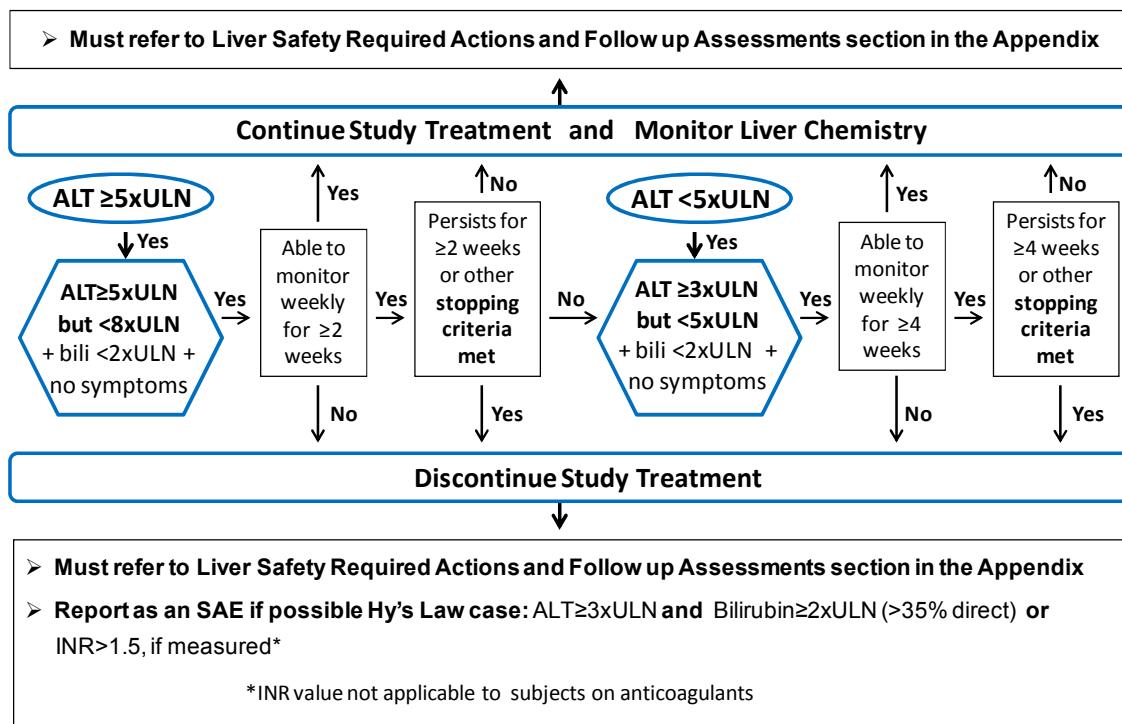
13.2. Appendix 2: Liver Chemistry Stopping and Increased Monitoring Algorithm

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 3](#).

Phase III-IV Liver Chemistry Increased Monitoring Algorithm with Continued Therapy for ALT ≥ 3 xULN but < 8 xULN



Liver Safety Required Actions and Follow up Assessments Section can be found in [Appendix 3](#).

13.3. Appendix 3: Liver Safety Required Actions and Follow up Assessments

Phase III-IV liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf>

Phase III-IV liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT \geq 8xULN
ALT Increase	ALT \geq 5xULN but <8 xULN persists for ≥ 2 weeks
	ALT \geq 3xULN but <5 xULN persists for ≥ 4 weeks
Bilirubin^{1,2}	ALT \geq 3xULN and bilirubin \geq 2xULN ($>35\%$ direct bilirubin)
INR²	ALT \geq 3xULN and International normalized ratio (INR) >1.5 , if INR measured
Cannot Monitor	ALT \geq 5xULN but <8 xULN and cannot be monitored weekly for ≥ 2 weeks ALT \geq 3xULN but <5 xULN and cannot be monitored weekly for ≥ 4 weeks
Symptomatic³	ALT \geq 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event

Actions	Follow Up Assessments
<ul style="list-style-type: none"> • Immediately discontinue study treatment • Report the event to GSK within 24 hours • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE² • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below) 	<ul style="list-style-type: none"> • Viral hepatitis serology⁴ • Only in those with underlying chronic hepatitis B at study entry (identified by positive hepatitis B surface antigen) quantitative hepatitis B DNA and hepatitis delta antibody⁵. • Blood sample for pharmacokinetic (PK) analysis, obtained within 72 hours after last dose⁶ • Serum creatine phosphokinase (CPK) and

<ul style="list-style-type: none"> Do not restart/rechallenge subject with study treatment. Permanently discontinue study treatment and may continue subject in the study for any protocol specified follow up assessments 	<ul style="list-style-type: none"> lactate dehydrogenase (LDH). Fractionate bilirubin, if total bilirubin $\geq 2 \times \text{ULN}$ Obtain complete blood count with differential to assess eosinophilia Record the appearance or worsening of clinical symptoms of liver injury, or hypersensitivity, on the AE report form Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter medications. Record alcohol use on the liver event alcohol intake case report form
<p>MONITORING:</p> <p>For bilirubin or INR criteria:</p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, aspartate aminotransferase [AST], alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24 hrs Monitor subjects twice weekly until liver chemistries resolve, stabilize or return to within baseline A specialist or hepatology consultation is recommended <p>For All other criteria:</p> <ul style="list-style-type: none"> Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within 24-72 hrs Monitor subjects weekly until liver chemistries resolve, stabilize or return to within baseline 	<p>For bilirubin or INR criteria:</p> <ul style="list-style-type: none"> Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects with definite or likely acetaminophen use in the preceding week [James, 2009]). Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease: complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that subject if ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT $\geq 3 \times \text{ULN}$ and bilirubin $\geq 2 \times \text{ULN}$ ($>35\%$ direct bilirubin) or ALT $\geq 3 \times \text{ULN}$ and INR >1.5 , if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding**

- studies of hepatic impairment or cirrhosis);** INR measurement is not required and the threshold value stated will not apply to subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
 4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
 5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
 6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	Actions
<p>ALT \geq5xULN and <8xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 2 weeks.</p> <p>OR</p> <p>ALT \geq3xULN and <5xULN and bilirubin <2xULN without symptoms believed to be related to liver injury or hypersensitivity, and who can be monitored weekly for 4 weeks.</p>	<ul style="list-style-type: none"> • Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT \geq5xULN and <8xULN to \geq3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline.

References

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, Davern TJ, Lee WM. Pharmacokinetics of Acetaminophen-Adduct in Adults with Acetaminophen Overdose and Acute Liver Failure. *Drug Metab Dispos* 2009; 37:1779-1784.

Le Gal F, Gordien E, Affolabi D, Hanslik T, Alloui C, Dény P, Gault E. Quantification of Hepatitis Delta Virus RNA in Serum by Consensus Real-Time PCR Indicates Different Patterns of Virological Response to Interferon Therapy in Chronically Infected Patients. *J Clin Microbiol*. 2005;43(5):2363–2369.

13.4. Appendix 4: Genetic Research

Genetic Research Objectives and Analyses

The objectives of the genetic research are to investigate the relationship between genetic variants and:

- Response to medicine, including FF/VI, FP or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

Genetic data may be generated while the study is underway or following completion of the study. Genetic evaluations may include focused candidate gene approaches and/or examination of a large number of genetic variants throughout the genome (whole genome analyses). Genetic analyses will utilize data collected in the study and will be limited to understanding the objectives highlighted above. Analyses may be performed using data from multiple clinical studies to investigate these research objectives.

Appropriate descriptive and/or statistical analysis methods will be used. A detailed description of any planned analyses will be documented in a Reporting and Analysis Plan (RAP) prior to initiation of the analysis. Planned analyses and results of genetic investigations will be reported either as part of the clinical RAP and study report, or in a separate genetics RAP and report, as appropriate.

Study Population

Any subject who is enrolled in the study can participate in genetic research. Any subject who has received an allogeneic bone marrow transplant must be excluded from the genetic research.

Study Assessments and Procedures

A key component of successful genetic research is the collection of samples during clinical studies. Collection of samples, even when no *a priori* hypothesis has been identified, may enable future genetic analyses to be conducted to help understand variability in disease and medicine response.

- A 2 ml saliva sample will be taken for Deoxyribonucleic acid (DNA) extraction. A saliva sample is collected at the randomisation visit, after the subject has been randomized and provided informed consent for genetic research. Instructions for collection and shipping of the genetic sample are described in the laboratory manual. The DNA from the saliva sample may undergo quality control analyses to confirm the integrity of the sample. If there are concerns regarding the quality of the sample, then the sample may be destroyed. The saliva sample is taken on a single occasion unless a duplicate sample is required due to an inability to utilize the original sample.

The genetic sample is labelled (or “coded”) with the same study specific number used to label other samples and data in the study. This number 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).

Samples will be stored securely and may be kept for up to 15 years after the last subject completes the study, or GSK may destroy the samples sooner. GSK or those working with GSK (for example, other researchers) will only use samples collected from the study for the purpose stated in this protocol and in the informed consent form. Samples may be used as part of the development of a companion diagnostic to support the GSK medicinal product.

Subjects can request their sample to be destroyed at any time.

Informed Consent

Subjects who do not wish to participate in the genetic research may still participate in the study. Genetic informed consent must be obtained prior to any saliva being taken.

Subject Withdrawal from Study

If a subject who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the subject will be given a choice of one of the following options concerning the genetic sample, if already collected:

- Continue to participate in the genetic research in which case the genetic DNA sample is retained
- Discontinue participation in the genetic research and destroy the genetic DNA sample

If a subject withdraws consent for genetic research or requests sample destruction for any reason, 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.

Genotype data may be generated during the study or after completion of the study and may be analyzed during the study or stored for future analysis.

- If a subject withdraws consent for genetic research and genotype data has not been analyzed, it will not be analyzed or used for future research.
- Genetic data that has been analyzed at the time of withdrawn consent will continue to be stored and used, as appropriate.

Screen and Baseline Failures

If a sample for genetic research has been collected and it is determined that the subject does not meet the entry criteria for participation in the study, then the investigator should instruct the subject that their genetic sample will be destroyed. No forms are required to complete this process as it will be completed as part of the consent and sample

reconciliation process. In this instance a sample destruction form will not be available to include in the site files.

Provision of Study Results and Confidentiality of Subject's Genetic Data

GSK may summarize the genetic research results in the clinical study report, or separately and may publish the results in scientific journals.

GSK may share genetic research data with other scientists to further scientific understanding in alignment with the informed consent. GSK does not inform the subject, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the subject's medical care at the time of the study, unless required by law. This is due to the fact that the information generated from genetic studies is generally preliminary in nature, and therefore the significance and scientific validity of the results are undetermined. Further, data generated in a research laboratory may not meet regulatory requirements for inclusion in clinical care.

13.5. Appendix 5: Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

13.5.1. Definition of Adverse Events

Adverse Event Definition:
<ul style="list-style-type: none"> • An AE is 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. • NOTE: 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.

Events <u>meeting</u> AE definition include:
<ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • 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 study treatment 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 study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. • The signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events <u>NOT</u> meeting definition of an AE include:
<ul style="list-style-type: none"> • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the

Events NOT meeting definition of an AE include:

- investigator to be more severe than expected for the subject's condition.
- 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.
 - 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.

13.5.2. Definition of Serious Adverse Events

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease, etc).

Serious Adverse Event (SAE) 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

Serious Adverse Event (SAE) is defined as any untoward medical occurrence that, at any dose:

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. Other situations:

- Medical or scientific judgment 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. Is associated with liver injury and impaired liver function defined as:

- ALT \geq 3xULN and total bilirubin^{*} \geq 2xULN (>35% direct), **or**
- ALT \geq 3xULN and INR^{**} $>$ 1.5.

* Serum bilirubin fractionation should be performed if testing is available; if unavailable, measure urinary bilirubin via dipstick. If fractionation is unavailable and ALT \geq 3xULN and total bilirubin \geq 2xULN, then the event is still to be reported as an SAE.

** INR testing not required per protocol and the threshold value does not apply to subjects receiving anticoagulants. If INR measurement is obtained, the value is to be recorded on the SAE form.

See [Appendix 3](#) for the required liver chemistry follow-up instructions

13.5.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:

Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs:

- Myocardial infarction/unstable angina
- Congestive heart failure
- Arrhythmias
- Valvulopathy
- Pulmonary hypertension
- Cerebrovascular events/stroke and transient ischemic attack
- Peripheral arterial thromboembolism
- Deep venous thrombosis/pulmonary embolism
- Revascularization

13.5.4. Recording of AEs and SAEs

AEs and SAE Recording:

- 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 in 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 GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of 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 will be documented as the AE/SAE and not the individual signs/symptoms.
- Subject-completed Value Evidence and Outcomes questionnaires and the collection of AE data are independent components of the study.
- Responses to each question in the Value Evidence and Outcomes questionnaire will be treated in accordance with standard scoring and statistical procedures detailed by the scale's developer.

- The use of a single question from a multidimensional health survey to designate a cause-effect relationship to an AE is inappropriate.

13.5.5. Evaluating AEs and SAEs

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and will assign it 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 will not be confused with an 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 at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment 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 study treatment will be considered and investigated.
- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- 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 the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.

- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as may be indicated or as requested by GSK to elucidate as fully as possible the nature and/or causality of the AE or SAE.
- The investigator is obligated to assist. This may include additional laboratory tests or investigations, histopathological examinations or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings, including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to GSK within the designated reporting time frames.

13.5.6. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the Medical Monitor
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the 'reviewed' box at the bottom of the eCRF page within 72 hours of submission of the SAE.
- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE reporting to GSK via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Medical Monitor
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable, with a copy of the SAE data collection tool sent by overnight mail
- Initial notification via the telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE receipt can be found at this beginning of the protocol on the Sponsor/Medical Monitor Contact Information page.

13.6. Appendix 6: Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) and Collection of Pregnancy Information

This list does not apply to FRP with same sex partners, when this is their preferred and usual lifestyle or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis.

- Contraceptive subdermal implant
- Intrauterine device or intrauterine system
- Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007]
- Injectable progestogen [Hatcher, 2007]
- Contraceptive vaginal ring [Hatcher, 2007]
- Percutaneous contraceptive patches [Hatcher, 2007]
- Male partner sterilization with documentation of azoospermia prior to the female subject's entry into the study, and this male is the sole partner for that subject [Hatcher, 2007].
- Male condom plus partner use of one of the contraceptive options below:
 - Contraceptive subdermal implant
 - Intrauterine device or intrauterine system
 - Oral Contraceptive, either combined or progestogen alone [Hatcher, 2007]
Injectable progestogen [Hatcher, 2007]
 - Contraceptive vaginal ring [Hatcher, 2007]
 - Percutaneous contraceptive patches [Hatcher, 2007]

This is an all inclusive list of those methods that meet the GSK definition of highly effective: having a failure rate of less than 1% per year when used consistently and, correctly and, when applicable, in accordance with the product label. For non-product methods (e.g. male sterility), the investigator determines what is consistent and correct use. The GSK definition is based on the definition provided by the ICH [ICH, M3 (R2) 2009].

The investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

13.6.1. Collection of Pregnancy Information

- Investigator will collect pregnancy information on any female subject, who becomes pregnant while participating in this study
- Information will be recorded on the appropriate form and submitted to GSK within 2 weeks of learning of a subject's pregnancy.

- Subject will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on mother and infant, which will be forwarded to GSK. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in [Appendix 5](#). While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female subject who becomes pregnant while participating

- Will discontinue study medication and be withdrawn from the study.

13.7. Appendix 7 - Country Specific Requirements

- No country-specific requirements exist.

13.8. Appendix 8 – Protocol Changes

13.8.1. Protocol Amendment 01

This protocol amendment has been created to include an additional exercise challenge procedure at 23 hours after the first dose of double-blinded study medication in each Treatment Period. The purpose is to demonstrate that inhaled FF/VI 100/25 mcg provides improved bronchoprotection against EIB compared with FP 250 mcg after 23 hours of treatment with blinded medication. In addition, it will allow for an evaluation of the presence and extent of tachyphylaxis.

The study title has been revised to indicate the study is a randomised study with a crossover design.

Other minor corrections and edits have been made.

Method of Amendment

Original and amended texts are specified as follows:

Original text: as written in the original protocol

Revised text: as written in Amendment No. 01 with revisions in bold font.

Amendment Details

Protocol title

Original title:

201832: A Double-Blind, Double-Dummy Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once Daily Versus Fluticasone Propionate 250 mcg Twice Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction

Revised title:

201832: A **Randomised**, Double-Blind, Double-Dummy **Crossover** Comparison of Fluticasone Furoate/Vilanterol 100/25 mcg Once Daily Versus Fluticasone Propionate 250 mcg Twice Daily in Adolescent and Adult Subjects with Asthma and Exercise-Induced Bronchoconstriction

Protocol Synopsis: Overall Design

Original text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will attend five evening visits over the course of the study. Standardized exercise challenge testing will be conducted at Visit 2 for eligibility determination, and at 12 and 23 hours post evening dose at Visits 3 and 5. Spirometry will be conducted at Screening (Visit 1),

and pre-dose at Visit 4, and prior to each exercise challenge at Visits 2, 3 and 5. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.

A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate. At Visit 1, subjects meeting eligibility criteria and will enter a 4 week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD).

