TITLE PAGE

Division: Worldwide Development
Information Type: Protocol Amendment

Title:	A Phase III, randomized, double-blind, active controlled, parallel group study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI with the fixed dose dual combination of FF/VI, administered once-daily via a dry powder inhaler in subjects with inadequately controlled asthma

Compound Number: GSK573719+GW642444+GW685698

Development Phase: III A

Effective Date: 05-DEC-2017

Protocol Amendment Number: 04

Author (s): PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N271022_00	2016-JUN-06	Original
2016N271022_01	2016-JUN-09	Re-Publishing
Following publication of the original protocol but prior to distribution of the document, an exploratory analysis of the psychometric properties of the Evaluating Respiratory Symptoms (E-RS) and Supplemental asthma items was included in the protocol (Section 9.4.6). This necessitated a re-publishing of the protocol.		
2016N271022_02	2016-DEC-13	Amendment No. 1
• The Medical Monitor details have been updated. • In Section 1, the protocol synopsis has been updated to mirror the information presented in the main body of the protocol. • In Section 2.1, the text has been updated to clarify that the Global Initiative for Asthma guidelines (GINA, 2016) recommends a long-acting muscarinic antagonist (LAMA) as an add-on treatment option. • In Section 3 and Section 7.3.1.3: o The Other Secondary endpoint "Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score" will be assessed over Weeks 21 to 24 (rather than over the first 24 weeks) of the treatment period. • In Section 3 and Section 7.3.1.4: o The Asthma Control Questionnaire (ACQ) total score that denotes controlled asthma has been corrected to align with Section 7.3.3.2 (Asthma Control Questionnaire). o The Other endpoints "Mean change from baseline in E-RS domain scores" and "Percent of patients meeting a responder threshold of ≥ 2 points improvement from baseline for the E-RS total score" will be assessed over Weeks 21 to 24 of the treatment period (rather than 'over the first 24 weeks of the treatment period' and 'at Week 24', respectively). • Section 4.2 and Section 6.9.2 have been updated to clarify that the last dose of ICS/LABA asthma medication has to be taken ≥24 hours prior to the Screening visit (Visit 1). • In Section 4.6.1, the Summary of Data/Rationale for Risk associated with Systemic ICS Effects has been updated to clarify that study HZA106851 assessed the effect of Investigational Product on 24 hour urinary (rather than serum) cortisol excretion. • In Section 5.1: o Inclusion Criteria number 4 (Asthma Control) has been amended. o The wording regarding acceptable doses of commonly prescribed ICS medication in Inclusion Criteria number 5 (Current Asthma Maintenance Therapy) has been amended.		

- In Section 5.2:
  - The Note related to Exclusion Criteria number 2 (Asthma Exacerbation) has been clarified.
  - Exclusion criteria number 3 (Chronic Obstructive Pulmonary Disease) has been clarified.
  - Exclusion criteria number 14 (Tobacco Use) has been clarified.
- In Section 5.6.1 and Section 6.3, the requirement to withdraw a subject from study treatment/the study following the unblinding of the study treatment assigned to a subject has been removed.
- In Section 5.6.4, the text has been amended to clarify that the QT interval corrected for heart rate by Fredericia's formula (i.e. QTcF), rather than Bazett's formula (i.e. QTcB), will be used throughout the study.
- In Section 6.1, use of the study-provided fluticasone propionate (FP) has been clarified.
- In Section 6.6, the instruction to contact the study sponsor/site monitor to discuss subject eligibility for continued participation in the study has been deleted.
- In Section 6.9, the time-period for recording asthma medication in the eCRF has been amended to align with the associated inclusion criterion for the study.
- In Section 6.9.1.1:
  - The permitted dose of systemic corticosteroids has been clarified.
  - The temporary use of medications for the treatment of moderate asthma exacerbations has been clarified.
- Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnea has been included as a permitted non-drug therapy in Section 6.9.1.3.
- In Section 6.9.2:
  - The temporary use of inhaled long-acting anticholinergics and inhaled long-acting beta$_2$-agonists (other than study treatment) has been prohibited.
  - Medical marijuana has been included as a prohibited medication.
- In Section 7.1:
  - The Time and Events Table has been updated to clarify the time-windows associated with Visit 1, Visit 2 and Visit 3.
  - Footnote 5 has been updated to clarify that the Informed Consent Form must be signed prior to 'protocol-specified' medication cessation.
  - Footnote 15 has been updated to clarify when the 3-week run-in period may commence should the airway reversibility assessment need to be repeated.
  - Footnote 18 has been updated to clarify the timing of the ECG assessments.
  - In Footnote 27, the timing of Early Withdrawal visit assessments has been clarified.
  - In Footnote 30, the pre-randomization use of the study-provided fluticasone propionate has been clarified.
- In Section 7.3.4.1, the washout period for short-acting β_2- agonists has been

clarified

- In Section 7.3.5, Section 7.3.6, Section 7.5.1.2 and Section 7.5.8, the description of the data collected on the Medical Problems/Medications Taken worksheet has been revised to allow for the collection of data related to study treatment (as well as non-study treatment).
- In Section 7.3.6, instructions for collecting the occurrence of asthma exacerbations in the electronic Case Report Form (eCRF) have been included.
- In Section 7.5.2, a blank row in the provided table has been deleted.
- In Section 7.5.6, the timing of the ECG assessments has been clarified.
- In Section 7.6, the order of assessments has been amended.
- In Section 9.2.2, the power for the key secondary endpoint (and associated graphs) has been re-calculated and updated.
- In Section 9.3.4, Level 3b and Level 5 of the Multiplicity Adjustment Plan have been updated to amend the wording of the 'mean change from baseline in E-RS score' endpoint (in order to align with the associated amendments made in Section 3 and Section 7.3.1.3).
- In Section 9.4, a typographical error has been corrected.

2016N271022_03	2017-JUN-23	Amendment No. 2

- In Section 3.0:
  - (Other Objectives) has been amended to remove the word 'morning'. Mean change from baseline in morning evening (PM) PEF over the first 24 weeks of the treatment period.
  - The responder threshold language has been amended for ACQ-7, ACQ-6 and ACQ-5 to state "≥0.5 points improvement (decrease) from baseline". Originally stated "≥0.5 in change from baseline".
  - Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period. Added the word "decrease).
  - Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24. Added the word "increase").
- In Section 5.1 Inclusion Criteria
  - Current Asthma Maintenance Therapy; added BTS/SIGN and Japanese guidance for adult asthma as additional supported guidance.
  - Spirometry; Has been expanded to <85%. A best pre-bronchodilator morning (AM) FEV1 ≥30% and <85% (was 80%) of the predicted normal value at Visit 1.
- In Section 5.3.1 Inclusion Criteria for Enrolment
  - Spirometry; Has been expanded to <90%. A best pre-bronchodilator morning (AM) FEV1 ≥30% and <90% (was 80%) of the predicted normal value at Visit 1.
- In Section 7.1:
  - In the Time and Events Table for the Screening Visit box, Serum pregnancy test, to include foot note #21; Assessments to be conducted in females of reproductive potential.

- In Section 7.3.1.4:
  - The responder threshold language has been amended for ACQ-7, ACQ-6 and ACQ-5 to state "≥0.5 points improvement (decrease) from baseline". Originally stated "≥0.5 in change from baseline".
  - Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period. Added the word "decrease).
  - Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24. Added the word "increase").
- In Section 7.3.5.1.6:
  - Clearly defined baseline value for alerts as 7 days prior to randomization.
- In Section 9.3.1, typographical error was corrected.
- In Section 9.3.4, Multiple Comparisons and Multiplicity:
  - Multiplicity adjustment plan has been updated to ensure the strong control on the family-wise Type I Error across multiple endpoints and multiple treatment comparisons.
- In Section 11.0, References:
  - An additional reference (Japanese guideline for adult asthma 2017) has been added for guidance.

2016N271022_04	2017-SEP-29	Amendment No. 3

- In Section 1: Protocol Synopsis for Study 205715; Treatment Arms and Duration
  - Update and define the variable treatment period and transition date to determine the planned end of study visit (Week 24, 36, or 52) for each randomized subject.
- In Section 4.2: Treatment Arms and Duration
  - Update and define the variable treatment period and transition date to determine the planned end of study visit (Week 24, 36, or 52) for each randomized subject.
- In Section 5.7: Subject and Study Completion
  - Update and define the variable treatment period and transition date to determine the planned end of study visit (Week 24, 36, or 52) for each randomized subject.
- In the Appendix; Section 12.7.1 Country Specific Requirements, was updated to remove minimum requirement for Japanese subjects.
- The following sections all had the statement referring to "country specific requirements" removed, see Section 4.3, Section 7.1 (foot note #22) and Section 7.6.1.1.

2016N271022_05	2017-DEC-05	Amendment No. 4

- Section 6.1: amended to reflect the fact that study-specific FP (provided to subjects at the Investigator's discretion for the treatment of symptoms of a moderate asthma exacerbation) does not need to be administered at a specific dose or via the DISKUS dry powder inhaler (DPI).

- Section 7.2: amended to clarify that dispensing FP to subjects at Visit 1 is at the Investigator's discretion.

SPONSOR SIGNATORY

PPD

5th Dec 2017

Steve Pascoe, MD
Vice President,
Head Unit Physician and
Medicines Development Leader
Respiratory Franchise

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	Site Address
Primary Medical Monitor	PPD	PPD Please refer to the Study Reference Manual (SRM) for phone number details.	Please refer to the SRM.	
Secondary Medical Monitor	PPD	PPD Please refer to the SRM for phone number details.	Please refer to the SRM.	
SAE contact information	Medical monitor as above			

Sponsor Legal Registered Address:

GlaxoSmithKline Research & Development Limited
Iron Bridge Road
Stockley Park West, Uxbridge, Middlesex, UB11 1BU, UK
Telephone: PPD

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 No. 114873; EudraCT No. 2016-001304-37

INVESTIGATOR PROTOCOL AGREEMENT PAGE

For protocol number 205715

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

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1. PROTOCOL SYNOPSIS FOR STUDY 205715

Rationale

Despite availability of treatments and published guidelines, patients may have asthma that is inadequately controlled. The prevalence of inadequately controlled asthma varies based on the definition used for control. In a sample of asthmatics visiting their healthcare provider for any reason, 58% of adult asthmatics were estimated to have uncontrolled asthma based on the Asthma Control Test (ACT, defined as an ACT score ≤19).

The GINA guidelines recommend a long-acting muscarinic antagonist (LAMA) as an add-on treatment option for adults with asthma that are currently taking medium to high dose inhaled corticosteroid/long-acting beta$_2$ agonist (ICS/ LABA) treatment and have a history of exacerbations. Exacerbations are an important endpoint in asthma therapy; however, symptom control is also important in determining what patients could benefit from step-up therapy. Data from the GlaxoSmithKline (GSK) PhIIb study 200699 demonstrated that the LAMA Umeclidinium (UMEC), when added to the ICS fluticasone furoate (FF), reduced albuterol/salbutamol use and improved symptoms in a sub-group of subjects with the primary diagnosis of asthma.

GSK is currently developing a once-daily 'closed' triple therapy of an ICS/LAMA/LABA combination [FF/UMEC/Vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma by improving lung function, health-related quality of life (HRQoL) and symptom control over established combination therapies. Through the comparison of a closed triple therapy to a standard of care ICS/LABA combination therapy this study will provide important information to prescribers regarding the benefit of step-up to closed triple therapy to patients uncontrolled on ICS/LABA.