Albuterol/salbutamol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs will be collected at each visit prior to spirometry and before and after each exercise challenge.

Physical activity levels will be monitored with the use of a physical activity monitor to assess activity outside the clinic worn for 7 days prior to Visit 2 (baseline), for 7 days during the last week of Treatment Period 1, for 7 days prior to Visit 4, and for 7 days during the last week of Treatment Period 2. Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate.

Asthma control will be assessed using the Asthma Control Test at Visits 2 through 5.

A follow up phone call will be conducted approximately 7 days after Visit 5.

Revised text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will attend **up to eight** visits over the course of the study. Standardized exercise challenge testing will be conducted at Visit 2 for eligibility determination, **Visit 3 and Visit 6 (after 23 hours of the first treatment dose in each Treatment Period)**; and at 12 and 23 hours post evening dose at Visits **4 and 7**. Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit **5**, and prior to each exercise challenge at Visits **2, 3, 4, 6 and 7**. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.

A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate. At Visit 1, subjects meeting eligibility criteria and will enter a 4 week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD).

Albuterol/salbutamol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs will be collected at each visit prior to spirometry and before and after each exercise challenge.

Physical activity levels will be monitored with the use of a physical activity monitor to assess activity outside the clinic worn for 7 days prior to Visit 2 (baseline), for 7 days during the last week of Treatment Period 1, for 7 days prior to Visit 5, and for 7 days during the last week of Treatment Period 2. Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate.

Asthma control will be assessed using the Asthma Control Test at Visits 2, **4, 5 and 7**.

A follow up phone call will be conducted approximately 7 days after Visit 7.

Protocol synopsis: Secondary and Other Endpoints

Original text:

Secondary Endpoints

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Time required for recovery to within 5% of pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose
- Area under the curve for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12-hours and 23 hours post evening dose (AUC 0-60 min)

Other Endpoints

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from pre-exercise baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Mean change from baseline in ACT score at the end of the treatment period
- Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the treatment period

- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, METs, sleep duration)

Revised text:

Secondary Endpoints

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Time required for recovery to within 5% of pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose **at the end of the 2-week treatment period**
- Area under the curve for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12-hours and 23 hours post evening dose (AUC 0-60 min) **at the end of the 2-week treatment period**

Other Endpoints

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose **at the end of the 2-week treatment period**) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from pre-exercise baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the **2-week treatment period**
- Mean change from baseline in ACT score at the end of the 2-week treatment period
- Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the **2-week treatment period**
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, METs, sleep duration)

Section 4.2: Secondary Endpoints

Original text:

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Time required for recovery to within 5% of pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose
- Area under the curve for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose (AUC 0-60 min)

Revised text:

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Time required for recovery to within 5% of pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose **at the end of the 2-week treatment period.**
- Area under the curve for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose (AUC 0-60 min) **at the end of the 2-week treatment period.**

Section 4.3: Other Endpoints

Original text:

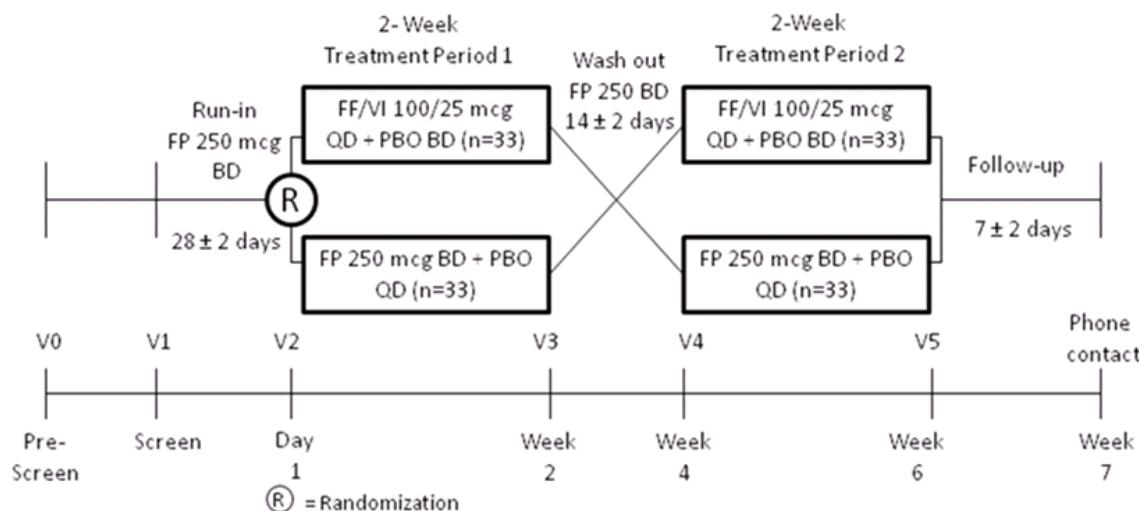
- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from pre-exercise baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Mean change from baseline in ACT score at the end of the treatment period
- Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the treatment period
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, METs, sleep duration)

Revised text:

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose **at the end of the 2-week treatment period**) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from pre-exercise baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Mean change from baseline in ACT score at the end of the **2-week** treatment period
- Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the **2-week** treatment period
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, METs, sleep duration)

Section 5.1: Overall Design**Original text:**

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will attend five evening visits over the course of the study. Standardized exercise challenge testing will be conducted at Visit 2 for eligibility determination, and at 12 and 23 hours post evening dose at Visits 3 and 5. Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 4, and prior to each exercise challenge at Visits 2, 3 and 5. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.



A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent (ICF) and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate. At Visit 1, subjects meeting eligibility criteria will enter a 4-week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD).

Albuterol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs will be collected at each visit prior to spirometry, and before and after exercise challenge testing.

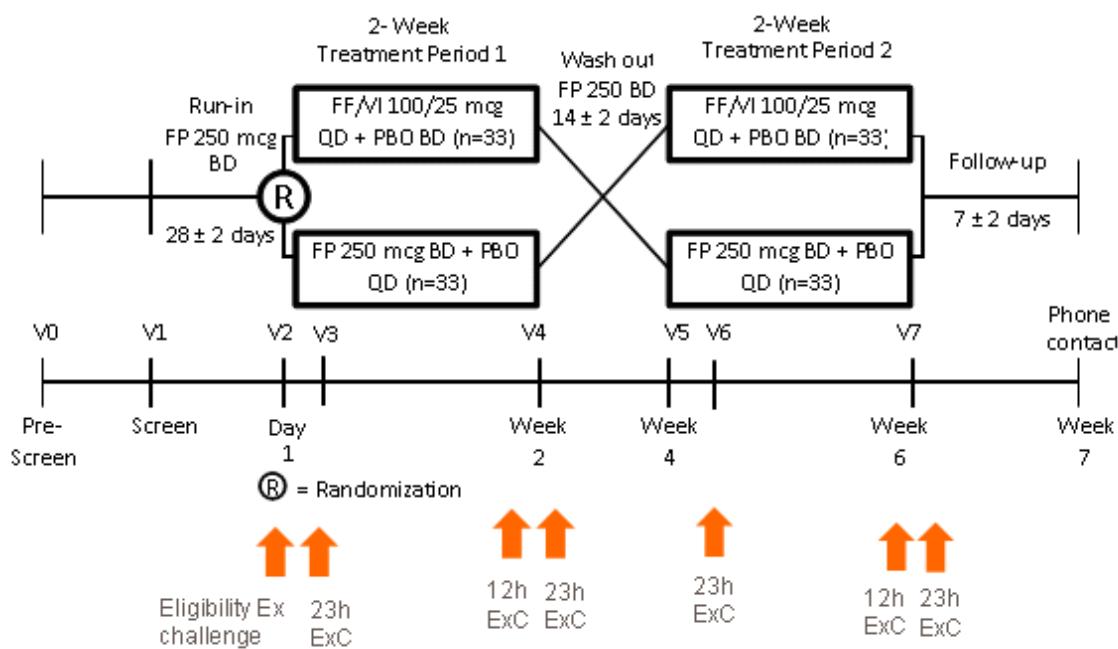
Asthma control will be assessed using the Asthma Control Test (ACT) at Visits 2 through 5.

Physical activity levels will be monitored to assess activity outside the clinic [Mitchell, 2014] using a physical activity monitor (SenseWear Armband accelerometer) worn for 7 days prior to Visit 2 (baseline), for 7 days prior to Visit 3 (during the last week of Treatment Period 1), for 7 days prior to Visit 4, and for 7 days prior to Visit 5 (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate. See Study Reference Manual (SRM) for additional details.

A follow up phone call will be conducted approximately 7 days after Visit 5.

Revised text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will attend **up to eight** visits over the course of the study. Standardized exercise challenge testing will be conducted at Visit 2 for eligibility determination, **Visit 3 and Visit 6 (after 23 hours of the first dose in each Treatment Period)**; and at 12 and 23 hours post evening dose at Visits **4 and 7**. Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit **5** and prior to each exercise challenge at Visits **2, 3, 4, 6 and 7**. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.



A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent (ICF) and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate. At Visit 1, subjects meeting eligibility criteria will enter a 4-week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD).

Albuterol will be issued for rescue use during the run-in, washout and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs will be collected at each visit prior to spirometry, and before and after exercise challenge testing.

Asthma control will be assessed using the Asthma Control Test (ACT) at Visits **2, 4, 5 and 7**.

Physical activity levels will be monitored to assess activity outside the clinic [Mitchell, 2014] using a physical activity monitor (SenseWear Armband accelerometer) worn for 7 days prior to Visit 2 (baseline), for 7 days prior to Visit **4** (during the last week of Treatment Period 1), for 7 days prior to Visit **5**, and for 7 days prior to Visit **7** (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate. See Study Reference Manual (SRM) for additional details.

A follow up phone call will be conducted approximately 7 days after Visit **7**.

Section 7.8: Treatment after the End of the Study

Original text:

Subjects will not receive any additional treatment from GSK after completion of the study as other treatment options are available for persistent asthma. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment. At the end of Visit 5, investigators should prescribe asthma medication appropriate to the severity of the subject's asthma in accordance with asthma guidelines [GINA, 2015; NIH, 2007]. Do not record asthma medications started on or after the final clinic visit in the eCRF.

Revised text:

Subjects will not receive any additional treatment from GSK after completion of the study as other treatment options are available for persistent asthma. The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment. At the end of **Visit 7**, investigators should prescribe asthma medication appropriate to the severity of the subject's asthma in accordance with asthma guidelines [GINA, 2015; NIH, 2007]. Do not record asthma medications started on or after the final clinic visit in the eCRF.

Section 8: Study Assessments and Procedures – Table 3 Time and Events Table

Original table:

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1		Treatment Period 2		Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹¹ Randomization	3 ¹¹	4 ¹¹	5 ¹¹		
Week		-4	0	2	4	6		7
Treatment Day		-26 to -30 days	1	14 (-2/+2) days	28 (-2/+2) days	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X							
Genetics Consent	X ¹							
Subject Demography		X						
Medical History (including CV)		X						
Disease (Asthma) History		X						
Medication History	X	X						
Inclusion/Exclusion Criteria		X						
Efficacy Assessments								
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ³	X ⁴		X ⁴		
Post-Challenge Serial FEV ₁ Measurements			X ³	X ⁵		X ⁵		
Asthma Control Test			X	X	X	X	X	
Dispense SenseWear accelerometer		X						
Collect SenseWear accelerometer						X	X	
Safety Assessments								
Concomitant Medication		X	X	X	X	X	X	X ⁶
Physical Examination		X						
Vital Signs		X	X ⁷	X ⁷	X	X ⁷	X	
12-lead ECG		X						
Adverse Event Assessment	X ⁸	X ⁸	X	X	X	X	X	X

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1		Treatment Period 2		Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹¹ Randomization	3 ¹¹	4 ¹¹	5 ¹¹		
Week		-4	0	2	4	6		7
Treatment Day		-26 to -30 days	1	14 (-2/+2) days	28 (-2/+2) days	42 (-2/+2) days		47 to 51 days
Issue Medical Conditions Diary Card		X	X	X	X			
Review Medical Conditions Diary Card			X ⁹	X ⁹	X ⁹	X ⁹	X	
Laboratory Assessments								
Genetics Saliva Sample			X ¹					
Urine Pregnancy Test		X	X		X		X	X ¹²
Investigational Product								
Dispense Fluticasone Propionate		X		X				
Collect Fluticasone Propionate			X		X			
Dispense Rescue Albuterol		X	X	X	X	X		
Collect Rescue Albuterol			X	X	X	X		
Dispense IP			X ¹⁰	X	X			
Assess study drug compliance			X	X	X	X	X	
Collect IP				X	X	X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and FVC testing), conducted immediately pre-exercise, if applicable. Subject should have withheld albuterol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. .
4. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 3 and 5.
5. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 5% of baseline FEV₁ values within 60 minutes.
6. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
7. Vital signs will be collected before and after each exercise challenge test.
8. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
9. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
10. An unblinding card will be dispensed along with double blind IP.
11. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 3, 4 and 5 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
12. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.

Revised table:

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
	Visit/Contact	0	1	2 ¹² Randomization	3	4 ¹²	5 ¹²	6		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X									
Genetics Consent	X ¹									
Subject Demography		X								
Medical History (including CV)		X								
Disease (Asthma) History		X								
Medication History	X	X								
Inclusion/Exclusion Criteria		X								
Evidence of EIB		X								
Efficacy Assessments										
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X ²	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ³	X ⁴	X ⁵		X ⁴	X ⁵		
Post-Challenge Serial FEV ₁ Measurements			X ³	X	X ⁶		X ⁶	X ⁶		
Asthma Control Test			X		X	X		X	X	
Dispense SenseWear accelerometer		X								
Collect SenseWear accelerometer								X	X	
Safety Assessments										
Concomitant Medication		X	X	X	X	X	X	X	X	X ⁷
Physical Examination		X								
Vital Signs		X	X ⁸	X ⁸	X ⁸	X	X ⁸	X ⁸	X	

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
	Visit/Contact	0	1	2 ¹² Randomization	3	4 ¹²	5 ¹²	6		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
12-lead ECG		X								
Adverse Event Assessment	X ⁹	X ⁹	X	X	X	X	X	X	X	X
Issue Medical Conditions Diary Card		X	X		X	X				
Review Medical Conditions Diary Card			X ¹⁰		X ¹⁰	X ¹⁰		X ¹⁰	X	
Laboratory Assessments										
Genetics Saliva Sample			X ¹							
Urine Pregnancy Test		X	X			X			X	X ¹³
Investigational Product										
Dispense Fluticasone Propionate		X			X					
Collect Fluticasone Propionate			X			X				
Dispense Rescue Albuterol		X	X		X	X		X		
Collect Rescue Albuterol			X		X	X		X		
Dispense IP			X ¹¹			X				
Assess study drug compliance			X		X	X		X	X	
Collect IP					X	X		X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and **forced vital capacity** (FVC) testing), conducted immediately pre-exercise, if applicable. Subject should have withheld albuterol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. **Subjects must demonstrate a decrease in FEV₁ of ≥20% at one time point within 30 minutes of the end of a standardized exercise challenge.**
4. **Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5**
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 5% of baseline FEV₁ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.

Section 8.2.1: Spirometry

Original text:

FEV₁ and FVC will be conducted at Visit 1, and pre-dose at Visit 4, and prior to each exercise challenge at Visits 2, 3 and 5. For full FEV₁/FVC testing, at least 3 valid and 2 repeatable (with no more than 8) efforts should be obtained using ATS/ERS guidelines. At each time point, the largest FEV₁ and FVC should be recorded, even if they do not come from the same effort.

Serial FEV₁ measurements only (not FVC) will be conducted serially as described in Table 3 following each exercise challenge at Visits 2, 3 and 5. For serial FEV₁ testing, two FEV₁ efforts will be obtained at each time point. At each time point, the largest FEV₁ will be selected.

Revised text:

FEV₁ and FVC will be conducted at Visit 1, and pre-dose at Visit **5**, and prior to each exercise challenge at Visits 2, 3, **4, 6 and 7**. For full FEV₁/FVC testing, at least 3 valid and 2 repeatable (with no more than 8) efforts should be obtained using ATS/ERS guidelines. At each time point, the largest FEV₁ and FVC should be recorded, even if they do not come from the same effort.

Serial FEV₁ measurements only (not FVC) will be conducted serially as described in Table 3 following each exercise challenge at Visits 2, 3, **4, 6 and 7**. For serial FEV₁ testing, two FEV₁ efforts will be obtained at each time point. At each time point, the largest FEV₁ will be selected.

Section 8.2.3.3: Visit 3 and Visit 6 (23 hours Post First Dose Exercise Challenge)

New text:

Visit 3 and Visit 6 begin between 5 PM and 11 PM and should begin at approximately the same time as Visit 1 (± 1 hour). These visits should begin prior to the subject's evening dose on that visit day.

Pre-exercise FEV₁: Spirometry will be performed at Visits 3 and 6 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 23 hours after the first dose in each treatment period. At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained before the exercise challenge.

Exercise Challenge: After the pre-exercise FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the exercise challenge, serial spirometry measurements will be performed at time points at 5, 10, 15, 30, 45 and 60 minutes post-challenge. Two FEV₁ efforts (not full FVC maneuvers) will be performed at each time point.