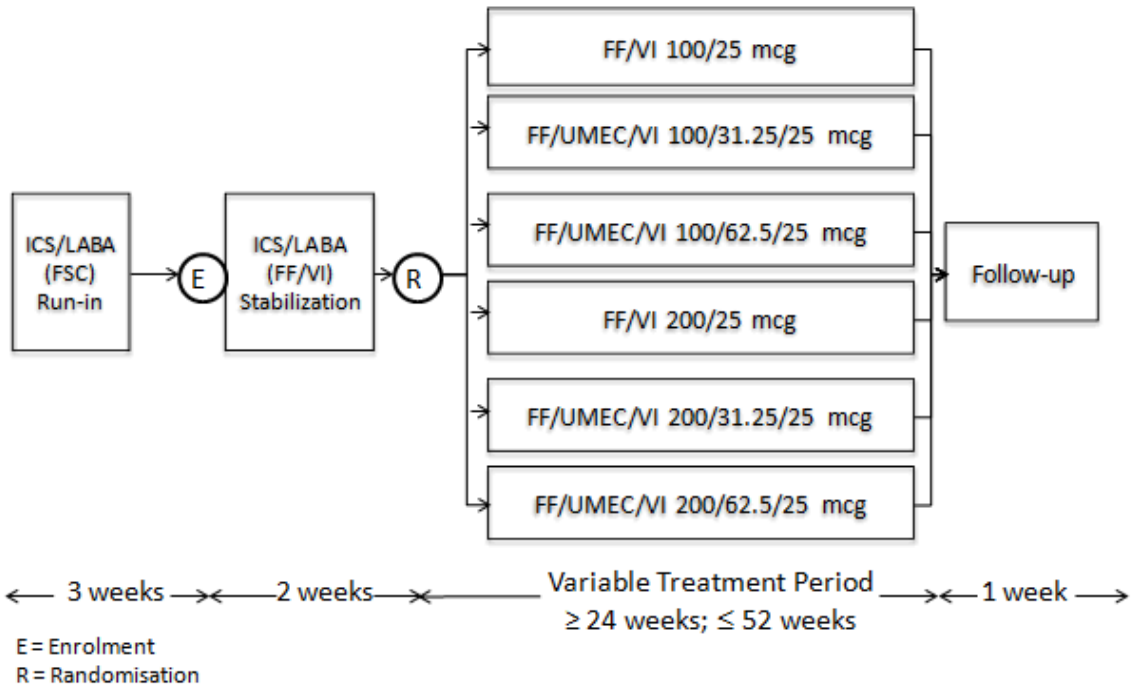
Objective(s)/Endpoint(s)

Objectives	Endpoints
Primary	
To evaluate the effects of FF/UMEC/VI on lung function compared with FF/VI after 24 weeks of treatment	Mean change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 24
Key Secondary	
To evaluate the efficacy of FF/UMEC/VI compared with FF/VI	Annualized rate of moderate/severe asthma exacerbations
Other Secondary	
To evaluate the efficacy of FF/UMEC/VI compared with FF/VI	• Mean change from baseline in clinic FEV1 at 3 hours post study treatment at Week 24 • Mean change from baseline in Asthma Control Questionnaire-7

Objectives	Endpoints
	(ACQ-7) total score at Week 24 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 • Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21 to 24 (inclusive) of the treatment period
To evaluate the safety of FF/UMEC/VI compared with FF/VI	• Incidence and type of adverse events • Electrocardiogram (ECG) measurements • Vital signs • Clinical hematological and chemistry parameters

Overall Design

This is a phase III, randomized, double-blind, active controlled, 6-arm parallel group, global multicenter study evaluating FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25 and 200/62.5/25 micrograms [mcg]) versus FF/VI (100/25 and 200/25 mcg), given once daily in the morning.



Treatment Arms and Duration

As the duration of the treatment period is variable (see below for details), eligible subjects will be requested to participate in the study for a minimum of approximately 32 weeks and a maximum of approximately 60 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, subjects will complete the following 5 phases of the study:

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) must be completed prior to initiating any Visit 1 procedures.
- **Screening / run-in:** Subjects who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 3 weeks in order to continue to assess the subject's eligibility for the study. Subjects will take the last dose of their usual (i.e. pre-study) ICS/LABA asthma medication ≥ 24 hours prior to the Screening Visit. Subjects satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with fixed dose ICS/LABA (fluticasone/salmeterol [FSC], 250/50 mcg, via the DISKUS™ dry powder inhaler [DPI]) to take 1 inhalation twice a day during the 3-week run-in period, and rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.
- **Enrolment / stabilization:** Subjects will self-administer their last dose of run-in FSC treatment on the morning prior to Visit 2 (i.e. ≥ 24 hours prior to the Enrolment Visit). At Visit 2 (the Enrolment Visit), subjects who meet all the eligibility criteria will be provided with fixed dose ICS/LABA (fluticasone/vilanterol [FF/VI], 100/25 mcg, via the ELLIPTA™ DPI) to take once a day during the 2-week stabilization period. The 2-week stabilization period is necessary in order to allow subjects to become accustomed to using the ELLIPTA DPI (having used the DISKUS DPI during the run-in period) as well as to continue to assess the subject's eligibility for the study and collect baseline eDiary data.
- **Treatment:** Subjects will self-administer their last dose of stabilization FF/VI treatment on the morning prior to Visit 3 (i.e. ≥24 hours prior to the Randomization Visit). At Visit 3 (the Randomization Visit), subjects who meet all of the randomization criteria will be randomised 1:1:1:1:1:1 to one of the following six double-blind study treatments:
  - FF/UMEC/VI 100/62.5/25 mcg once daily (QD)
  - FF/UMEC/VI 200/62.5/25 mcg QD
  - FF/UMEC/VI 100/31.25/25 mcg QD
  - FF/UMEC/VI 200/31.25/25 mcg QD
  - FF/VI 100/25 mcg QD
  - FF/VI 200/25 mcg QD

  Study treatment will be administered via the ELLIPTA DPI in the morning.

The duration of the treatment period is variable but will be a minimum of 24 weeks and a maximum of 52 weeks. In accordance with the protocol-defined visit schedule, subjects will have up to 6 on-treatment clinic visits scheduled at Visits 3, 4, 5, 6, 7 and 8/End of Study (EOS) (Weeks 0, 4, 12, 24, 36 and 52, respectively).

The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date.

To determine when the final treatment/EOS visit will occur for each randomized subject in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a date henceforth referred to as the transition date will be communicated to the study sites by GSK. GSK will communicate a *provisional* transition date to all study sites on an ongoing basis during the study, until a fixed *actual* transition date is communicated at least 20 weeks in advance of the selected date (unless extenuating circumstances dictate otherwise). The date selected by GSK as the actual transition date will always be more than 12 days prior to the study completion date. At the Investigator's discretion, subjects should be informed of the transition date (provisional and actual) on an ongoing basis during the study so that their expected final treatment/EOS visit can be planned using the provisional transition date and then confirmed once the actual transition date is known.

Subjects who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit.