Medication Dosing: At the end of Visits 3 and 6, the evening dose should be administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Section 8.2.3.4: Visit 3 and Visit 5 (Blinded Treatment Exercise Challenge)

Original text:

Visit 3 and Visit 5 begin between 5 PM and 11 PM and are conducted over approximately 24 hours. These visits should begin at approximately the same time as Visit 1 (± 1 hour) and approximately at the end of the dosing period for each IP.

Dosing: At the beginning of Visit 3 and Visit 5, subjects will administer their evening doses of double-blinded study medication in the clinic and the time of dosing will be recorded. Subjects will return to the clinic 12 (± 1) hours and 23 (± 1) hours after dosing for exercise challenge testing.

Pre-exercise FEV₁: At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained just prior to EACH exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.2.1.1) should be determined based on the pre-exercise FEV₁.

Exercise challenge testing: Exercise challenge testing will occur at 12 (± 1) hours and 23 (± 1) hours after administering the evening dose. (The 12-hour exercise challenge and spirometry measurements should occur prior to dosing of the study Diskus medication.)

Following each challenge, serial spirometry measurements will be performed at time points at 5, 10, 15, 30, 45 and 60 minutes post-challenge. Two FEV₁ efforts (not full FVC maneuvers) will be performed at each time point.

Washout Medication Dosing: At the end of Visit 3, the washout medication should be dispensed and first evening dose administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Revised text:**Section 8.2.3.4: Visit 4 and Visit 7 (Blinded Treatment Exercise Challenge)**

Visit 4 and Visit 7 begin between 5 PM and 11 PM and are conducted over approximately 24 hours. These visits should begin at approximately the same time as Visit 1 (± 1 hour) and approximately at the end of the dosing period for each IP.

Dosing: At the beginning of Visit 4 and Visit 7, subjects will administer their evening doses of double-blinded study medication in the clinic and the time of dosing will be recorded. Subjects will return to the clinic 12 (± 1) hours and 23 (± 1) hours after dosing for exercise challenge testing.

Pre-exercise FEV₁: At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained just prior to EACH exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.2.1.1) should be determined based on the pre-exercise FEV₁.

Exercise challenge testing: Exercise challenge testing will occur at 12 (± 1) hours and 23 (± 1) hours after administering the evening dose. (The 12-hour exercise challenge and spirometry measurements should occur prior to dosing of the study Diskus medication.)

Following each challenge, serial spirometry measurements will be performed at time points at 5, 10, 15, 30, 45 and 60 minutes post-challenge. Two FEV₁ efforts (not full FVC maneuvers) will be performed at each time point.

Washout Medication Dosing: At the end of Visit 4, the washout medication should be dispensed and first evening dose administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Section 8.2.3.5: Visit 5**Original text:**

Period 2 pre-exercise baseline FEV₁: Spirometry will be performed at Visit 4 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with the washout medication. At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained.

Dosing: Subjects will administer their evening doses of double-blinded study medication following the spirometry.

Revised text:

Period 2 pre-exercise baseline FEV₁: Spirometry will be performed at Visit 5 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with the washout medication. At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained.

Dosing: Subjects will administer their evening doses of double-blinded study medication following the spirometry.

Section 8.2.4 Physical Activity Monitor**Original text:**

Subjects should refrain from significant changes in their exercise level (e.g., joining a gym), except as instructed by the investigator, for the duration of the study.

A clinically validated physical activity monitor (accelerometer) will be used to measure specific levels of physical activity. There will be 4 assessment periods, including an initial baseline assessment in order to provide a reliable estimate of habitual physical activity. The physical activity monitor will be worn by the study subjects during the weeks prior to Visit 2, Visit 3, Visit 4 and Visit 5. Further details will be provided in the SRM.

Subjects will be contacted by telephone 8-9 days prior to Visits 2, 3, 4 and 5 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.

Revised text:

Subjects should refrain from significant changes in their exercise level (e.g., joining a gym), except as instructed by the investigator, for the duration of the study.

A clinically validated physical activity monitor (accelerometer) will be used to measure specific levels of physical activity. There will be 4 assessment periods, including an initial baseline assessment in order to provide a reliable estimate of habitual physical activity. The physical activity monitor will be worn by the study subjects during the weeks prior to Visit 2, Visit 4, Visit 5 and Visit 7. Further details will be provided in the SRM.

Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.

Section 10.1 Hypotheses**Original text:**

If the primary hypothesis on the primary endpoint for the ITT population is rejected then the following hierarchy of tests will be performed using the ITT population;

1. Test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease in FEV₁ from pre-exercise at 23 hrs post-dose is zero.
2. If 1 is significant then test at the 5% level the null hypothesis that the true probability distributions for the treatment groups for not recovering to within 5% of pre-exercise FEV₁ at 12 hrs post-dose (i.e. the “survival” distributions for the endpoint time to recovery to within 5% of pre-exercise FEV₁ at 12 hrs post-dose) are equal.
3. If 2 is significant then test at the 5% level the null hypothesis that the true population probability distributions for the treatment groups for not recovering to within 5% of pre-exercise FEV₁ at 23 hrs post-dose (i.e. the “survival” distributions for the endpoint time to recovery to within 5% of pre-exercise FEV₁ at 23 hrs post-dose) are equal.
4. If 3 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in AUC for percentage decrease in FEV₁ from pre-exercise FEV₁ at 12 hrs post-dose is zero.
5. If 4 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in AUC for percentage decrease in FEV₁ from pre-exercise FEV₁ at 23 hrs post-dose is zero.

Revised text:

If the primary hypothesis on the primary endpoint for the ITT population is rejected then the following hierarchy of tests will be performed using the ITT population;

1. Test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease in FEV₁ from pre-exercise at 23 hrs post-dose **at the end of the 2-week treatment period** is zero.
2. If 1 is significant then test at the 5% level the null hypothesis that the true probability distributions for the treatment groups for not recovering to within 5% of pre-exercise FEV₁ at 12 hrs post-dose **at the end of the 2-week treatment period** (i.e. the “survival” distributions for the endpoint time to recovery to within 5% of pre-exercise FEV₁ at 12 hrs post-dose) are equal.
3. If 2 is significant then test at the 5% level the null hypothesis that the true population probability distributions for the treatment groups for not recovering to within 5% of pre-exercise FEV₁ at 23 hrs post-dose **at the end of the 2-week treatment period** (i.e. the “survival” distributions for the endpoint time to recovery to within 5% of pre-exercise FEV₁ at 23 hrs post-dose) are equal.

4. If 3 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in AUC for percentage decrease in FEV₁ from pre-exercise FEV₁ at 12 hrs post-dose **at the end of the 2-week treatment period** is zero.
5. If 4 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in AUC for percentage decrease in FEV₁ from pre-exercise FEV₁ at 23 hrs post-dose **at the end of the 2-week treatment period** is zero.

Section 10.2.1: Sample Size Assumptions

Original text:

For the primary efficacy endpoint of maximal percent decrease in FEV₁ following exercise challenge at 12 hours post-dose, given an assumed 10% screen failure rate, a 55% run-in failure rate, and a 15% withdrawal rate post-randomisation, a total of approximately 165 subjects will be screened. Given these assumed failure and withdrawal rates we expect 148 subjects will enter the run-in period, of which 66 subjects will be randomized, of which 56 subjects will be evaluable, that is completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. With 56 evaluable subjects this study has approximately 90% power assuming a true population difference of 5% in maximal percent decrease in FEV₁ between the two treatment groups. This assumes a within-subject standard deviation (SD) of 8% where significance is declared at the two-sided 5% significance level.

Revised text:

For the primary efficacy endpoint of maximal percent decrease in FEV₁ following exercise challenge at 12 hours post-dose **at the end of the 2-week treatment period**, given an assumed 10% screen failure rate, a 55% run-in failure rate, and a 15% withdrawal rate post-randomisation, a total of approximately 165 subjects will be screened. Given these assumed failure and withdrawal rates we expect 148 subjects will enter the run-in period, of which 66 subjects will be randomized, of which 56 subjects will be evaluable, that is completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. With 56 evaluable subjects this study has approximately 90% power assuming a true population difference of 5% in maximal percent decrease in FEV₁ between the two treatment groups. This assumes a within-subject standard deviation (SD) of 8% where significance is declared at the two-sided 5% significance level.

Section 10.3.3.1: Primary Comparisons of Interest

Original text:

The primary treatment comparison is the comparison of group means for the FF/VI combination and FP for the primary endpoint of maximal percent decrease in FEV₁ from pre-exercise at 12 hrs post-evening dose. This comparison is to be performed using the ITT Population.

Revised text:

The primary treatment comparison is the comparison of group means for the FF/VI combination and FP for the primary endpoint of maximal percent decrease in FEV₁ from pre-exercise at 12 hrs post-evening dose **at the end of the 2-week treatment period**. This comparison is to be performed using the ITT Population.

Section 10.3.5: Key Elements of Analysis Plan

Original text:

Any tests for interactions will be 2-sided at the 10% level of significance. In all cases, if any assumptions of the proposed methods of analyses are not met, alternative methods of analyses will be used.

The baseline FEV₁ for all endpoints will be the pre-treatment FEV₁ value obtained at the start of each Treatment Period (Visit 2 or Visit 4).

Revised text:

Any tests for interactions will be 2-sided at the 10% level of significance. In all cases, if any assumptions of the proposed methods of analyses are not met, alternative methods of analyses will be used.

The baseline FEV₁ for all endpoints will be the pre-treatment FEV₁ value obtained at the start of each Treatment Period (Visit 2 or Visit 5).

Section 10.3.5.1.2: Secondary Analyses

Original text:

Summaries and analyses for secondary endpoints will be provided for the ITT population.

Maximal percent decrease from pre-exercise FEV₁ following exercise challenge (at 23 hours post-dose):

This endpoint will be summarized and analyzed as for the primary endpoint of maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post-dose.

Time required for recovery to within 5% of the pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the challenge (at 12 hours and 23 hours post-dose):

The time required for recovery to within 5% of the pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post-dose for both treatment groups will be compared using a log-rank test. The log rank test will test the null hypotheses that the survival distributions of the two treatment groups are equal. In addition the estimated hazard ratio, confidence interval and p-value will be presented. Kaplan-Meier plots showing the cumulative incidence curves for each treatment group will be produced.

AUC (0-60 min) for percentage decrease from pre-exercise FEV₁ after exercise (at 12 hours and 23 hours post-dose):

A comparison will be made of the estimated means of the two treatment groups in AUC of the percentage decrease in FEV₁ from pre-exercise at 12 and 23 hrs post-dose using a LMM to adjust for covariate effects. The LMM will include the following covariates: treatment, subject-level mean of the pre-treatment FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the pre-treatment FEV₁ period baselines), gender, age, treatment period and smoking history as fixed effects, and a random intercept for each subject.

Revised text:

Summaries and analyses for secondary endpoints will be provided for the ITT population.

Maximal percent decrease from pre-exercise FEV₁ following exercise challenge (at 23 hours post-dose at the end of the 2-week treatment period):

This endpoint will be summarized and analyzed as for the primary endpoint of maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post-dose.

Time required for recovery to within 5% of the pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the challenge (at 12 hours and 23 hours post-dose at the end of the 2-week treatment period):

The time required for recovery to within 5% of the pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post-dose for both treatment groups will be compared using a log-rank test. The log rank test will test the null hypotheses that the survival distributions of the two treatment groups are equal. In addition the estimated hazard ratio, confidence

interval and p-value will be presented. Kaplan-Meier plots showing the cumulative incidence curves for each treatment group will be produced.

*AUC (0-60 min) for percentage decrease from pre-exercise FEV₁ after exercise (at 12 hours and 23 hours post-dose **at the end of the 2-week treatment period**):*

A comparison will be made of the estimated means of the two treatment groups in AUC of the percentage decrease in FEV₁ from pre-exercise at 12 and 23 hrs post-dose using a LMM to adjust for covariate effects. The LMM will include the following covariates: treatment, subject-level mean of the pre-treatment FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the pre-treatment FEV₁ period baselines), gender, age, treatment period and smoking history as fixed effects, and a random intercept for each subject.

13.8.2. Protocol Amendment 02

This amendment applies to all trial centres participating in study 201832.

This protocol is being amended to make the following changes:

- Increase the screen failure rate to 20% (from 10%) and the run-in failure rate to 70% (from 55%). This takes into consideration the challenge of enrolling EIB subjects with symptomatic allergic rhinitis (SAR) at screening and also the challenge for subjects to demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of the exercise challenge at Visit 2; after taking fluticasone propionate for approximately four weeks during the run-in period.
- Allow subjects with symptomatic allergic rhinitis at screening to be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded. Eligible subjects will enter the run-in phase for 4 weeks on FP before the first exercise challenge at Visit 2.
- Allow subjects who are asymptomatic at screening, who become symptomatic during the study to remain in the study and be treated with intranasal corticosteroids at a constant dose for the duration of the study. Therefore, the randomisation exclusion criterion 6 (symptomatic allergic rhinitis) has been deleted.
- Include tobacco/marijuana use and pregnancy (which were omitted in error in the original protocol) as exclusion criteria.
- Clarify the expectations for subjects for Visits 4 and 7 with regards to the number of anticipated clinic visits (and procedures) over the 24-hour period for both visits.
- Extend the time window for the repeat exercise challenge from 24-48 hours to up to one week; taking into consideration the challenge for subjects to return within 48 hours for a repeat procedure.
- Replace the ACT questionnaire with the ACQ-5 questionnaire, given the mismatch between treatment periods of two weeks and the recall period of 4 weeks for the

ACT. ACT will not clearly represent asthma control for the specific treatment periods.

- Increase the restriction period for caffeinated beverages to 4 hours prior to spirometry and the exercise challenge procedure (previously 2 hours prior to spirometry) due to the possibility of inducing refractoriness.
- The time to recovery endpoint (time to recovery to within 5% of pre-exercise FEV₁ as measured from the time of maximal decline in post-exercise FEV₁) has been changed to a binary endpoint defining recovery as those subjects who have a 30 minute post-exercise FEV₁ measurement that is no more than 5% lower than their pre-exercise FEV₁. This binary endpoint has also been included in the “other endpoints” at all the remaining post-exercise spirometry time points.
- The statistical testing hierarchy has been changed to prioritise the maximal percentage FEV₁ reduction (primary endpoint) and binary recovery endpoints following the 12 hour post-dose exercise challenge.
- Other edits and minor corrections have been made.

Method of Amendment

Original and amended texts are specified as follows:

Original text: as written in the Protocol Amendment No. 01

Revised text: as written in Amendment No. 02 with revisions in **bold** font.

Amendment Details

Protocol Synopsis and Section 4.2: Secondary Endpoints

Original text:

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period
- Time required for recovery to within 5% of pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period.
- Area under the curve for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose (AUC 0-60 min) at the end of the 2-week treatment period.

Revised text:

- Maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 23 hours post evening dose at the end of the 2-week treatment period

- **Proportion of subjects with a 30 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period**
- **Weighted mean** for percentage decrease from pre-exercise FEV₁ following exercise challenge at 12-hours and 23 hours post evening dose (**weighted mean** 0-60 min) at the end of the 2-week treatment period

Protocol Synopsis and Section 4.3: Other Endpoints

Original text:

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from pre-exercise baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period
- Mean change from baseline in ACT score at the end of the 2-week treatment period
- Percentage of subjects controlled defined as an Asthma Control Test (ACT) score ≥20 at the end of the 2-week treatment period
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, METs, sleep duration)

Revised text:

- Categorical treatment response evaluation of the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁ (at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period) of:
 - <10%,
 - ≥10% to <20%,
 - ≥20%
- Maximal percent decrease from **treatment period** baseline FEV₁ following exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period.
- **Mean change from baseline in Asthma Control Questionnaire -5 (ACQ-5) score at the end of the 2-week treatment period.**

- **Percentage of subjects controlled, defined as an ACQ-5 score ≤ 0.75 , at the end of the 2-week treatment period.**
- **Percentage of subjects achieving an improvement of ≥ 0.5 or greater in ACQ-5 score at the end of the 2-week treatment.**
- Change in physical activity measures as assessed by a biosensor (SenseWear Armband) in terms of physical activity endpoints (e.g. daily step count, Metabolic Equivalent of Tasks (METs), sleep duration).
- **Proportion of subjects with a 5 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period. Repeat for the 10, 15, 45 and 60 minute time points.**

Protocol Synopsis: Overall Design

Original text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will attend up to eight visits over the course of the study. Standardized exercise challenge testing will be conducted at Visit 2 for eligibility determination, Visit 3 and Visit 6 (after 23 hours of the first treatment dose in each Treatment Period); and at 12 and 23 hours post evening dose at Visits 4 and 7. Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 5, and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.

A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate. At Visit 1, subjects meeting eligibility criteria and will enter a 4 week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD).

Albuterol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs will be collected at each visit prior to spirometry and before and after each exercise challenge.

Physical activity levels will be monitored with the use of a physical activity monitor to assess activity outside the clinic worn for 7 days prior to Visit 2 (baseline), for 7 days during the last week of Treatment Period 1, for 7 days prior to Visit 5, and for 7 days during the last week of Treatment Period 2. Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate.

Asthma control will be assessed using the Asthma Control Test at Visits 2, 4, 5 and 7.