After the actual transition date is communicated, subjects must adhere to their study visit schedule and complete a minimum of 24 weeks of study treatment. A subject's final treatment/EOS visit will be defined as follows:

- Subjects whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at their Week 24 clinic assessment visit.

- Subjects who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time-windows).

The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the subject completes all of the protocol-defined procedures for Visit 8/EOS or, if applicable, the Early Withdrawal Visit. A subject will be considered to have completed the study upon completion of all assessments and procedures for Visit 8/EOS and including a successful follow-up contact/visit.

Type and Number of Subjects

Patients with inadequately controlled asthma (i.e. patients with an ACQ-6 score ≥1.5) despite treatment with maintenance asthma medication (>250 mcg/day FP or equivalent plus LABA).

The total number of randomized subjects required is approximately 2250, with 375 subjects randomized to each of the 6 double-blind treatment arms. Randomization will be stratified by pre-study ICS treatment strength (mid, high) at screening to ensure treatment balance within each stratum.

Analysis

This is a superiority study to demonstrate the add-on benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg in a single inhaler when compared to FF/VI. For each test on each efficacy endpoint, the null hypothesis is that there is no difference between treatment groups. The alternative hypothesis is that there is a difference between treatment groups. The primary efficacy analysis for the primary endpoint of change from baseline in trough FEV_1 will evaluate the "de facto" type estimand in the Intent-to-Treat population, using a mixed-model repeated measures (MMRM) analysis, including all trough FEV_1 recorded post randomization.

2. INTRODUCTION

2.1. Study Rationale

The Global Initiative for Asthma guidelines [GINA 2016] recommend a long-acting muscarinic antagonist (LAMA) as an add-on treatment option for adults (≥18 years) with asthma that are currently taking medium-to-high dose inhaled corticosteroid and long-acting $beta_2$ agonist (ICS/LABA) maintenance therapy and have a history of exacerbations. Exacerbations are an important endpoint in asthma therapy; however, symptom control is also important in determining what patients could benefit from step-up therapy.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma, by improving lung function, symptom control and health-related quality of life (HRQoL) over established combination therapies. Through the comparison of a closed triple therapy to a standard of care ICS/LABA combination

therapy this study will provide important information to prescribers regarding the benefit of step-up to closed triple therapy to patients uncontrolled on ICS/LABA.

2.2. Brief Background

Despite the availability of treatments and published guidelines, patients may have asthma that is inadequately controlled. The prevalence of inadequately controlled asthma varies based on the definition used for control. In a sample of asthmatics visiting their healthcare provider for any reason, 58% of adult asthmatics were estimated to have uncontrolled asthma based on the Asthma Control Test (ACT, defined as an ACT score ≤19) [Stanford 2010].

Consistent with these observations, an analysis of asthma patients in the United States (US) found that 29%-31% of asthma patients treated with high dose ICS/LABA therapy experienced exacerbations [Schatz 2014]. In a Dutch survey of 929 patients treated with high dose ICS/LABA or medium/high dose ICS/LABA and maintenance oral corticosteroid (OCS), who self-reported asthma or chronic obstructive pulmonary disease (COPD) with <10 smoking pack years, 74% of patients were classified as difficult to control (Asthma Control Questionnaire (ACQ) score >1.5, or experienced ≥3 exacerbations in a year, or ≥1 hospitalization in a year). Half (50.6%) of these patients had an ACQ score >1.5, 21.7% had ≥3 exacerbations in a year, and 21.7% had ≥1 hospitalization in a year. Based on this sample, an estimated 17.4% of the Dutch asthma population was estimated to be on high dose ICS/LABA or medium/high dose ICS/LABA and maintenance OCS and have difficult to control asthma [Hekking 2015]. Although patients with asthma can be effectively treated with available controller medications, a subset of patients do not adequately respond to current standard therapy, as measured by symptom questionnaires (ACT, ACQ) and exacerbations.

The goal of asthma treatment is to achieve and maintain asthma control and to reduce the future risk of exacerbations. ICSs are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [National Institutes of Health (NIH) 2007; GINA 2016]. Treatment with ICS controls asthma symptoms, improves quality of life and lung function, decreases airway hyper-responsiveness, controls airway inflammation, and reduces the frequency and severity of asthma exacerbations, thereby reducing asthma morbidity. The dose of ICS is selected based on the severity of the patient's asthma. In patients who are symptomatic on ICS alone, add-on therapy with another controller, in particular a LABA is preferred to increasing the dose of ICS to achieve asthma control. The addition of a LABA to an ICS improves symptom scores, decreases nocturnal asthma symptoms, improves lung function and reduces the number of asthma exacerbations [Ducharme 2010]. Combination ICS/LABA inhalation products have been developed as a result of this need. In difficult to treat persistent asthma, some patients continue to be symptomatic despite treatment with ICS and LABA combination medications and the current guidelines [GINA 2016; NIH 2007; British Thoracic Society / Scottish Intercollegiate Guidelines Network (BTS/SIGN) 2016] recommend treatment with high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications.

In the European Union (EU), tiotropium bromide (LAMA) is licensed as an add-on maintenance bronchodilator treatment in adult patients with asthma who are currently treated with the maintenance combination of ICS (≥800 micrograms (mcg) budesonide/day or equivalent) and LABA and who experienced one or more severe exacerbations in the previous year [Spiriva Respimat Summary of Product Characteristics (SPC) 2016]. In the US, tiotropium bromide was recently approved for the maintenance treatment of asthma, in patients 12 years of age and older [Spiriva Respimat United States Product Insert (USPI), 2016]. The benefit of adding a LAMA to both ICS monotherapy and ICS/LABA fixed combination therapy was demonstrated in four Phase III confirmatory studies (416, 417 [Kerstjens 2012]; 418 and 419 [Kerstjens 2015]), in symptomatic asthma patients (ACQ score ≥1.5). The Phase III studies supporting the tiotropium application showed that addition of tiotropium bromide to ICS/LABA maintenance therapy significantly improved lung function and reduced the risk of severe asthma exacerbation.