A follow up phone call will be conducted approximately 7 days after Visit 7.

Revised text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will participate in up to eight study visits (Visit 0 to Visit 7) over the course of the study and a follow up phone call approximately a week after Visit 7. Visits 1, 2, 3, 5 and 6 are evening visits that will be conducted between 5PM and 11PM. Visit 4 and Visit 7 are also evening visits that will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will be required to attend three clinic visits during this 24-hour period.

Standardized exercise challenge testing (**using a treadmill**) will be conducted at Visit 2 for eligibility determination, Visit 3 and Visit 6 (after 23 hours of the first treatment dose in each Treatment Period); and at 12 and 23 hours post evening dose at Visits 4 and 7.

Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 5, and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. **At Visit 2, subjects must demonstrate a decrease in FEV₁ of ≥20% when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to <20% may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures once within a week of the original procedure.** Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.

A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent, **demography** and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate.

At Visit 1, subjects meeting eligibility criteria and will enter a 4 week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD). **Subjects with symptomatic allergic rhinitis at Visit 1 (screening) may be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Only one repeat screening visit will be performed following treatment with intranasal corticosteroids. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded. Eligible subjects will enter the run-in period. Subjects who are asymptomatic at screening, who become symptomatic during the study will remain in the study and may be treated with intranasal corticosteroids at a constant dose for the duration of the study.**

Albuterol/**salbutamol** will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs **including pulse rate and systolic and diastolic blood pressure will be obtained at each clinic visit, including any Early Withdrawal visit. At all time points where both vital signs and spirometry are performed, vital signs will be done before the spirometry measurement. At visits where the exercise challenge is performed, vitals will be measured before (prior to the pre-exercise spirometry) and after the exercise challenge.**

Asthma control will be assessed using the **ACQ-5** at Visits 2, 4, 5 and 7.

Physical activity levels will be monitored **to assess activity outside the clinic** with the use of a physical activity monitor (**SenseWear Armband accelerometer**) worn for 7 days prior to Visit 2 (baseline), for 7 days **prior to Visit 4** (during the last week of Treatment Period 1), for 7 days prior to Visit 5, and for 7 days **prior to Visit 7** (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate.

A follow up phone call will be conducted approximately 7 days after Visit 7.

Section 2.2: Study rationale

Original text:

In patients with persistent asthma, improvements in protection from exercise-induced bronchoconstriction (EIB) with ICS/LABA combination product FP/salmeterol (Advair®) have been demonstrated [Murray, 2011; Pearlman, 2009; Weiler, 2005]. However, differences between FP/salmeterol and FP monotherapy have not consistently been observed [Murray, 2011; Weiler, 2005]. In a study that evaluated the effect of FP/salmeterol compared to FP over the 12 hour dosing interval [Weiler, 2005], a large percentage of subjects in both the FP/salmeterol (18%) and FP (36% and 33% at Day 1 and Week 4, respectively) treatment arms failed to complete the second exercise challenge test 8.5 hours after dosing, suggesting loss of protection against EIB towards the end of the 12 hour dosing interval

Revised text:

In patients with persistent asthma, improvements in protection from exercise-induced bronchoconstriction (EIB) with ICS/LABA combination product **Fluticasone propionate** (FP)/salmeterol (Advair®) have been demonstrated [Murray, 2011; Pearlman, 2009; Weiler, 2005]. However, differences between FP/salmeterol and FP monotherapy have

not consistently been observed [Murray, 2011; Weiler, 2005]. In a study that evaluated the effect of FP/salmeterol compared to FP over the 12 hour dosing interval [Weiler, 2005], a large percentage of subjects in both the FP/salmeterol (18%) and FP (36% and 33% at Day 1 and Week 4, respectively) treatment arms failed to complete the second exercise challenge test 8.5 hours after dosing, suggesting loss of protection against EIB towards the end of the 12 hour dosing interval.

Protocol Synopsis and Section 5.2: Treatment Arms and Duration

Original text:

Two treatment arms will be employed for the study:

- FF/VI 100/25 mcg QD via ELLIPTA + Placebo BD via Diskus
- FP 250 mcg BD via Diskus + Placebo QD via ELLIPTA

As this is a 2-period cross-over study, all randomized subjects will receive both treatments in the study, either in Treatment Period 1 or Treatment Period 2. Also, each subject will receive a Diskus and ELLIPTA inhaler in Treatment Period 1 and Treatment Period 2.

Subjects will complete a 4-week run-in on FP 250 mcg, followed by 2-week Treatment Period 1 on randomized treatment, a 2-week washout period on FP 250 mcg, 2-week Treatment Period 2 receiving the alternative treatment, and follow-up contact approximately 7-days after completing Treatment Period 2. The total duration of study participation is approximately 11 weeks.

Revised text:

Two treatment arms will be employed for the study:

- FF/VI 100/25 mcg QD via ELLIPTA + Placebo BD via Diskus
- FP 250 mcg BD via Diskus + Placebo QD via ELLIPTA

As this is a 2-period cross-over study, all randomized subjects will receive both treatments in the study, either in Treatment Period 1 or Treatment Period 2. Also, each subject will receive a Diskus and ELLIPTA inhaler in Treatment Period 1 and Treatment Period 2.

Subjects will complete a 4-week **single-blind** run-in on FP 250 mcg BID, followed by 2-week **double-blind** Treatment Period 1 on randomized treatment, a 2-week **single-blind** washout period on FP 250 mcg BID, 2-week **double-blind** Treatment Period 2 receiving the alternative treatment, and follow-up contact approximately 7-days after completing Treatment Period 2. The total duration of study participation is approximately 11 weeks; **and up to 15 weeks for subjects with SAR at screening who may need to be treated with intranasal corticosteroids followed by repeat screening visit.**

Protocol Synopsis and Section 5.3: Type and Number of Subjects

Original text:

Approximately 165 subjects with persistent asthma with evidence of EIB and current use of a low- to moderate-dose inhaled corticosteroid (ICS) will be screened in order to randomize 66 subjects, assuming a 10% screen failure rate and 55% run-in failure rate. This is to achieve 56 evaluable subjects completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. This calculation assumes a 15% withdrawal rate during the study.

Revised text:

Approximately **275** subjects with persistent asthma with evidence of EIB and current use of a low- to moderate-dose inhaled corticosteroid (ICS) will be screened in order to randomize 66 subjects, assuming a **20%** screen failure rate and **70%** run-in failure rate. This is to achieve 56 evaluable subjects completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. This calculation assumes a 15% withdrawal rate during the study.

Protocol Synopsis: Analysis

Original text:

The primary treatment comparison will be between the FF/VI combination and FP and will be performed using the ITT Population. Demonstration of efficacy for the treatments will be based on a hypothesis testing approach whereby the null hypothesis is that there is no difference between the population treatment groups and the alternative hypothesis is that there is a difference between the population treatment groups.

Revised text:

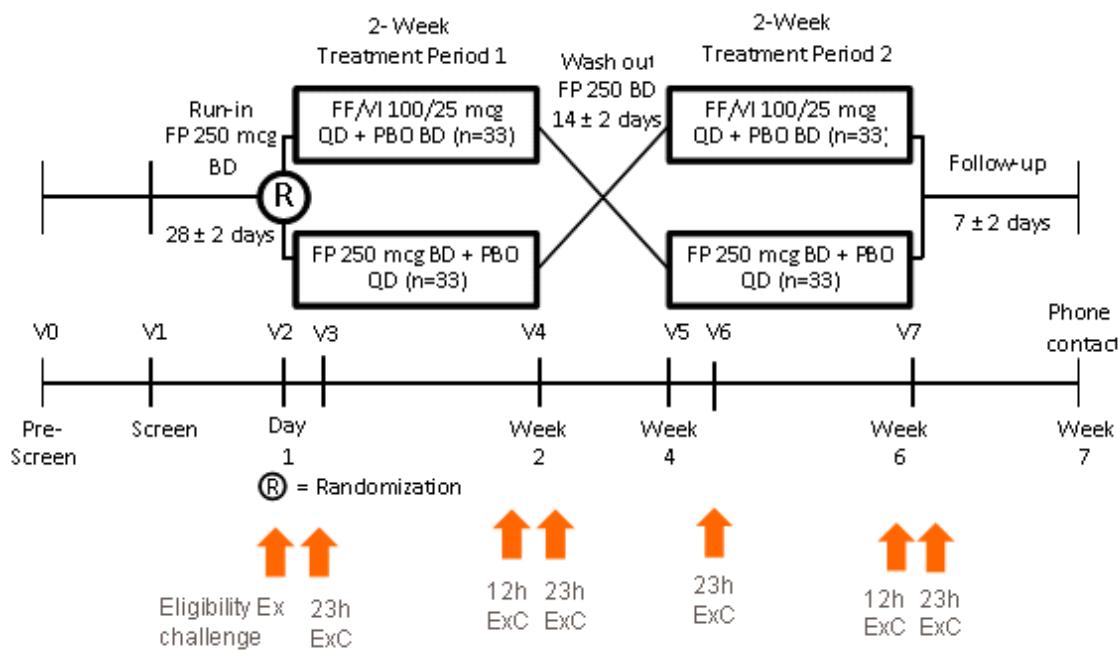
The primary treatment comparison will be between the FF/VI combination and FP and will be performed using the **intent-to-treat** (ITT) Population. Demonstration of efficacy for the treatments will be based on a hypothesis testing approach whereby the null hypothesis is that there is no difference between the population treatment groups and the alternative hypothesis is that there is a difference between the population treatment groups

Section 5.1: Overall Design

Original text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will

attend up to eight visits over the course of the study. Standardized exercise challenge testing will be conducted at Visit 2 for eligibility determination, Visit 3 and Visit 6 (after 23 hours of the first dose in each Treatment Period); and at 12 and 23 hours post evening dose at Visits 4 and 7. Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 5 and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.



A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent (ICF) and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate. At Visit 1, subjects meeting eligibility criteria will enter a 4-week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD).

Albuterol will be issued for rescue use during the run-in, washout and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. Vital signs will be collected at each visit prior to spirometry, and before and after exercise challenge testing.

Asthma control will be assessed using the Asthma Control Test (ACT) at Visits 2, 4, 5 and 7.

Physical activity levels will be monitored to assess activity outside the clinic [Mitchell, 2014] using a physical activity monitor (SenseWear Armband accelerometer) worn for 7 days prior to Visit 2 (baseline), for 7 days prior to Visit 4 (during the last week of Treatment Period 1), for 7 days prior to Visit 5, and for 7 days prior to Visit 7 (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate. See Study Reference Manual (SRM) for additional details.

A follow up phone call will be conducted approximately 7 days after Visit 7.

For determination of subject disposition, subjects will be considered to have completed the study upon completion of Visit 7. For entry into the electronic case report form (eCRF), study completion will be defined as completion of the follow up contact.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion, as asthma treatments including ICS/LABA combination products are available worldwide.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

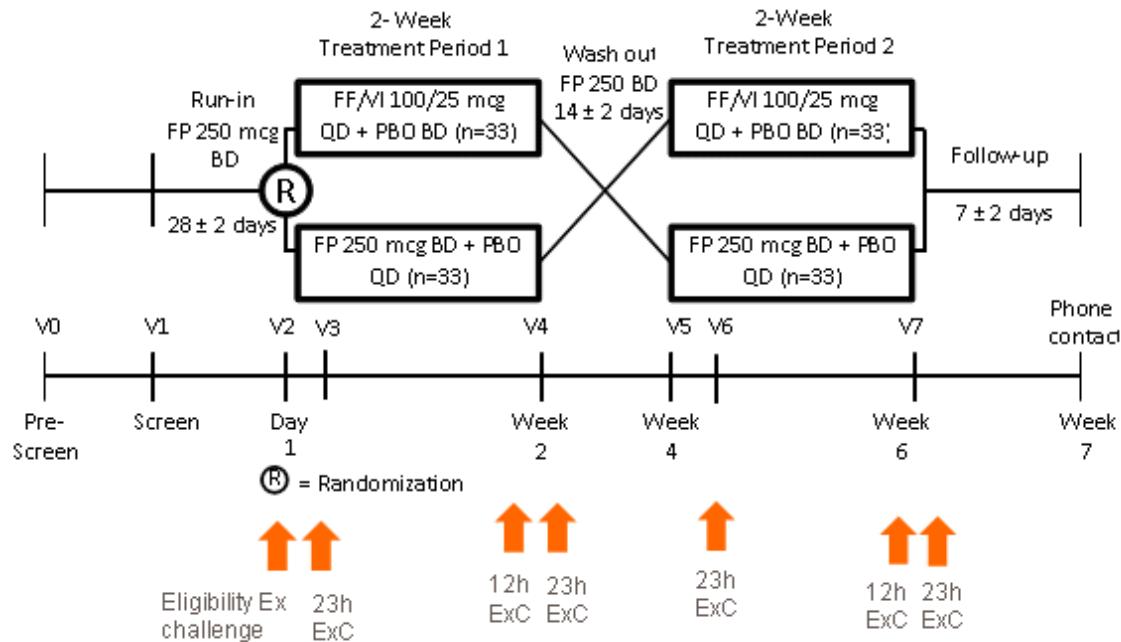
Revised text:

This is a multicenter, randomized, double-blind, double-dummy, crossover study with two 2-week treatment periods separated by a 2-week wash-out period. Subjects will participate in up to eight study visits (**Visit 0 to Visit 7**) over the course of the study and a follow up phone call approximately a week after Visit 7. Visits 1, 2, 3, 5 and 6 are evening visits that will be conducted between 5PM and 11PM. Visit 4 and Visit 7 are also evening visits that will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will be required to attend three clinic visits during this 24-hour period.

Standardized exercise challenge testing (**using a treadmill**) will be conducted at Visit 2 for eligibility determination, Visit 3 and Visit 6 (after 23 hours of the first dose in each Treatment Period); and at 12 and 23 hours post evening dose at Visits 4 and 7.

Spirometry will be conducted at Screening (Visit 1), and pre-dose at Visit 5 and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. Serial spirometry (6 time points over 60 minutes) as FEV₁ only will be conducted after each exercise challenge test. At Visit 2, subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to <20% may continue taking their daily run-in medication and

repeat the eligibility exercise challenge and associated procedures once within a week of the original procedure. Subjects should be monitored until they reach a recovery level where their FEV₁ value represents a 95% recovery of the pre-exercise FEV₁ result. Additional spirometry and rescue medication may be used as needed during recovery.



A Pre-Screening Visit (Visit 0) is included to obtain a signed Informed Consent (ICF), **demography** and to review concomitant medications, and may be conducted on the same day as Visit 1, if appropriate.

At Visit 1, subjects meeting eligibility criteria will enter a 4-week single-blinded run-in period on fluticasone propionate (FP) 250 mcg twice daily (BD). **Subjects with symptomatic allergic rhinitis at Visit 1 (screening) may be treated for up to four weeks with intranasal corticosteroids followed by a repeat screening visit to determine eligibility prior to entry into the study. Only one repeat screening visit will be performed following treatment with intranasal corticosteroids. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded.** Eligible subjects will enter the run-in period. Subjects who are asymptomatic at screening, who become symptomatic during the study will remain in the study and may be treated with intranasal corticosteroids at a constant dose for the duration of the study.

Albuterol/salbutamol will be issued for rescue use during the run-in, wash-out and treatment periods as needed. Subjects will be instructed to contact the site if they develop worsening asthma.

All subjects will be given a paper diary during the run-in, washout and treatment periods to record any medical problems experienced during the study, any medications taken, and rescue medication usage.

A screening electrocardiogram (ECG) and a complete physical examination will be conducted at Visit 1. **Vital signs including pulse rate and systolic and diastolic blood pressure will be obtained at each clinic visit, including any Early Withdrawal visit. At all time points where both vital signs and spirometry are performed, vital signs will be done before the spirometry measurement. At visits where the exercise challenge is performed, vitals will be measured before (prior to the pre-exercise spirometry) and after the exercise challenge.**

Asthma control will be assessed using the **ACQ-5** at Visits 2, 4, 5 and 7.

Physical activity levels will be monitored to assess activity outside the clinic [Mitchell, 2014] using a physical activity monitor (SenseWear Armband accelerometer) worn for 7 days prior to Visit 2 (baseline), for 7 days prior to Visit 4 (during the last week of Treatment Period 1), for 7 days prior to Visit 5, and for 7 days prior to Visit 7 (during the last week of Treatment Period 2). Subjects unwilling or unable to participate in daily physical activity monitoring may still participate in the study, if appropriate. See Study Reference Manual (SRM) for additional details.

A follow up phone call will be conducted approximately 7 days after Visit 7.

Re-screening of subjects is not allowed in this study with the exception of subjects with symptomatic allergic rhinitis at screening who may have a repeat screening visit after treatment with intranasal corticosteroids.

There are no plans to routinely provide any of the study treatments for compassionate use following study completion, as asthma treatments including ICS/LABA combination products are available worldwide.

Supplementary study conduct information not mandated to be present in this protocol is provided in the SRM. The SRM will provide the site personnel with administrative and detailed technical information that does not impact subject safety.

Section 6.1.2: Exclusion Criteria #4

Original text:

Symptomatic Allergic Rhinitis: Subjects with symptomatic allergic rhinitis within the past two weeks are excluded from the study.