3. OBJECTIVE(S) AND ENDPOINT(S)

Objectives	Endpoints
Primary	
To evaluate the effects of FF/UMEC/VI on lung function compared with FF/VI after 24 weeks of treatment	Mean change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 24
Key Secondary	
To evaluate the efficacy of FF/UMEC/VI compared with FF/VI	Annualized rate of moderate/severe asthma exacerbations

Objectives	Endpoints
Other Secondary	
To evaluate the efficacy of FF/UMEC/VI compared with FF/VI	• Mean change from baseline in clinic FEV_1 at 3 hours post study treatment at Week 24 • Mean change from baseline in ACQ-7 total score at Week 24 • Mean change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Week 24 • Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over Weeks 21 to 24 (inclusive) of the treatment period.
To evaluate the safety of FF/UMEC/VI compared with FF/VI	• Incidence and type of adverse events (AEs) • Electrocardiogram (ECG) measurements • Vital signs • Clinical hematological and chemistry parameters
Other Objectives	
To evaluate other efficacy assessments of FF/UMEC/VI compared with FF/VI	• Mean change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period • Mean change from baseline in home daily trough FEV_1 over the first 24 weeks of the treatment period • Annualized rate of severe asthma exacerbations • Time to first severe asthma exacerbation • Time to first moderate/severe asthma exacerbation • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a

Objectives	Endpoints
	responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24 • Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24 • Mean change from baseline in SGRQ domain scores at Week 24 • Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24 • Mean change from baseline in E-RS domain scores over Weeks 21 to 24 (inclusive) of the treatment period • Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period • Mean change from baseline in the Asthma Quality of Life Questionnaire (AQLQ) total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline

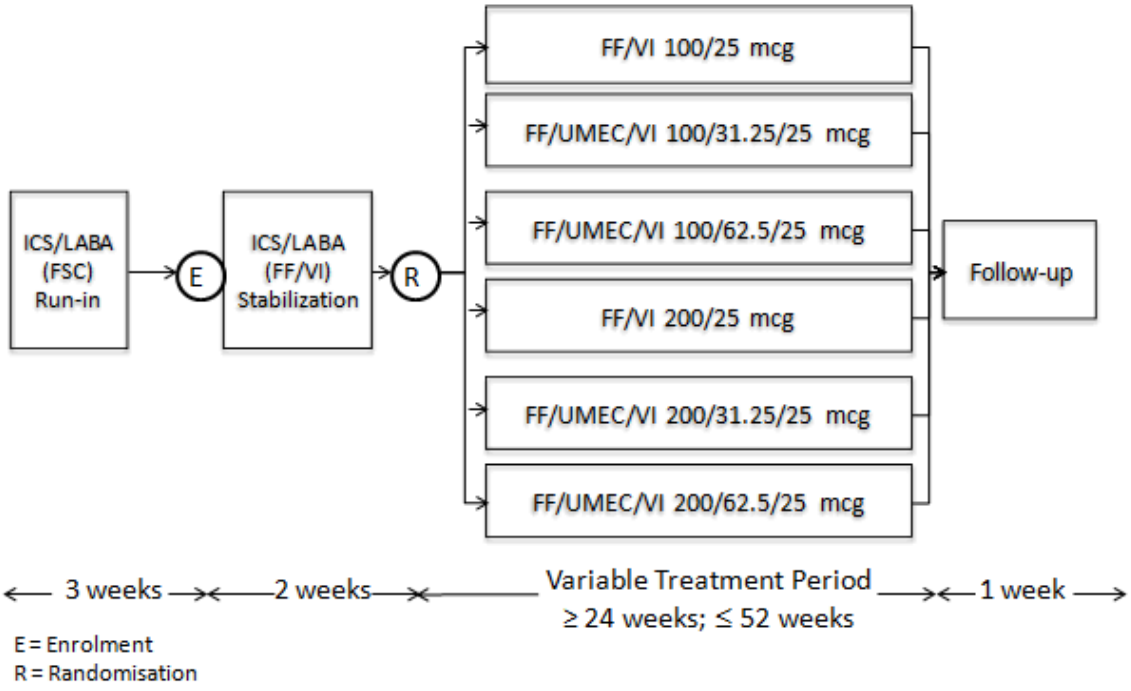
Objectives	Endpoints
	for the AQLQ total score at Week 24 • Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the first 24 weeks of the treatment period • Mean change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period • Mean change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period [1] • Mean change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period • Mean change from baseline in daily rescue medication use over the first 24 weeks of the treatment period • Unscheduled asthma-related healthcare resource utilization over the first 24 weeks of the treatment period
To evaluate the systemic exposure of FF, UMEC and VI following FF/UMEC/VI	Area Under the Curve (AUC(0-τ) [τ=24h]), Cmax
To collect blood samples for a genetics research study	To be described in a separate document

[1] Assessed using eDiary data (excluding E-RS total/domain scores and supplemental asthma questions).

4. STUDY DESIGN

4.1. Overall Design

This study employs a multi-centre, active-controlled, double-blind, parallel-group design. At the conclusion of the 3-week run-in period (Visit 2), all subjects who meet the pre-defined criteria will be enrolled to receive FF/VI (100/25 mcg via the ELLIPTA dry powder inhaler [DPI]) once a day, in the morning, during the 2-week stabilization period. At the conclusion of the stabilization period (Visit 3), all subjects who meet the pre-defined criteria will be randomised 1:1:1:1:1:1 to receive either FF/UMEC/VI (100/31.25/25; 100/62.5/25; 200/31.25/25; 200/62.5/25 mcg) or FF/VI (100/25; 200/25 mcg) via the ELLIPTA DPI once daily in the morning for the duration of the treatment period (see Section 4.2 for further details on study treatment assignment and duration).



Subjects who permanently discontinue study treatment are not required to withdraw from the study. Subjects who have permanently discontinued study treatment and have not withdrawn consent are encouraged to continue in the study and complete all remaining protocol specified clinic visits (see Section 5.6).