Revised text:

Symptomatic Allergic Rhinitis: Subjects with symptomatic allergic rhinitis **at Visit 1 may be treated for up to four weeks with intranasal corticosteroids followed by a**

repeat screening visit to determine eligibility prior to entry into the study. Subjects that continue to be symptomatic after up to four weeks of treatment will be excluded.

Section 6.1.2: Screening Exclusion Criteria #5

Original text:

12-Lead Electrocardiogram (ECG): A subject is not eligible if he/she has an abnormal, clinically significant ECG at the Screening Visit.

Revised text:

12-Lead Electrocardiogram (ECG): A subject is not eligible if he/she has an abnormal, clinically significant ECG as determined by the investigator at the Screening Visit.

Section 6.1.2: New Screening Exclusion Criterion

Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.

Section 6.1.2: Screening Exclusion Criteria #10

Original text:

Allergies:

- a) **Drug Allergy:** Any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy, or excipients used with FF/VI 100/25 or FP 250 (i.e., drug, lactose or magnesium stearate).
- b) **Milk Protein Allergy:** History of severe milk protein allergy.

Revised text:

- a) **Drug Allergy:** Any adverse reaction including immediate or delayed hypersensitivity to any beta₂-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy, or excipients used with FF/VI 100/25 or FP 250 (i.e., drug, lactose or magnesium stearate).
- b) **Milk Protein Allergy:** History of severe milk protein allergy.
- c) **Latex Allergy: History of allergy or sensitivity to latex that in the opinion of the investigator contraindicates the subject's participation in the study.**

Section 6.1.2: New Screening Exclusion Criterion

Tobacco/Marijuana Use: Current tobacco smoker or has a smoking history of ≥ 10 pack-years (20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products or inhaled marijuana within the past 3 months (e.g., cigarettes, cigars, electronic cigarettes, or pipe tobacco)

Section 6.2.1: Randomisation Inclusion Criteria #2

Original text:

FEV₁ Target: Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge. Subjects who achieve a decrease in FEV₁ of 15% to $<20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge once within 24 to 48 hours.

Revised text:

FEV₁ Target: Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge. Subjects who achieve a decrease in FEV₁ of 15% to $<20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge **and associated procedures once within a week of the original procedure.**

Section 6.2.2: Randomisation Exclusion Criteria

Original text:

1. **Pregnancy:** Positive urine pregnancy test at Visit 2.
2. **Asthma Medication Changes:** Changes in asthma medication after Visit 1 (excluding albuterol inhalation aerosol provided at Visit 1) are not permitted.
3. **Prohibited Medication:** No use of any prohibited medications (Section 7.10.2) during the run-in period or at Visit 2.
4. **Respiratory Infections:** Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
5. **Asthma Exacerbation:** Evidence of a severe exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department (ED) visit due to asthma that required systemic corticosteroids between Visits 1 and 2.

6. **Symptomatic Allergic Rhinitis:** Subjects with symptoms of allergic rhinitis within the 2 weeks prior to the randomization visit (Visit 2).

Revised text:

1. **Pregnancy:** Positive urine pregnancy test at Visit 2.
2. **Asthma Medication Changes:** Changes in asthma medication after Visit 1 (excluding albuterol/**salbutamol** inhalation aerosol provided at Visit 1) are not permitted.
3. **Prohibited Medication:** Use of any prohibited medications (Section 7.9.2) during the run-in period or at Visit 2.
4. **Respiratory Infections:** Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
5. **Asthma Exacerbation:** Evidence of a severe exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or an in-patient hospitalization or emergency department (ED) visit due to asthma that required systemic corticosteroids between Visits 1 and 2.

Section 6.3: Screening/Baseline/Run-in Failures**Original text:**

Screen failures are defined as subjects who consent to participate in the clinical trial but are never subsequently randomized. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure reason details, Eligibility Criteria, and any Serious Adverse Events.

A subject who is assigned a subject number, has signed the informed consent, and has completed at least one study procedure, but does not enter the run-in period of the study is considered a 'screen failure'.

A subject who completes the screening visit and is dispensed FP 250 mcg, albuterol for rescue use, and a medical conditions card is considered to have entered the run-in period. A subject who has entered the run-in period, but is not randomized to study treatment medication, is classified as a 'run-in failure'.

At a minimum, the following information will be collected for subjects who fail screening or run-in:

1. Demographic information for race, age and gender
2. Reason for screen/run-in failure (screen/run-in failure eCRF page, inclusion/exclusion criteria eCRF page, and randomization criteria eCRF page [if applicable])
3. SAE information
4. Investigator signature page

Revised text:

In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required including Demography, Screen Failure reason details, Eligibility Criteria, and any Serious Adverse Events.

A subject who is assigned a subject number, has signed the informed consent, and has completed at least one study procedure, but does not enter the run-in period of the study is considered a 'screen failure'.

A subject who completes the screening visit and is dispensed FP 250 mcg, albuterol/salbutamol for rescue use, and a medical conditions diary card is considered to have entered the run-in period. A subject who has entered the run-in period, but is not randomized to study treatment medication, is classified as a 'run-in failure'.

At a minimum, the following information will be collected for subjects who fail screening or run-in:

1. Demographic information for race, age and gender
2. Reason for screen/run-in failure (screen/run-in failure eCRF page, inclusion/exclusion criteria eCRF page, and randomization criteria eCRF page [if applicable])
3. SAE information
4. Investigator signature page

Re-screening of subjects is not allowed in this study with the exception of subjects with symptomatic allergic rhinitis at screening who may have a repeat screening visit after treatment with intranasal corticosteroids.

Section 6.4.2: Reasons for Study Withdrawal

Original text:

The primary reason for Study Withdrawal will be recorded in the eCRF and any data collected up until the point of withdrawal will be used in the data analyses.

General reasons for withdrawal may include:

1. Adverse event
2. Withdrew consent
3. Lost to follow-up
4. Protocol violation impacting safety
5. Lack of efficacy
6. Subject reached protocol-defined withdrawal criteria
 - Liver function
 - Asthma Exacerbation
 - Asthma Worsening
 - Pregnancy
 - ECG
7. Non-compliance
8. Injury during the exercise challenge
9. Study closed/terminated

Revised text:

The primary reason for Study Withdrawal will be recorded in the eCRF and any data collected up until the point of withdrawal will be used in the data analyses.

General reasons for withdrawal may include:

1. Adverse event
2. Withdrew consent
3. Lost to follow-up
4. Protocol **deviation** impacting safety
5. Lack of efficacy
6. Subject reached protocol-defined withdrawal criteria
 - Liver function

- Asthma Exacerbation
 - Asthma Worsening
 - Pregnancy
 - ECG
7. Non-compliance
 8. Injury during the exercise challenge
 9. Study closed/terminated

Section 7: Study Treatment

Original text:

Albuterol will be given to all subjects to use throughout the study to treat acute asthma symptoms as needed per product label. Only study-supplied albuterol should be used for rescue during the study. Rescue usage will be recorded twice daily in the subject's paper diary. **Do not record albuterol use in the eCRF.**

Revised text:

Albuterol/**salbutamol** will be given to all subjects to use throughout the study to treat acute asthma symptoms as needed per product label. Only study-supplied albuterol/**salbutamol** should be used for rescue during the study. Rescue usage will be recorded **once** daily in the subject's paper diary. **Do not record albuterol/salbutamol use in the eCRF.**

Section 7.1: New sub-title included

Section 7.1: Investigational product and other study treatment

Section 7.2.1: Assignment of Subject Number

Original text:

At Visit 1, a unique **Subject Number** (CRF number) will be assigned to any subject who has at least one Visit 1 procedure performed, other than informed consent. The unique Subject Number will be used to identify individual subjects during the course of the study.

Revised text:

At Visit 1, a unique **Subject Number** (CRF number) will be assigned to any subject who has at least one Visit 1 procedure performed, other than informed consent. The unique

Subject Number will be used to identify individual subjects during the course of the study.

All subjects that have a repeat screening visit following treatment for symptomatic allergic rhinitis will continue to use the same subject number assigned at the original screening visit.

Section 7.9.1.2: Permitted Non-Asthma Medications

Original text:

The following non-asthma medications are permitted. This list is not all inclusive. For any questions contact the Medical Monitor.

- **Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers:** **Administer with caution** as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.
- **Strong cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin): Use with caution.** May cause systemic corticosteroid and cardiovascular effects.
- **Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs):** **Administer with extreme caution** as they may potentiate the effects of beta-agonists on the vascular system.
- **Diuretics:** **Caution** is advised in the co-administration of beta-agonists with non potassium-sparing diuretics.
- **Decongestants:** Subjects may take decongestants during the study except during the 24 hours prior to ECG measurements.
- **Antihistamines:** Short-acting and long-acting antihistamines are allowed to control symptoms of allergic disorders, however **are not permitted the week prior to exercise testing.** In addition, antihistamine eye drops are allowed during the study.
- **Intranasal corticosteroids:** Subjects may take intranasal corticosteroids to control symptoms of allergic disorders as long as the dose remains constant for the duration of the study.
- **Topical corticosteroids:** Subjects may use topical corticosteroids ($\leq 1\%$ hydrocortisone) for dermatological diseases.

Revised text:

The following non-asthma medications are permitted. This list is not all inclusive. For any questions contact the Medical Monitor.

- **Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers:** **Administer with caution** as they may block bronchodilatory effects of beta-agonists and produce severe bronchospasm.
- **Strong cytochrome P450 3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin): Use with caution.** May cause systemic corticosteroid and cardiovascular effects.
- **Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs):** **Administer with extreme caution** as they may potentiate the effects of beta-agonists on the vascular system.
- **Diuretics:** **Caution** is advised in the co-administration of beta-agonists with non potassium-sparing diuretics.
- **Decongestants:** Subjects may take decongestants during the study except during the 24 hours prior to ECG measurements.
- **Antihistamines:** Short-acting and long-acting antihistamines are allowed to control symptoms of allergic disorders, however **are not permitted the week prior to exercise testing.** In addition, antihistamine eye drops are allowed during the study. **Subjects should be reminded to avoid taking any antihistamines a week before each exercise challenge procedure.**
- **Intranasal corticosteroids:** Subjects may take intranasal corticosteroids to control symptoms of allergic disorders as long as the dose remains constant for the duration of the study.
- **Topical corticosteroids:** Subjects may use topical corticosteroids ($\leq 1\%$ hydrocortisone) for dermatological diseases.
- **Influenza and/or pneumonia vaccination.**
- **All medications for other disorders as long as the dose remains constant wherever possible and their use is not expected to affect the subjects' lung function or safety assessments.**

Section 8: Assessments and Procedures – Table 3 Time and Events Table

Original table:

Table 7 Time and Events Table

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ¹²	5 ¹²	6	7 ¹²		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X									
Genetics Consent	X ¹									
Subject Demography		X								
Medical History (including CV)		X								
Disease (Asthma) History		X								
Medication History	X	X								
Inclusion/Exclusion Criteria		X								
Evidence of EIB		X								
Efficacy Assessments										
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ³	X ⁴	X ⁵		X ⁴	X ⁵		
Post-Challenge Serial FEV ₁ Measurements			X ³	X ⁶	X ⁶		X ⁶	X ⁶		
Asthma Control Test			X		X	X		X	X	
Dispense SenseWear accelerometer		X								
Collect SenseWear accelerometer								X	X	

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
	Visit/Contact	0	1	2 ¹² Randomization	3	4 ¹²	5 ¹²	6		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Safety Assessments										
Concomitant Medication		X	X	X	X	X	X	X	X	X ⁷
Physical Examination		X								
Vital Signs		X	X ⁸	X ⁸	X ⁸	X	X ⁸	X ⁸	X	
12-lead ECG		X								
Adverse Event Assessment	X ⁹	X ⁹	X	X	X	X	X	X	X	X
Issue Medical Conditions Diary Card		X	X		X	X				
Review Medical Conditions Diary Card			X ¹⁰		X ¹⁰	X ¹⁰		X ¹⁰	X	
Laboratory Assessments										
Genetics Saliva Sample			X ¹							
Urine Pregnancy Test		X	X			X			X	X ¹³
Investigational Product										
Dispense Fluticasone Propionate		X			X					
Collect Fluticasone Propionate			X			X				
Dispense Rescue Albuterol		X	X		X	X		X		
Collect Rescue Albuterol			X		X	X		X		
Dispense IP			X ¹¹			X				
Assess study drug compliance			X		X	X		X	X	
Collect IP					X	X		X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and FVC testing), conducted immediately pre-exercise, if applicable. Subject should have withheld albuterol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge.
4. Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 5% of baseline FEV₁ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.

Revised table:**Section 8.1: Time and Events Table****Table 8 Time and Events Table**

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12; 14}	5 ¹²	6	7 ^{12; 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X									
Genetics Consent	X ¹									
Subject Demography	X									
Medical History (including CV)		X								
Disease (Asthma) History		X								
Medication History	X	X								
Smoking history/status		X								
Inclusion/Exclusion Criteria		X								
Evidence of EIB		X								
Efficacy Assessments										
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ^{3, 17}	X ⁴	X ⁵		X ⁴	X ⁵		
Post-Challenge Serial FEV ₁ Measurements			X ³	X ⁶	X ⁶		X ⁶	X ⁶		
Asthma Control Questionnaire-5			X		X	X		X	X	

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12; 14}	5 ¹²	6	7 ^{12; 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Dispense SenseWear ¹⁵ accelerometer		X								
Collect SenseWear accelerometer								X	X	
Safety Assessments										
Concomitant Medication	X	X	X	X	X	X	X	X	X	X ⁷
Physical Examination		X								
Vital Signs		X	X ⁸	X ⁸	X ⁸	X	X ⁸	X ⁸	X	
12-lead ECG		X								
Adverse Event Assessment	X ⁹	X ⁹	X	X	X	X	X	X	X	X
Issue Medical Conditions Diary Card		X	X		X	X				
Review Medical Conditions Diary Card			X ¹⁰	X	X ¹⁰	X ¹⁰	X	X ¹⁰	X	
Laboratory Assessments										
Genetics Saliva Sample			X ¹							
Urine Pregnancy Test		X	X			X			X	X ¹³
Investigational Product										
Dispense Fluticasone Propionate		X			X					
Collect Fluticasone Propionate			X			X				
Dispense Rescue ¹⁶ Albuterol/salbutamol		X	X	X	X	X	X			
Collect Rescue Albuterol/salbutamol			X		X	X		X		
Dispense IP			X ¹¹			X				
Assess study drug compliance			X	X	X	X	X	X	X	
Collect IP					X			X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and FVC testing), conducted immediately pre-exercise (**and after vital signs**), if applicable. Subject should have withheld **albuterol/salbutamol** within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge.
4. Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 5% of baseline FEV₁ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before (**prior to the pre-exercise spirometry**) and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.
14. **Visit 4 and Visit 7 will begin between 5PM and 11PM and continue over a period of approximately 24 hours. After the evening visit, subjects will return to the clinic at 12 hours and 23 hours (after the evening dose of study medication) for an exercise challenge procedure.**
15. **Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.**
16. **Collect and re-dispense rescue as needed from Visit 1**
17. **Subjects who achieve a decrease in FEV₁ of 15% to <20% may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures once within a week of the original procedure.**

Section 8.2: Screening and Critical Baseline Assessments

Original text:

The following data will be captured at Visit 1:

1. Demographic parameters for year of birth, sex, race and ethnicity
2. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.1.
3. Asthma history (including duration of asthma)
4. Evidence of EIB questions
5. Asthma and non-asthma concurrent medications
6. Concurrent medical conditions
7. Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.
8. Reason for screen failure (if applicable)
9. Screening lung function
10. Vital signs (including height and weight)
11. Serious Adverse Events related to study participation

Revised text:

Critical Baseline Assessments

During the pre-screening visit (Visit 0); each subject will have the following information collected:

- 1. Demographic history (including gender, ethnic origin and date of birth)**
- 2. Concomitant medication review**
- 3. Adverse event assessment**

The following data will be captured at Visit 1:

1. Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 6.1.
- 2. Smoking history**
3. Asthma history (including duration of asthma)
4. Evidence of EIB questions
5. Asthma and non-asthma concurrent medications

6. Concurrent medical conditions
7. Cardiovascular medical history/risk factors (as detailed in the eCRF) will be assessed at screening.
8. Reason for screen failure (if applicable)
9. Screening lung function
10. Vital signs (including height and weight)
11. Serious Adverse Events related to study participation

Section 8.3.1: Spirometry

Original text:

Subjects will be required to withhold their rescue medication (albuterol) for at least 6 hours before each visit.

Exercise challenges should not be performed within 24 hours of exercise in cold air.

Subjects should abstain from smoking or drinking beverages with high caffeine content such as tea or coffee for 2 hours prior to pulmonary function testing.

The FEV₁ should be measured using spirometry equipment that meets or exceeds the minimal recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [Miller, 2005]. All sites will use standardized spirometry equipment provided by an external vendor.

FEV₁ and FVC will be conducted at Visit 1, and pre-dose at Visit 5, and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7. For full FEV₁/FVC testing, at least 3 valid and 2 repeatable (with no more than 8) efforts should be obtained using ATS/ERS guidelines. At each time point, the largest FEV₁ and FVC should be recorded, even if they do not come from the same effort.

Serial FEV₁ measurements only (not FVC) will be conducted serially as described in Table 3 following each exercise challenge at Visits 2, 3, 4, 6 and 7. For serial FEV₁ testing, two FEV₁ efforts will be obtained at each time point. At each time point, the largest FEV₁ will be selected.

Revised text:

Subjects should abstain from drinking beverages with high caffeine content such as tea or coffee for 4 hours prior to the spirometry procedure.

FEV₁ should be measured using spirometry equipment that meets or exceeds the minimal recommendations of the American Thoracic Society (ATS)/European Respiratory Society (ERS) [Miller, 2005]. All sites will use standardized spirometry equipment provided by an external vendor. Full FEV₁ and FVC will be conducted at Visit 1, and pre-dose at Visit 5, and prior to each exercise challenge at Visits 2, 3, 4, 6 and 7.

For full FEV₁ and FVC testing at Screening and at randomisation (Visit 2), at least **two** valid and two repeatable (with no more than 8) efforts should be obtained using ATS/ERS guidelines. For all other visits where full FEV₁ and FVC testing is performed (prior to each exercise test at visits 3, 4, 6 and 7), at least two valid efforts should be obtained. At each time point, the largest FEV₁ and FVC should be recorded, even if they do not come from the same effort.

Serial FEV₁ measurements only (not FVC) will be conducted serially as described in Table 3 following each exercise challenge at Visits 2, 3, 4, 6 and 7.

Subjects must have a FEV1 of at least 70% of their predicted normal value to be eligible to take part in the study at Visit 1.

After Visit 1, subjects will always be required to withhold their albuterol/salbutamol for at least 6 hours before each clinic visit.

Subjects must not administer study drug prior to coming to the clinic on study visit days.

Section 8.3.2: Exercise Challenge Testing

Original text:

The exercise challenge test is a stepped challenge on a treadmill at a speed and incline that will allow the subject's heart rate to reach between 80% to 95% of their maximum heart rate. All exercise challenges will be performed on a treadmill. During the exercise challenge, subjects will breathe medical grade dry air at ambient temperature from a reservoir using a two-way non-rebreathing valve.

Subjects will exercise sufficiently to attain a heart rate between 80 to 95% of their predicted maximum within 4 minutes and maintain this heart rate with exercise for an additional 6 minutes for a total of 10 minutes of exercise. The challenge will be followed immediately by serial spirometry (FEV₁ efforts only) at 6 time points over 60 minutes (5, 10, 15, 30, 45 and 60 minutes post-exercise). The information gained from the eligibility challenge(s) regarding incline and speed will be used to obtain the target heart rate in the subsequent exercise challenges.

Additional instructions on exercise challenge testing can be found in the SRM.

Revised text:

The exercise challenge test is a stepped challenge on a treadmill at a speed and incline that will allow the subject's heart rate to reach between 80% to 95% of their maximum heart rate. All exercise challenges will be performed on a treadmill. During the exercise challenge, subjects will breathe medical grade dry air at ambient temperature from a reservoir using a two-way non-rebreathing valve.

Subjects will exercise sufficiently to attain a heart rate between 80 to 95% of their predicted maximum within 4 minutes and maintain this heart rate with exercise for an additional 6 minutes for a total of 10 minutes of exercise. The challenge will be followed immediately by serial spiroometry (FEV₁ efforts only) at 6 time points over 60 minutes (5, 10, 15, 30, 45 and 60 minutes post-exercise). The information gained from the eligibility challenge(s) regarding incline and speed will be used to obtain the target heart rate in the subsequent exercise challenges.

Exercise challenges should not be performed within 24 hours of exercise in cold air.

Subjects should abstain from drinking beverages with high caffeine content such as tea or coffee for 4 hours prior to the exercise challenge.

Additional instructions on exercise challenge testing can be found in the SRM.

Section 8.3.3.1: Visit 1 (Screening)

Original text:

Spirometry will be performed at Visit 1 between 5:00 PM and 11:00 PM, ideally at the end of the subjects ICS dosing interval. Full FEV₁ and FVC testing will be conducted. Subjects must have a best pre-bronchodilator FEV₁ of $\geq 70\%$ of their predicted normal value to be eligible to take part in the study.

Revised text:

Spirometry will be performed at Visit 1 between 5:00 PM and 11:00 PM, ideally at the end of the subjects ICS dosing interval. Full FEV₁ and FVC testing will be conducted. **At least two valid and two repeatable spirometry efforts should be obtained.** Subjects must have a best pre-bronchodilator FEV₁ of $\geq 70\%$ of their predicted normal value to be eligible to take part in the study.

Section 8.3.3.2: Visit 2 (Randomization)

Original text:

Pre-exercise baseline (Period 1 baseline) FEV₁: Spirometry will be performed at Visit 2 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with run-in medication (FP 250 mcg). At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained before the first exercise challenge.

From this spiroometry testing, the target FEV₁ values (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Eligibility Exercise Challenge: After the pre-exercise baseline FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the eligibility exercise challenge, two FEV₁ efforts (not full FVC maneuvers) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

To qualify for randomization, subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to $<20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge once within 24 to 48 hours.

Dosing: Eligible subjects will administer their evening doses of double-blinded study medication following the eligibility exercise challenge/serial spirometry. Evening dosing should occur between 5 PM and 11PM.

Revised text:

Treatment period 1 baseline FEV₁: Spirometry will be performed at Visit 2 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with run-in medication (FP 250 mcg). At least two **valid** and **two** repeatable spirometry efforts should be obtained before the first exercise challenge.

From this spirometry testing, the target FEV₁ values **#2 and #3** (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Eligibility Exercise Challenge: After the pre-exercise baseline FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the eligibility exercise challenge, serial spirometry (FEV₁) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

To qualify for randomization, subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ when compared to the FEV₁ obtained immediately pre-exercise for at least one of the post-exercise spirometry efforts obtained within 30 minutes post-challenge. Subjects who achieve a decrease in FEV₁ of 15% to $<20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge **once** within a week. **In the event where a repeat visit is required for the exercise challenge, spirometry and vital signs measurements will be performed pre- and post- exercise challenge as detailed in Table 3. In addition, ACQ-5 and a review of concomitant medication and adverse events will be performed at the repeat visit.**

Dosing: Eligible subjects will administer their evening dose of double-blinded study medication following the eligibility exercise challenge/serial spirometry. Evening dosing should occur between 5 PM and 11PM.

Section 8.3.3.3: Visit 3 and Visit 6 (23 hours Post First Dose Exercise Challenge)**Original text:**

Visit 3 and Visit 6 begin between 5 PM and 11 PM and should begin at approximately the same time as Visit 1 (± 1 hour). These visits should begin prior to the subject's evening dose on that visit day.

Pre-exercise FEV₁: Spirometry will be performed at Visits 3 and 6 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 23 hours after the first dose in each treatment period. At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained before the exercise challenge.

Exercise Challenge: After the pre-exercise FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the exercise challenge, serial spirometry measurements will be performed at time points at 5, 10, 15, 30, 45 and 60 minutes post-challenge. Two FEV₁ efforts (not full FVC maneuvers) will be performed at each time point.

Medication Dosing: At the end of Visits 3 and 6, the evening dose should be administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Revised text:

Visit 3 and Visit 6 begin between 5 PM and 11 PM and should begin at approximately the same time as Visit 1 (± 1 hour). These visits should begin prior to the subject's evening dose on that visit day.

Pre-exercise FEV₁: Spirometry will be performed at Visits 3 and 6 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 23 hours after the first dose in each treatment period. At least two valid spirometry efforts should be obtained before the exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Exercise Challenge: After the pre-exercise FEV₁ has been determined, an exercise challenge will be performed according to the method described in the SRM.

Post-exercise Serial Spirometry: Following the **eligibility** exercise challenge **at each** visit, serial spirometry (FEV₁) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

Medication Dosing: At the end of Visits 3 and 6, the evening dose **of study treatment** medication should be administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Section 8.3.3.4: Visit 4 and Visit 7 (Blinded Treatment Exercise Challenges)

Original text:

Visit 4 and Visit 7 begin between 5 PM and 11 PM and are conducted over approximately 24 hours. These visits should begin at approximately the same time as Visit 1 (± 1 hour) and approximately at the end of the dosing period for each IP.

Dosing: At the beginning of Visit 4 and Visit 7, subjects will administer their evening doses of double-blinded study medication in the clinic and the time of dosing will be recorded. Subjects will return to the clinic 12 (± 1) hours and 23 (± 1) hours after dosing for exercise challenge testing.

Pre-exercise FEV₁: At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained just prior to EACH exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Exercise challenge testing: Exercise challenge testing will occur at 12 (± 1) hours and 23 (± 1) hours after administering the evening dose. (The 12-hour exercise challenge and spirometry measurements should occur prior to dosing of the study Diskus medication.)

Following each challenge, serial spirometry measurements will be performed at time points at 5, 10, 15, 30, 45 and 60 minutes post-challenge. Two FEV₁ efforts (not full FVC maneuvers) will be performed at each time point.

Washout Medication Dosing: At the end of Visit 4, the washout medication should be dispensed and first evening dose administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Revised text:

Visit 4 and Visit 7 begin between 5 PM and 11 PM and are conducted over approximately 24 hours. **Subjects will be required to attend three clinic visits during each 24-hour period for Visit 4 and Visit 7.** The evening visit should begin at approximately the same time as Visit 1 (± 1 hour).

Dosing: At the beginning of Visit 4 and Visit 7, subjects will administer their evening doses of double-blinded study medication in the clinic and the time of dosing will be recorded. **In addition to administering the evening dose, vital signs will be measured and a review of concomitant medication and AEs performed.**

Subjects will return to the clinic 12 (± 1) hours and 23 (± 1) hours after evening dosing for exercise challenge testing.

Pre-exercise FEV₁: At least two **valid** spirometry efforts with full FEV₁ and FVC maneuvers should be obtained just prior to each exercise challenge.

From this spirometry testing, the target FEV₁ values #2 and #3 (Section 8.3.1.1) should be determined based on the pre-exercise FEV₁.

Exercise challenge testing: Exercise challenge testing will occur at 12 (± 1) hours and 23 (± 1) hours after administering the evening dose. (The 12-hour exercise challenge and spirometry measurements should occur prior to dosing of the study medication).

Post-exercise Serial Spirometry: Following the eligibility exercise challenge at each visit, serial spirometry (FEV₁) will be performed at 5, 10, 15, 30, 45 and 60 minutes post-exercise.

Washout Medication Dosing: At the end of Visit 4, the washout medication should be dispensed and first evening dose administered following completion of the 23-hour post evening dose exercise challenge/serial spirometry, and prior to the subject's leaving the clinic.

Section 8.3.3.5: Visit 5

Original text:

Period 2 pre-exercise baseline FEV₁: Spirometry will be performed at Visit 5 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with the washout medication. At least two adequate and repeatable spirometry efforts with full FEV₁ and FVC maneuvers should be obtained.

Dosing: Subjects will administer their evening doses of double-blinded study medication following the spirometry.

Revised text:

Treatment period 2 baseline FEV₁: Spirometry will be performed at Visit 5 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with the washout medication. At least two valid spirometry efforts should be obtained.

Dosing: Subjects will administer their evening doses of double-blinded study medication following the spirometry.

Section 8.3.5: Asthma Control Test (ACT)

Original text:

The ACT is a five-item questionnaire developed as a measure of subjects' asthma control that can be quickly and easily completed in clinical practice. The questions are designed to be self-completed by the subject. It is recommended that the ACT be administered at the same time during each visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACT.

The subject should be given a quiet area in which to complete the questionnaire.

The investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous 4 weeks. The subject should be reassured that there are no right or wrong answers. The investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

Revised text:

Asthma Control Questionnaire-5 (ACQ-5) (New text)

The ACQ-5 will be completed at the beginning of all study visits where the form is completed.

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of subject' asthma control that can be quickly and easily completed [Juniper, 2005]. The questions are designed to be self-completed by the subject. The five questions enquire about the frequency and/or severity of symptoms (nocturnal awakening on waking in the morning, activity limitation, and shortness of breath, wheeze). The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale.

The subject should be given a quiet area in which to complete the questionnaire. The investigator should ask the subject to complete the questions as accurately as possible. If the subject requests help or clarification with any of the questions, he/she will be asked to re-read the instructions and give the answer that best reflects how he/she felt over the previous week. The subject should be reassured that there are no right or wrong answers. The investigator should not provide the subject with any answer or attempt to interpret any portion of a question.

It is recommended that the ACQ-5 be administered at the same time during each visit. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaire and should be completed

before any procedures are performed on the subject to avoid influencing the subject's response. Adequate time should be allowed to complete all items on the ACQ-5.

Section 8.4: Safety

Original text:

Safety will be assessed, as indicated in the Time and Events Time and Events Table Table 3, by monitoring of AEs, a physical examination at screening, and vital signs (systolic and diastolic blood pressure and heart rate [pulse] at each visit. A screening 12-ECG will be conducted.

Planned time points for all safety assessments are listed in the Time and Events Table (Time and Events Table Table 3).

Revised text:

Safety will be assessed, as indicated in the Time and Events Time and Events Table Table 3, by monitoring of AEs, a physical examination at screening, and vital signs (systolic and diastolic blood pressure and heart rate [pulse] at each visit. A screening 12-ECG will be conducted.

In cases of suspected pneumonia, a confirmatory chest x-ray should be conducted within 48 hours.

Planned time points for all safety assessments are listed in the Time and Events Table (Time and Events Table Table 3).

Section 8.4.5: Vital Signs

Original text:

- Vital signs will be measured in semi-supine position after 5 minutes rest prior to spirometry and will include temperature, systolic and diastolic blood pressure and pulse rate.
- Vital signs (systolic and diastolic blood pressure and pulse rate) will be measured again before and after each exercise challenge and recorded in the eCRF. Heart rate and oxygen saturation will be measured during each exercise challenge.
- If there are any clinically significant abnormalities noted, further examinations must be performed until the abnormality is resolved.

Revised text:

- Vital signs **including** pulse rate and systolic and diastolic blood pressure **will be obtained at each clinic visit, including any Early Withdrawal visit.**
- **Vital signs will be obtained after subjects have rested for approximately 5 minutes in a semi-supine position.**
- **At all time points where vital signs and spirometry are performed, vital signs will be done before the spirometry measurement.**
- Heart rate will be measured during each exercise challenge.
- If there are any clinically significant abnormalities noted, further examinations must be performed until the abnormality is resolved.

Section 8.4.6: Electrocardiogram (ECG)**Original text:**

- A pre-dose, 12-lead ECG will be performed and interpreted by the investigator or his/her suitably qualified designee at Visit 1. The ECG will be recorded after 5 minutes rest prior to performing spirometry.
- Investigators will use a site ECG machine and perform a manual reading of the ECG parameters to determine whether a subject meets the eligibility criteria for enrolment in the study at screening (Visit 1).
- The ECG interpretation including the paper trace will be maintained at the site within the source documentation.

Revised text:

- A 12-lead ECG will be performed and interpreted by the investigator or his/her suitably qualified designee at Visit 1. The ECG will be recorded after 5 minutes rest **after vital signs and** prior to performing spirometry.
- Investigators will use a site ECG machine and perform a manual reading of the ECG parameters to determine whether a subject meets the eligibility criteria for enrolment in the study at screening (Visit 1).
- The ECG interpretation including the paper trace will be maintained at the site within the source documentation.

Section 10.1: Hypotheses

Original text:

The primary endpoint is the maximal percent decrease in FEV₁ following exercise challenge at 12-hours post-dose at the end of the 2-week treatment period.

The treatment comparison is the FF/VI combination versus FP. Demonstration of efficacy for this treatment comparison will be based on a hypothesis testing approach whereby the null hypothesis is that there is no difference between treatment groups and the alternative hypothesis is that there is a difference between treatment groups.

A 2-sided 5% probability associated with incorrectly rejecting the null hypothesis (significance level) is considered acceptable for this study. In order to account for multiplicity, this primary hypothesis test on the primary endpoint for the ITT (Intent-to-Treat) population will act as a gatekeeper for all other hypothesis tests using the secondary endpoints, where these tests will proceed in a pre-defined order.

If the primary hypothesis on the primary endpoint for the ITT population is rejected then the following hierarchy of tests will be performed using the ITT population;

1. Test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease in FEV1 from pre-exercise at 23 hrs post-dose at the end of the 2-week treatment period is zero.
2. If 1 is significant then test at the 5% level the null hypothesis that the true probability distributions for the treatment groups for not recovering to within 5% of pre-exercise FEV1 at 12 hrs post-dose at the end of the 2-week treatment period (i.e. the “survival” distributions for the endpoint time to recovery to within 5% of pre-exercise FEV1 at 12 hrs post-dose) are equal.
3. If 2 is significant then test at the 5% level the null hypothesis that the true population probability distributions for the treatment groups for not recovering to within 5% of pre-exercise FEV1 at 23 hrs post-dose at the end of the 2-week treatment period (i.e. the “survival” distributions for the endpoint time to recovery to within 5% of pre-exercise FEV1 at 23 hrs post-dose) are equal.
4. If 3 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in AUC for percentage decrease in FEV1 from pre-exercise FEV1 at 12 hrs post-dose at the end of the 2-week treatment period is zero.
5. If 4 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in AUC for percentage decrease in FEV1 from pre-exercise FEV1 at 23 hrs post-dose at the end of the 2-week treatment period is zero.