4.2. Treatment Arms and Duration

As the duration of the treatment period is variable (see Table 1 for details), eligible subjects will be requested to participate in the study for a minimum of approximately 32 weeks and a maximum of approximately 60 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, subjects will complete the 5 phases of the study described in Table 1:

Table 1 Study Phases

Phase	Phase Title	Duration	Description
1	Pre-screening	Between 1 and 14 days	Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) must be completed prior to initiating any Screening Visit (Visit 1) procedures. Subjects will continue treatment with their regular (i.e. pre-study) asthma medication(s) during the pre-screening period; however, medications that are prohibited within a specified time interval prior to Visit 1 are

Phase	Phase Title	Duration	Description
			defined in Section 6.9.2.
2	Screening / Run-in	3 weeks	Subjects who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 3 weeks to continue assessing the subject's eligibility for the study. Subjects will take the last dose of their regular (i.e. pre-study) ICS/LABA asthma medication ≥ 24 hours prior to Visit 1 (i.e. ≥ 24 hours prior to the Screening Visit). Subjects satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with fixed dose ICS/LABA (fluticasone/salmeterol [FSC], 250/50 mcg, via the DISKUS DPI) to take twice a day during the 3-week run-in period, and rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study. Those subjects that are not eligible to continue in the study at the end of the 3-week run-in period (Visit 2) will be deemed run-in failures (see Section 5.5).
3	Enrolment/Stabilization	2 weeks	Subjects will self-administer their last dose of run-in FSC treatment on the morning prior to Visit 2 (i.e. ≥ 24 hours prior to the Enrolment Visit). At Visit 2 (Enrolment), subjects who meet all the eligibility criteria will be provided with fixed dose ICS/LABA (fluticasone/vilanterol [FF/VI], 100/25 mcg, via the ELLIPTA DPI) to take once a day, in the morning, during the 2-week stabilization period. Those subjects that are not eligible to continue in the study at the end of the 2-week stabilization period (Visit 3) will be deemed stabilization failures (see Section 5.5).
4	Treatment	A minimum of 24 weeks; a	Subjects will self-administer their last dose of stabilization FF/VI treatment on the morning prior to Visit 3 (i.e. ≥ 24 hours prior to the Randomization Visit).

Phase	Phase Title	Duration	Description
		maximum of 52 weeks	At Visit 3 (Randomization), subjects who meet all of the randomization criteria will be randomized 1:1:1:1:1:1 to one of the following six double-blind study treatments during the treatment period (stratified by pre-study ICS treatment strength [mid, high]): • FF/UMEC/VI 100/62.5/25 mcg once daily (QD) • FF/UMEC/VI 200/62.5/25 mcg QD • FF/UMEC/VI 100/31.25/25 mcg QD • FF/UMEC/VI 200/31.25/25 mcg QD • FF/VI 100/25 mcg QD • FF/VI 200/25 mcg QD Study treatment will be administered via the ELLIPTA DPI in the morning. The duration of the treatment period is variable but will be a minimum of 24 weeks and a maximum of 52 weeks. In accordance with the protocol-defined visit schedule, subjects will have up to 6 on-treatment clinic visits scheduled at Visits 3, 4, 5, 6, 7 and 8/End of Study (EOS) (Weeks 0, 4, 12, 24, 36 and 52, respectively). The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. To determine when the final treatment/EOS visit will occur for each randomized subject in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a date henceforth referred to as the transition date will be communicated to

Phase	Phase Title	Duration	Description
			the study sites by GSK. GSK will communicate a *provisional* transition date to all study sites on an ongoing basis during the study, until a fixed *actual* transition date is communicated at least 20 weeks in advance of the selected date (unless extenuating circumstances dictate otherwise). The date selected by GSK as the actual transition date will always be more than 12 days prior to the study completion date. At the Investigator's discretion, subjects should be informed of the transition date (provisional and actual) on an ongoing basis during the study so that their expected final treatment/EOS visit can be planned using the provisional transition date and then confirmed once the actual transition date is known. Subjects who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit. After the actual transition date is communicated, subjects must adhere to their study visit schedule and complete a minimum of 24 weeks of study treatment. A subject's final treatment/EOS visit will be defined as follows: – Subjects whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at their Week 24 clinic

Phase	Phase Title	Duration	Description
			assessment visit. – Subjects who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time-windows). The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.
5	Safety Follow-up	See Description column for details	A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the subject completes all of the protocol-defined procedures for Visit 8/EOS or, if applicable, the Early Withdrawal visit. A subject will be considered to have completed the study upon completion of all assessments and procedures for Visit 8/EOS and including a successful follow-up contact/visit.

4.3. Type and Number of Subjects

Patients with inadequately controlled asthma (i.e. patients with an ACQ-6 score ≥1.5 prior to enrolment at Visit 2) despite treatment with maintenance asthma medication.

The total number of randomized subjects required is approximately 2250, with 375 subjects randomized to each of the 6 double-blind treatment arms (to ensure approximately 337 evaluable subjects per treatment arm; see Section 9.2.1). Randomization will be stratified by pre-study ICS treatment strength (mid, high) at screening to ensure treatment balance within each stratum.

4.4. Design Justification

This study will use a multicenter, randomized, double-blind, active-controlled, parallel-group design. This is a well-established design to evaluate the efficacy and safety of an investigational drug. A placebo arm is not included as it is not considered appropriate for patients with inadequately controlled asthma despite maintenance therapy. In addition, the comparison of interest is FF/UMEC/VI versus FF/VI for each UMEC dose. FF/UMEC and UMEC/VI treatment arms are not included as these are not fixed dose combinations that are currently available for asthma patients.

The aim of the study is to evaluate if patients with inadequately controlled asthma, despite treatment with ICS/LABA, can benefit from a once-daily fixed dose combination of FF/UMEC/VI. Eligible subjects must have the clinical need for daily asthma maintenance therapy, namely ICS/LABA, for at least 12 weeks prior to Screening. Subjects are required to wash-out their current asthma maintenance therapy and switch to FSC (250/50 mcg twice daily) treatment, administered via the DISKUS DPI, during the 3-week run-in period. The 3-week run-in period is necessary to standardize asthma maintenance therapy in all patients prior to the baseline collection period (i.e. the stabilization period). Subjects will take their last dose of FSC the morning prior to the Enrolment Visit (i.e. ≥ 24 hours prior to Visit 2). At Visit 2, all eligible subjects will be enrolled into the study to receive FF/VI (100/25 mcg QD) for 2 weeks during the stabilization period; at Visit 3 eligible subjects will be randomised to receive one of the possible six double-blind study treatments during the treatment period. The 2-week stabilization period is necessary in order to establish baseline symptoms for all subjects, on the same once-daily maintenance therapy, as well as to allow subjects to become accustomed to using the ELLIPTA DPI (having previously used the DISKUS DPI during the run-in period). Subjects will take their last dose of stabilization period FF/VI treatment the morning prior to commencing double-blind study treatment at Visit 3 (i.e. ≥ 24 hours prior to the Randomization Visit).