Revised text:

The primary endpoint is the maximal percent decrease in FEV₁ following exercise challenge at 12-hours post-dose at the end of the 2-week treatment period.

The treatment comparison is the FF/VI combination versus FP. Demonstration of efficacy for this treatment comparison will be based on a hypothesis testing approach whereby the null hypothesis is that there is no difference between treatment groups and the alternative hypothesis is that there is a difference between treatment groups.

A 2-sided 5% probability associated with incorrectly rejecting the null hypothesis (significance level) is considered acceptable for this study. In order to account for multiplicity, this primary hypothesis test on the primary endpoint for the ITT (Intent-to-Treat) population will act as a gatekeeper for all other hypothesis tests using the secondary endpoints, where these tests will proceed in a pre-defined order.

If the primary hypothesis on the primary endpoint for the ITT population is rejected then the following hierarchy of tests will be performed using the ITT population;

- 1. Test at the 5% level the null hypothesis that the true odds ratio between the two treatment groups of recovering to within 5% of pre-exercise FEV₁ at the 30 minute post-exercise time point following the exercise challenge at 12 hours post evening dose is equal to one.**
- 2. Test at the 5% level the null hypothesis that the true population difference between the treatment group means in maximal percent decrease in FEV₁ from pre-exercise at 23 hrs post-dose at the end of the 2-week treatment period is zero.**
- 3. Test at the 5% level the null hypothesis that the true odds ratio between the two treatment groups of recovering to within 5% of pre-exercise FEV₁ at the 30 minute post-exercise time point following the exercise challenge at 23 hours post evening dose is equal to one.**
- 4. If 3 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in weighted mean 0-60 minutes for percentage decrease in FEV₁ from pre-exercise FEV₁ at 12 hrs post-dose at the end of the 2-week treatment period is zero.**
- 5. If 4 is significant then test at the 5% level the null hypothesis that the true population difference between the treatment group means in weighted mean 0-60 minutes for percentage decrease in FEV₁ from pre-exercise FEV₁ at 23 hrs post-dose at the end of the 2-week treatment period is zero.**

Section 10.2.1: Sample Size Assumptions

Original text:

For the primary efficacy endpoint of maximal percent decrease in FEV₁ following exercise challenge at 12 hours post-dose at the end of the 2-week treatment period, given an assumed 10% screen failure rate, a 55% run-in failure rate, and a 15% withdrawal rate post-randomisation, a total of approximately 165 subjects will be screened. Given these assumed failure and withdrawal rates we expect 148 subjects will enter the run-in period, of which 66 subjects will be randomized, of which 56 subjects will be evaluable, that is completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. With 56 evaluable subjects this study has approximately 90% power assuming a true population difference of 5% in maximal percent decrease in FEV₁ between the two treatment groups. This assumes a within-subject standard deviation (SD) of 8% where significance is declared at the two-sided 5% significance level.

Subjects will be centrally randomized to one of the two treatment sequences shown below in Table 4 in a 1:1 ratio:

Revised text:

For the primary efficacy endpoint of maximal percent decrease in FEV₁ following exercise challenge at 12 hours post-dose at the end of the 2-week treatment period, given an assumed **20%** screen failure rate, a **70%** run-in failure rate, and a 15% withdrawal rate post-randomisation, a total of approximately **275** subjects will be screened. Given these assumed failure and withdrawal rates we expect **220** subjects will enter the run-in period, of which 66 subjects will be randomized, of which 56 subjects will be evaluable, that is completing the exercise challenges and the FEV₁ evaluations at the end of both treatment periods. With 56 evaluable subjects this study has approximately 90% power assuming a true population difference of 5% in maximal percent decrease in FEV₁ between the two treatment groups. This assumes a within-subject standard deviation (SD) of 8% where significance is declared at the two-sided 5% significance level.

Subjects will be centrally randomized to one of the two treatment sequences shown below in Table 4 in a 1:1 ratio:

Other measures of efficacy include the evaluation of a categorical treatment response evaluating the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁<10%, a decrease $\geq 10\%$ to $<20\%$, or a decrease $\geq 20\%$, and an evaluation of maximal percent decrease from pre-treatment baseline in FEV₁ (period baseline) following exercise challenge (at 12 hours and 23 hours post-dose). Additional endpoints include evaluation of physical activity monitoring and Asthma Control Test. All endpoints will be described further in the RAP.

Section 10.4.1.2: Secondary Analyses

Original text:

Summaries and analyses for secondary endpoints will be provided for the ITT population.

Maximal percent decrease from pre-exercise FEV₁ following exercise challenge (at 23 hours post-dose at the end of the 2-week treatment period):

This endpoint will be summarized and analyzed as for the primary endpoint of maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post-dose.

Time required for recovery to within 5% of the pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following the challenge (at 12 hours and 23 hours post-dose at the end of the 2-week treatment period):

The time required for recovery to within 5% of the pre-exercise FEV₁ from the time of the maximal percentage decrease from pre-exercise FEV₁ following exercise challenge at 12 hours and 23 hours post-dose for both treatment groups will be compared using a log-rank test. The log rank test will test the null hypotheses that the survival distributions of the two treatment groups are equal. In addition the estimated hazard ratio, confidence interval and p-value will be presented. Kaplan-Meier plots showing the cumulative incidence curves for each treatment group will be produced.

AUC (0-60 min) for percentage decrease from pre-exercise FEV₁ after exercise (at 12 hours and 23 hours post-dose at the end of the 2-week treatment period):

A comparison will be made of the estimated means of the two treatment groups in AUC of the percentage decrease in FEV₁ from pre-exercise at 12 and 23 hrs post-dose using a LMM to adjust for covariate effects. The LMM will include the following covariates: treatment, subject-level mean of the pre-treatment FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the pre-treatment FEV₁ period baselines), gender, age, treatment period and smoking history as fixed effects, and a random intercept for each subject.

Revised text:

Summaries and analyses for secondary endpoints will be provided for the ITT population.

Maximal percent decrease from pre-exercise FEV₁ following exercise challenge (at 23 hours post-dose at the end of the 2-week treatment period):

This endpoint will be summarized and analyzed as for the primary endpoint of maximal percent decrease from pre-exercise FEV₁ following exercise challenge at 12 hours post-dose.

Proportion of subjects with a 30 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period

This endpoint will be analysed using a logistic regression model separately for the 12 and 23 hour challenges using the covariates baseline FEV₁, treatment group, gender, age, and smoking history.

Weighted mean 0-60 minutes for percentage decrease from pre-exercise FEV₁ after exercise (at 12 hours and 23 hours post-dose at the end of the 2-week treatment period):

A comparison will be made of the estimated means of the two treatment groups in for **weighted mean 0-60 minutes** of the percentage decrease in FEV₁ from pre-exercise at 12 and 23 hrs post-dose using a LMM to adjust for covariate effects. The LMM will include the following covariates: treatment, subject-level mean of the pre-treatment FEV₁ period baselines (mean of the 2 period baselines per subject), centered period-level baseline FEV₁ (period baselines centered using subject-level mean of the pre-treatment FEV₁ period baselines), gender, age, treatment period and smoking history as fixed effects, and a random intercept for each subject.

Section 10.4.1.2.1: Other Efficacy Analyses

Original text:

Other measures of efficacy include the evaluation of a categorical treatment response evaluating the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁<10%, a decrease $\geq 10\%$ to $<20\%$, or a decrease $\geq 20\%$, and an evaluation of maximal percent decrease from pre-treatment baseline in FEV₁ (period baseline) following exercise challenge (at 12 hours and 23 hours post-dose). Additional endpoints include evaluation of physical activity monitoring and Asthma Control Test. All endpoints will be described further in the RAP.

Revised text:

Other measures of efficacy include the evaluation of a categorical treatment response evaluating the percentage of subjects who demonstrate a decrease from pre-exercise challenge FEV₁<10%, a decrease $\geq 10\%$ to $<20\%$, or a decrease $\geq 20\%$, and an evaluation of maximal percent decrease from **treatment period** baseline in FEV₁ (period baseline) following exercise challenge (at 12 hours and 23 hours post-dose). **Additional endpoints include evaluation of physical activity monitoring the ACQ-5 score, and the proportion of subjects with a 5 minute post-challenge FEV₁ that was no more than 5% lower than their pre-exercise FEV₁ following the exercise challenge at 12 hours and 23 hours post evening dose at the end of the 2-week treatment period (repeat for the 10, 15, 45 and 60 minute time points).**

Section 12: References

Original text:

European Medicines Agency (EMA). Note for guidance on clinical investigation of medicinal products for treatment of asthma. 27Jun2013. CHMP/EWP/2922/01 Rev.1.

FDA Guidance for Industry: Exercise Induced Bronchospasm (EIB)—Development of Drugs to Prevent EIB, February 2002.

Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. GINA, www.ginasthma.org; 2015.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, 2009; EMA/CPMP/ICH/286/1995

Jones A, Fay JK, Burr ML, Stone M, Hood K, Roberts G. Inhaled Corticosteroids Effects on Bone Metabolism in Asthma and Mild Chronic Obstructive Pulmonary Disease. *Cochrane Database of Systemic Reviews*. 2002;1:1-21.

König P, Hillmana L, Cervantesa C, Levinea C, et al. Bone Metabolism in Children with Asthma Treated with Inhaled Beclomethasone Dipropionate. *The Journal of Paediatrics*. 1993;122:219-226.

McFadden ER, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330:1362-1367.

McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics*. 2011;Nov;128(5):e1147-54.

Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.

Mitchell KE, Johnson-Warrington V, Apps LD, Bankart LS, Williams JE, Rees K, Jolly K, Steiner M, Morgan M, Singh SJ. A Self-Management Programme for COPD: a Randomised Controlled Trial. *Eur Respir J*. 2014;44:1538-1547.

Murray JJ, Waikus-Edwards KR, Yancey SW. Evaluation of Fluticasone Propionate and Fluticasone Propionate/Salmeterol Combination on Exercise in Pediatric and Adolescent Patients with Asthma. *Open Resp Med J*, 2011, 5, 11-18.

National Institutes of Health (NIH). *Guidelines for the Diagnosis and Management of Asthma - Expert Panel Report 3* 2007. U.S. Department of Health and Human Services, Bethesda, MD; 2007. NIH Publication No. 07-4051.

Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016–1027.

Pearlman D, Qaqundah P, Matz J, Yancey SJ, Stempel DA, Ortega HG. Fluticasone Propionate/Salmeterol and Exercise-Induced Asthma in Children With Persistent Asthma. *Pediatric Pulm* 2009;44:429–435.

Poppius H, Muittari A, Kreus KE, Korhonen O, Vilhanen A. Exercise Asthma and Disodium Cromoglycate. *Br Med J* 1970;4:337-339.

Quanjer P, Stanojevic S, Cole T, Baur X, Hall G, Enright P, et al. on behalf of the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3–95 year age range: the global lung function 2012 equations. *Eur Respir J*, 2012; 40: 1324–1343.

Turpeinen M, Pelkonen AS, Nikander K, Sorva R, Selroos O, Juntunen-Backman K, Haahtela T. Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki Early Intervention Childhood Asthma study. *Paediatric Research*. 2010;68(2):169-173.

Weiler J, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Ann Allerg Asthma Immunol* 2010;105 (6 Supp): S1-S47.

Weiler J, Nathan RA, Rupp NT, Kalberg CJ; Emmett A, Dorinsky PM. Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann. Allergy Asthma Immunol.* 2005;94:65-72.

Revised text:

European Medicines Agency (EMA). Note for guidance on clinical investigation of medicinal products for treatment of asthma. 27Jun2013. CHMP/EWP/2922/01 Rev.1.

FDA Guidance for Industry: Exercise Induced Bronchospasm (EIB)—Development of Drugs to Prevent EIB, February 2002.

Global Initiative for Asthma (GINA). *Global Strategy for Asthma Management and Prevention*. GINA, www.ginasthma.org; 2015.

Hatcher RA, Trussell J, Nelson AL, Cates W Jr, Stewart F, Kowal D, editors. Contraceptive Technology. 19th edition. New York: Ardent Media, 2007(a): 24. Table 3-2.

ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals, 2009; EMA/CPMP/ICH/286/1995

Jones A, Fay JK, Burr ML, Stone M, Hood K, Roberts G. Inhaled Corticosteroids Effects on Bone Metabolism in Asthma and Mild Chronic Obstructive Pulmonary Disease. *Cochrane Database of Systemic Reviews*. 2002;1:1-21.

Juniper EF, Svensson K, Mörk AC, Ståhl E. Modification of the Asthma Quality of Life Questionnaire (standardised) in patients 12 years and older. *Health and Quality of Life Outcomes*. 2005; 3:58.

König P, Hillmana L, Cervantesa C, Levine C, **Maloney C, Douglass B**, et al. Bone Metabolism in Children with Asthma Treated with Inhaled Beclomethasone Dipropionate. *The Journal of Paediatrics*. 1993;122:219-226.

McFadden ER, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330:1362-1367.

McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2 -adrenergic receptor agonists. *Pediatrics*. 2011;Nov;128(5):e1147-54.

Miller MR, Hankinson J, Brusasco V, **Burgos F, Casaburi F, Coates A**, et al. Standardisation of spirometry. *Eur Respir J*. 2005;26:319-338.

Mitchell KE, Johnson-Warrington V, Apps LD, Bankart LS, Williams JE, Rees K, et al. A Self-Management Programme for COPD: a Randomised Controlled Trial. *Eur Respir J*. 2014;44:1538-1547.

Murray JJ, Waikus-Edwards KR, Yancey SW. Evaluation of Fluticasone Propionate and Fluticasone Propionate/Salmeterol Combination on Exercise in Pediatric and Adolescent Patients with Asthma. *Open Resp Med J*, 2011, 5, 11-18.

National Institutes of Health (NIH). *Guidelines for the Diagnosis and Management of Asthma - Expert Panel Report 3* 2007. U.S. Department of Health and Human Services, Bethesda, MD; 2007. NIH Publication No. 07-4051.

Parsons JP, Hallstrand TS, Mastronarde JG, Kaminsky DA, Rundell KW, **Hull JH**, et al. An Official American Thoracic Society Clinical Practice Guideline: Exercise-induced Bronchoconstriction. *Am J Respir Crit Care Med* 2013;187:1016–1027.

Pearlman D, Qaqundah P, Matz J, Yancey SJ, Stempel DA, Ortega HG. Fluticasone Propionate/Salmeterol and Exercise-Induced Asthma in Children With Persistent Asthma. *Pediatric Pulm* 2009;44:429–435.

Poppius H, Muittari A, Kreus KE, Korhonen O, Vilhanen A. Exercise Asthma and Disodium Cromoglycate. *Br Med J* 1970;4:337-339.

Quanjer P, Stanojevic S, Cole T, Baur X., Hall G, Enright P, et al. on behalf of the ERS Global Lung Function Initiative. Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function 2012 equations. *Eur Respir J*, 2012; 40: 1324–1343.

Turpeinen M, Pelkonen AS, Nikander K, Sorva R, Selroos O, Juntunen-Backman K, et al. Bone mineral density in children treated with daily or periodical inhaled budesonide: the Helsinki Early Intervention Childhood Asthma study. *Paediatric Research*. 2010;68(2):169-173.

Weiler J, **Anderson SD, Randolph C, Bonini S, Craig TJ, Pearlman DS**, et al. Pathogenesis, prevalence, diagnosis, and management of exercise-induced bronchoconstriction: a practice parameter. *Ann Allerg Asthma Immunol* 2010;105 (6 Supp): S1-S47.

Weiler J, Nathan RA, Rupp NT, Kalberg CJ; Emmett A, Dorinsky PM. Effect of fluticasone/salmeterol administered via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann. Allergy Asthma Immunol*. 2005;94:65-72.

13.8.3. Protocol Amendment 03 (25-MAY-2016) from Protocol Amendment 02 (16-DEC-2015)

Amendment 3 is applicable to all investigator sites in study 201832.

This amendment has been written to clarify text regarding timing of visits to ensure that the intention of the protocol is correctly reflected. Other amendments were made where deemed necessary.