As this is not primarily a severe asthma exacerbation study, up to 52 weeks of data will be sufficient to demonstrate a robust and persistent treatment effect for a bronchodilator. A minimum treatment period of 24 weeks is considered to be of adequate duration in order to assess the efficacy of FF/UMEC/VI, compared to FF/VI, in terms of lung function and other efficacy endpoints. To allow evaluation of the effect of FF/UMEC/VI on non-lung function endpoints, including moderate/severe exacerbations, the data from the two FF/UMEC/VI arms for each fixed UMEC dose will be pooled and compared to

pooled data from the two FF/VI arms. The integrated analyses will provide a more precise overall estimate for the treatment effect size of the addition of UMEC to FF/VI and also allows us to determine the effect of adding UMEC to the current standard of care (which could be FF100/VI or FF200/VI). In this instance, pooling is considered similar to respiratory studies evaluating the effect of one medication in a separate inhaler added to the patient's existing therapy approach which isn't standardized.

A treatment period of up to 52 weeks is considered to be of suitable duration to collect asthma exacerbation data as well as to assess the safety of FF/UMEC/VI (given the extensive studies conducted in the mono- and dual-therapy programs for FF, UMEC, FF/VI, and UMEC/VI).

4.5. Dose Justification

The FF/UMEC/VI (100/31.25/25, 100/62.5/25, 200/31.25/25 and 200/62.5/25 mcg) doses were selected based on the doses licensed by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for FF/VI for the treatment of asthma, and data from GSK Phase IIb study 200699, a dose-ranging study that evaluated four doses of umeclidinium in combination with fluticasone furoate (100 mcg) over a 4-week treatment period, in reversible subjects with fixed airway obstruction. The primary endpoint was the change from baseline in trough FEV_1.

The 200699 data showed UMEC 62.5 mcg to be an effective dose; after 4 weeks of treatment in patients with a primary diagnosis of asthma, an increase in trough FEV1 of 136ml (milliliters) was observed in those subjects treated with FF/UMEC (100/62.5 mcg) compared to those subjects treated with FF (100 mcg) alone. However, study 200699 did not assess the UMEC 31.25 mcg dose, therefore, the efficacy and safety profile of this dose will be assessed in this study. No safety signal was identified with any of the UMEC doses (15.6, 62.5, 125 and 250 mcg) evaluated in the 200699 study.

4.6. Benefit: Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with GSK GW685698+GW642444+GSK573719 (FF/UMEC/VI) can be found in the Investigator's Brochure (IB). Marketed ICS/LABA products will be used for run-in (FSC), stabilization (FF/VI) and comparator (FF/VI) treatments. These products will be used in accordance with the product labels and further details on the experience with these products can be found in the Investigator Brochures and/or product labelling. The following section outlines the risk assessment and mitigation strategy for this protocol:

4.6.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GSK685698+GSK573719+GW642444]		
Cardiovascular effects of UMEC and VI	UMEC Cardiovascular effects are a potential class effect associated with anti-muscarinic therapies. In the UMEC/VI clinical development program in Chronic Obstructive Pulmonary Disease (COPD) patients, UMEC/VI was generally well tolerated. Overall, a low number of atrial arrhythmias were reported based on 12-lead ECGs, Holter ECGs, or AEs, of which some occurred with a higher incidence in active treatment groups compared to placebo. There was no additive effect with the combination over individual components. Few of these findings were reported as Serious Adverse Events (SAEs) and none were fatal. In a narrow* Major Adverse Cardiac Event (MACE) analysis, the incidence of non-fatal myocardial infarction (Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) of myocardial infarction and acute myocardial infarction) was low (<1%) across all treatment groups, although small imbalances in exposure adjusted frequency were observed between UMEC- and VI containing treatment groups when compared with placebo and tiotropium. There was no obvious dose relationship or additive effect from the combination. Whether this represents a true effect is difficult to determine due to the small numbers. During clinical studies in COPD (62.5 and 125mcg daily dose of UMEC) and in Healthy Volunteers (in the Thorough QT study, UMEC 500mcg daily dose), no effect was observed on heart rate, blood pressure or QT.	Mitigation strategy for UMEC and VI: - Exclusion criteria as specified in Section 5.2 of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per schedule in Section 7.1 . - Vital sign assessments (heart rate and blood pressure) as per schedule in Section 7.1 . - Cardiovascular AEs and Serious AEs (SAEs) will be captured on the electronic Case Report Form (eCRF) (see Section 12.4.3) - Protocol defined stopping criteria as per Section 5.6. -MACE analysis -Instream review of blinded data