Method of Amendment

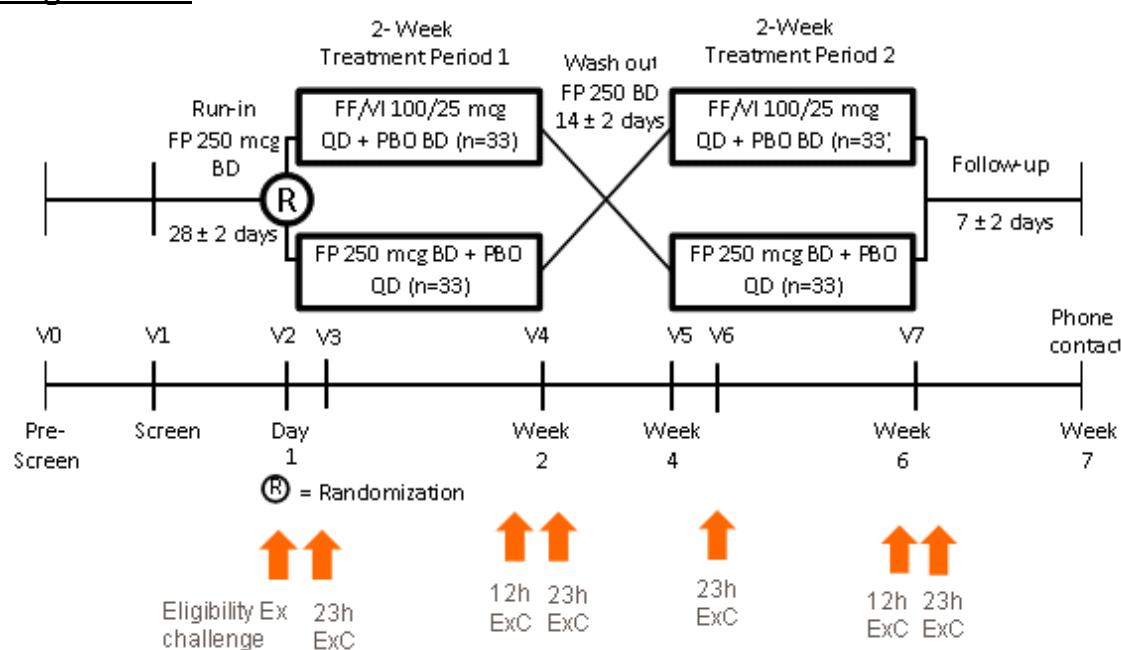
Original and revised texts are specified as follows:

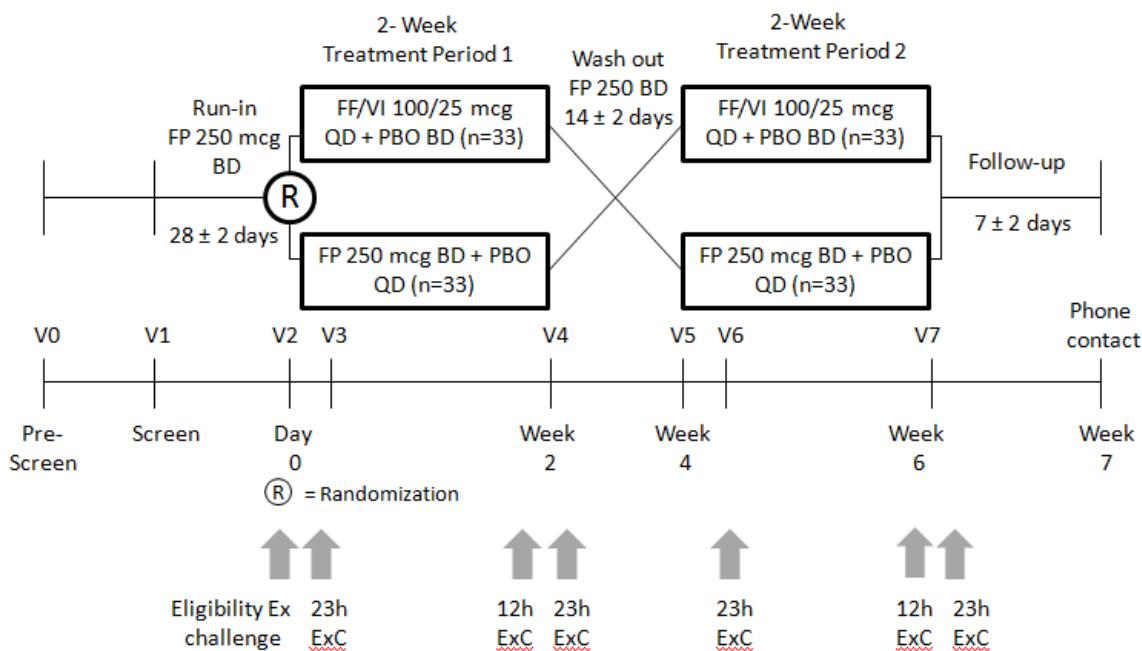
- Original text: as written in the Amendment No. 2
- Revised text: as written in Amendment No. 03 with additional or revised text indicated by **bold font**, or **bold underline** (Time and Events Table).

Amendment Details

Section 5.1 Overall Design

Original text:



Revised text:**Rationale:**

Day 1 redefined as Day 0 to better reflect the intention of the protocol to ensure that the two treatment periods are 14 days in length.

Section 6.2 Randomisation Criteria**Original text:**

At the end of the run-in period, a subject will be eligible for Randomization to double-blinded study treatment if he/she meets all the following criteria at Visit 2. Visit 2 may be conducted over the course of 48 hours (within the designated window), if the eligibility exercise challenge is repeated.

Revised Text:

At the end of the run-in period, a subject will be eligible for Randomization to double-blinded study treatment if he/she meets all the following criteria at Visit 2.

Rationale:

Visit 2 repeat timelines were updated in Amendment 2 but this text was not updated in error.

Section 7.1 Investigational Product and Other Study Treatment**Original text:**

Albuterol/salbutamol inhalation aerosol will be supplied by GSK

Revised Text:

Albuterol/salbutamol inhalation aerosol will be supplied as detailed in the SRM.

Rationale:

Change in strategy for rescue medication supply.

Section 7.2.1 Assignment of Subject Number**Original text:**

At Visit1, a unique **Subject Number** (CRF number) will be assigned to any subject who has at least one Visit 1 procedure performed, other than informed consent. The unique Subject Number will be used to identify individual subjects during the course of the study.

Revised Text:

At the **Pre-screen visit**, a unique **Subject Number** (CRF number) will be assigned to any subject who has **given** informed consent. The unique Subject Number will be used to identify individual subjects during the course of the study.

Rationale:

Subject numbers must be assigned as soon as informed consent is given and the informed consent form signed, regardless of study procedures.

Section 7.10.2 Prohibited Medications and Non-Drug Therapies**Original text:**

The following asthma medications are prohibited during the conduct of the study or within the specified time frame:

Within 12 weeks of Visit 1 and during the study:

- Systemic (oral, parenteral or depot) corticosteroids
- Anti-IgE (e.g. Xolair)

Revised Text:

The following asthma medications are prohibited during the conduct of the study or within the specified time frame:

Within 12 weeks of Visit 1 and during the study:

- Systemic (oral, parenteral or depot) corticosteroids
- Anti-IgE (e.g. Xolair, **NucalaTM**)

Rationale:

Nucala has recently received a license for asthma and should be excluded.

Table 3 Time and Events Table

Original text:

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12, 14}	5 ¹²	6	7 ^{12, 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X									
Genetics Consent	X ¹									
Subject Demography	X									
Medical History (including CV)		X								
Disease (Asthma) History		X								
Medication History	X	X								
Smoking history/status		X								
Inclusion/Exclusion Criteria		X								
Evidence of EIB		X								
Efficacy Assessments										
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ^{3, 17}	X ⁴	X ⁵		X ⁴	X ⁵		
Post-Challenge Serial FEV ₁ Measurements			X ³	X ⁶	X ⁶		X ⁶	X ⁶		
Asthma Control Questionnaire-5			X		X	X		X	X	
Dispense SenseWear ¹⁵ accelerometer		X								
Collect SenseWear accelerometer								X	X	
Safety Assessments										
Concomitant Medication	X	X	X	X	X	X	X	X	X	X ⁷
Physical Examination		X								

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12, 14}	5 ¹²	6	7 ^{12, 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	1	2	14 (-2/+2) days	28 (-2/+2) days	29 (-2/+2)	42 (-2/+2) days		47 to 51 days
Vital Signs		X	X ⁸	X ⁸	X ⁸	X	X ⁸	X ⁸	X	
12-lead ECG		X								
Adverse Event Assessment	X ⁹	X ⁹	X	X	X	X	X	X	X	X
Issue Medical Conditions Diary Card		X	X		X	X				
Review Medical Conditions Diary Card			X ¹⁰	X	X ¹⁰	X ¹⁰	X	X ¹⁰	X	
Laboratory Assessments										
Genetics Saliva Sample			X ¹							
Urine Pregnancy Test		X	X			X			X	X ¹³
Investigational Product										
Dispense Fluticasone Propionate		X			X					
Collect Fluticasone Propionate			X			X				
Dispense Rescue ¹⁶ Albuterol/salbutamol		X	X	X	X	X	X			
Collect Rescue Albuterol/salbutamol			X		X	X		X		
Dispense IP			X ¹¹			X				
Assess study drug compliance			X	X	X	X	X	X	X	
Collect IP					X			X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and forced vital capacity (FVC) testing), conducted immediately pre-exercise (and after vital signs), if applicable. Subject should have withheld albuterol/salbutamol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge.
4. Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to 5% of baseline FEV₁ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before (prior to the pre-exercise spirometry) and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.
14. Visit 4 and Visit 7 will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will return to the clinic at 12 hours and 23 hours (after the evening dose of study medication from the evening visit) for an exercise challenge procedure.
15. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.
16. Collect and re-dispense rescue as needed from Visit 1
17. Subjects who achieve a decrease in FEV₁ of 15% to $<20\%$ may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures **once** within a week of the original procedure.

Revised Text:

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12, 14}	5 ¹²	6	7 ^{12, 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	0	1 ¹⁸	14 (-2/+2) days	28 (-2/+2) days	29 ¹⁸	42 (-2/+2) days		47 to 51 days
Written Informed Consent	X									
Genetics Consent	X ¹									
Subject Demography	X									
Medical History (including CV)		X								
Disease (Asthma) History		X								
Medication History	X	X								
Smoking history/status		X								
Inclusion/Exclusion Criteria		X								
Evidence of EIB		X								
Efficacy Assessments										
Spirometry (full FEV ₁ and FVC)		X	X ²	X ²	X ²	X	X ²	X ²	X	
Exercise Challenge Testing (Treadmill)			X ^{3, 17}	X ⁴	X ⁵		X ⁴	X ⁵		
Post-Challenge Serial FEV ₁ Measurements			X ³	X ⁶	X ⁶		X ⁶	X ⁶		
Asthma Control Questionnaire-5			X		X	X		X	X	
Dispense SenseWear ¹⁵ accelerometer		X								
Collect SenseWear accelerometer								X	X	
Safety Assessments										
Concomitant Medication	X	X	X	X	X	X	X	X	X	X ⁷
Physical Examination		X								
Vital Signs		X	X ⁸	X ⁸	X ⁸	X	X ⁸	X ⁸	X	

Procedures	Pre-Screen	Screen/ Run-in	Treatment Period 1			Treatment Period 2			Early Withdrawal Visit	Follow- up Phone Call
Visit/Contact	0	1	2 ¹² Randomization	3	4 ^{12, 14}	5 ¹²	6	7 ^{12, 14}		
Week		-4	0	0	2	4	4	6		7
Treatment Day		-26 to -30 days	0	1 ¹⁸	14 (-2/+2) days	28 (-2/+2) days	29 ¹⁸	42 (-2/+2) days		47 to 51 days
12-lead ECG		X								
Adverse Event Assessment	X ⁹	X ⁹	X	X	X	X	X	X	X	X
Issue Medical Conditions Diary Card		X	X		X	X				
Review Medical Conditions Diary Card			X ¹⁰	X	X ¹⁰	X ¹⁰	X	X ¹⁰	X	
Laboratory Assessments										
Genetics Saliva Sample			X ¹							
Urine Pregnancy Test		X	X			X			X	X ¹³
Investigational Product										
Dispense Fluticasone Propionate		X			X					
Collect Fluticasone Propionate			X			X				
Dispense Rescue ¹⁶ Albuterol/salbutamol		X	X	X	X	X	X			
Collect Rescue Albuterol/salbutamol			X		X	X		X		
Dispense IP			X ¹¹			X				
Assess study drug compliance			X	X	X	X	X	X	X	
Collect IP					X			X	X	

1. Genetics saliva sample collected at Visit 2 (following Randomization) or at any scheduled visit thereafter. Genetics consent MUST be obtained PRIOR to collection of the Genetics sample.
2. Pre-exercise spirometry (full FEV₁ and forced vital capacity (FVC) testing), conducted immediately pre-exercise (and after vital signs), if applicable. Subject should have withheld albuterol/salbutamol within previous 6 hours.
3. Performed for determination of eligibility. Serial spirometry performed 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Subjects must demonstrate a decrease in FEV₁ of $\geq 20\%$ at one time point within 30 minutes of the end of a standardized exercise challenge.
4. Exercise challenge testing will be performed at 23 hours following the evening study treatment doses given at Visit 2 and Visit 5
5. Exercise challenge testing will be performed at 12 hours and 23 hours following the evening study treatment doses given at the beginning of Visits 4 and 7.
6. Serial spirometry performed at time points 5, 10, 15, 30, 45 and 60 minutes post- exercise challenges. Longer monitoring may be required for those subjects who do not return to **95%** of baseline FEV₁ values within 60 minutes.
7. Concomitant medications collected for adverse events only between end of treatment and follow-up phone contact.
8. Vital signs will be collected before (prior to the pre-exercise spirometry) and after each exercise challenge test.
9. Adverse Event and Serious Adverse Events to be collected from the start of study Drug (Visit 1) until the follow up contact. However, any SAE related to study participation will be recorded from the time of Informed Consent
10. Review medical conditions diary card, including an assessment of any potential change in exercise capacity
11. An unblinding card will be dispensed along with double blind IP.
12. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear accelerometer for the 7 days preceding these visits.
13. Pregnancy test will be conducted via home test kit and results will be reported at the Follow-up phone contact.
14. Visit 4 and Visit 7 will begin between 5PM and 11PM and continue over a period of approximately 24 hours. Subjects will return to the clinic at 12 hours (**± 1 hour**) and 23 hours (**± 1 hour**) (after the evening dose of study medication from the evening visit) for an exercise challenge procedure.
15. Subjects will be contacted by telephone 8-9 days prior to Visits 2, 4, 5 and 7 and reminded to wear the SenseWear Armband accelerometer for the 7 days preceding these visits.
16. Collect and re-dispense rescue as needed from Visit 1
17. Subjects who achieve a decrease in FEV₁ of 15% to <20% may continue taking their daily run-in medication and repeat the eligibility exercise challenge and associated procedures **once** within a week of the original procedure.
18. **Visit 3 must be performed on the day immediately following Visit 2. Visit 6 must be performed on the day immediately following Visit 5.**

Rationale:

Corresponding Day for Visit 2 and Visit 3 updated to better reflect the intention of the protocol to ensure that the two treatment periods are 14 days in length. Other minor adjustments made to clarify the timing of visits.

Section 8.3.3.2 Visit 2 (Randomization)

Original text:

Treatment period 1 baseline FEV₁: Spirometry will be performed at Visit 2 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with run-in medication (FP 250 mcg). At least two valid and two repeatable spirometry efforts should be obtained before the first exercise challenge.

Revised Text:

Treatment period 1 baseline FEV₁: Visit 2 begins between 5 PM and 11 PM and should begin at approximately the same time as Visit 1 (± 1 hour). Spirometry will be performed at Visit 2 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours (± 1 hour) after dosing with run-in medication (FP 250 mcg). At least two valid and two repeatable spirometry efforts should be obtained before the first exercise challenge.

Rationale:

To ensure clarity of the timing of visit 2.

Section 8.3.3.3 - Visit 3 and Visit 6 (23 hours Post First Dose Exercise Challenge)

Original text:

Pre-exercise FEV₁: Spirometry will be performed at Visits 3 and 6 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 23 hours after the first dose in each treatment period. At least two valid spirometry efforts should be obtained before the exercise challenge.

Revised Text:

Pre-exercise FEV₁: Spirometry will be performed at Visits 3 and 6 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 23 hours (± 1 hour) after the first dose in each treatment period. At least two valid spirometry efforts should be obtained before the exercise challenge.

Rationale:

To ensure clarity of the timing of Spirometry at visits 3 and 6.

Section 8.3.3.5 – Visit 5

Original text:

Treatment period 2 baseline FEV₁: Spirometry will be performed at Visit 5 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours after dosing with the washout medication. At least two valid spirometry efforts should be obtained.

Revised Text:

Treatment period 2 baseline FEV₁: Spirometry will be performed at Visit 5 at approximately the same time as at Visit 1 (± 1 hour). The FEV₁ should be measured approximately 12 hours (**± 1 hour**) after dosing with the washout medication. At least two valid spirometry efforts should be obtained.

Rationale:

To ensure clarity of the timing of Spirometry at visit 5.

Section 8.4.5**Original Text:**

Vital signs will be obtained after subjects have rested for approximately 5 minutes in a semi-supine position.

Revised Text:

Vital signs will be obtained after subjects have rested for approximately 5 minutes in a semi-supine position, **except in the case of the post exercise test vital signs which will be performed immediately following the end of the exercise test.**

Rationale

The post exercise vital signs will be performed immediately following the exercise test to ensure that the 5mins post exercise spirometry can be performed on time.

Section 13.1 – Appendix 1 – Abbreviations and Trademarks -**Original text:****Trademark Information**

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
ADVAIR	
DISKUS	
ELLIPTA	
RELVAR/BREO	SenseWear Armband

Revised Text:
Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
ADVAIR	
DISKUS	
ELLIPTA	
RELVAR/BREO	
NUCALA	SenseWear Armband

Rationale:

Addition of Trademark to reflect addition of prohibited medication.