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	VI In the FF/VI clinical development program in patients with COPD, the cardiovascular safety profile of VI and FF/VI was broadly consistent with the known pharmacology of LABAs in patients with COPD. VI at doses up to 100mcg in healthy subjects and subjects with asthma or COPD was not consistently associated with clinically relevant or statistically significant effects on blood pressure after either single or repeat dose administration. Data from Thorough QT (TQT) studies with FF, FF/VI and UMEC/VI suggest that, at the doses to be used in phase III studies, the closed triple (FF/UMEC/VI) is unlikely to cause clinically relevant effects on QTc[1]. No difference in QTcF[2] was observed between UMEC/VI 125/25mcg or UMEC 500mcg and placebo. UMEC/VI 500/100mcg increased QTcF on average by 8.2msec (milliseconds) (90% Confidence Intervals (CI): 6.2, 10.2) at 30 minutes (min) only. A lack of effect was demonstrated for QTcF with FF/VI 200/25mcg (for 7 days). At a supratherapeutic dose of FF/VI (800/100mcg for 7 days), the largest mean time-matched difference from placebo was 9.6 msec (90% CI: 7.2, 12.0) at 30 min only. *[1] QT interval corrected for heart rate* *[2] QT interval corrected for heart rate by Fridericia's formula*	
Anticholinergic effects (including constipation nausea, dry mouth, glaucoma, raised intraocular pressure and blurred vision, urinary retention)	In clinical studies in COPD, few anticholinergic effects were associated with UMEC; those observed included dry mouth, constipation and cough. Based on post-marketing experience dysgeusia has been added as an Adverse Drug Reaction (ADR) for inhaled UMEC and UMEC/VI. ICS has a similar class risk of glaucoma and elevated intraocular pressure (IOP); however, these effects occur by a different mechanism that is not	- Patients with known narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that, in the opinion of the Investigator, contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	expected to be synergistic or additive when FF is used in combination with UMEC.	- Review AEs/SAEs
Systemic ICS effects -Adrenal suppression -Cataracts & glaucoma -Reduced bone mineral density and associated fractures	No studies have shown a clinically relevant effect of FF/VI or FF on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), which assessed the effects of FF/VI 100/25 and 200/25 on serum cortisol and 24 hour urinary cortisol excretion, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. During clinical development of FF & FF/VI no events of Adrenal Suppression were reported. There has been no evidence for adrenal suppression based on post-marketing experience to date. In study HZA106839 (FF/VI, FF and fluticasone propionate (FP) in subjects with asthma), formal Ophthalmic assessments were conducted (including Lens Opacities Classification System III (LOCS III) evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline assessment. During studies in both subjects with asthma and COPD, no associated affect on ocular disorders was observed. Spontaneous data received to date does not alter the understanding of this risk. A decrease in bone mineral density and the risk of fractures is a class concern for any ICS-containing product for the treatment of COPD. In two replicate 12 month studies in the FF/VI clinical program, in a total of 3,255 patients with COPD, the incidence of bone fractures overall was low in all treatment groups, with a higher incidence in all FF/VI groups (2%) compared with the VI 25 mcg group (<1%). Although there were more	- Review AEs/SAEs - The occurrence of bone fractures will be recorded in the eCRF.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	fractures in the FF/VI groups compared with the VI 25 mcg group, fractures typically associated with corticosteroid use (e.g., spinal compression/thoracolumbar vertebral fractures, hip and acetabular fractures) occurred in <1% of the FF/VI and VI treatment arms. In an integrated analysis of 11 studies in asthma with FF/VI (7,034 patients) and 10 studies in asthma with FF (6,219), the incidence of fractures with FF/VI and FF was ≤1%, and usually associated with trauma.	
Pneumonia	While ICS use is a recognised risk for pneumonia in patients with COPD. A clear causal relationship between inhaled corticosteroid use and pneumonia in subjects with asthma has not been established. In an 18 study integration in the FF/VI asthma program, the incidence of pneumonia (adjusted for exposure) observed with FF/VI 100/25 and FF 100 (8.5/1000 patient years and 9.6/1000 patient years, respectively) was similar to that seen with placebo (9.3/1000 patient years). A higher incidence in the FF/VI 200/25 and FF 200 arms were observed (18.3/1000 patient years and 23.6/1000 patient years, respectively). However, the 95% CIs were wide and overlapped across all treatment groups, including placebo. Few of the pneumonia events led to hospitalisation with either strength, and there were no observed differences in the incidence of serious events between the two treatment strengths. The risk of pneumonia in asthma patients is very low and is consistent with the risk of other ICS. <u>Pneumonia experience with UMEC</u> In the All Clinical Studies grouping, the incidence of on-treatment AEs in the Pneumonia and lower respiratory tract infection (LRTI) adverse events of special interest (AESI) category with UMEC 62.5 mcg (1%; 34.6/1000SY)	Exclusion criteria: - Immune suppression (e.g., Human Immunodeficiency Virus [HIV], Lupus) or other risk factors for pneumonia (e.g.,neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis). -Subjects at potentially high risk (e.g., very low body mass index [BMI] or severely malnourished) will only be included at the discretion of the Investigator. Medical history will also be taken for pneumonia in previous 12 months, including recording of any episodes resulting in hospitalisation. The occurrence of pneumonia will be recorded in the eCRF.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	was similar to placebo (1%; 34.8/1000SY) and lower than the incidence reported in the UMEC 125 mcg (3%; 72.6/1000SY). A higher incidence of AEs in the Pneumonia AESI category was reported for UMEC 125 mcg (2%; 37.4/1000SY) compared with UMEC 62.5 mcg (<1%; 19.8/1000SY) and placebo (<1%; 10.7/1000SY). The proportion of subjects with SAEs in the Pneumonia AESI category was similar between both UMEC treatment groups, UMEC 62.5 mcg (<1%; 4.9/1000SY) and UMEC 125 mcg (<1%; 17.6/1000SY) and placebo (<1%; 10.7/1000SY).	Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a subject has a suspected pneumonia. All reports of pneumonia (radiographically confirmed and unconfirmed) must be reported as an AE or SAE, if applicable Instream review of blinded data. Review of AESI relevant for pneumonia using pre-specified MedDRA preferred terms. AE terms relating to other Lower Respiratory Tract Infections (excluding pneumonia) will also be reviewed.
Hypersensitivity	There have been post-marketing reports of hypersensitivity reactions with FF/VI and UMEC/VI, including anaphylaxis, angioedema, rash, and urticaria. The formulation also contains lactose.	Subjects with a history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate are excluded from participation in this study (Section 5.2). -Review AEs/SAEs
Paradoxical bronchospasm	Rare reports of paradoxical bronchospasm (which may be life threatening) with other inhalational products have been reported. There have been rare post-marketing reports of paradoxical bronchospasm with FF/VI and UMEC/VI.	Patients will undergo regular medical assessments during clinical studies. -Review AEs/SAEs
Pregnancy and lactation	There are no data from the use of FF/UMEC/VI in pregnant women.	Females who are pregnant or breast-

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	There has been limited pregnancy exposure to FF and FF/VI in humans. Animal studies have shown reproductive toxicity after administration of corticosteroids and beta2-agonists. There is a limited amount of data from the use of umeclidinium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is limited information on the excretion of FF or VI or their metabolites in human milk. However, other corticosteroids and beta2-agonists are detected in human milk. It is unknown whether umeclidinium is excreted in human milk. The excretion of FF/UMEC/VI in breast milk has not been evaluated. A risk to breastfed newborns/infants cannot be excluded.	feeding are not eligible for participating in the study. Females of child-bearing potential will need to follow the contraceptive requirements that are specified in Appendix 5.

The risks for FF/VI and FSC are recognised pharmacological class effects associated with ICS and LABA therapy. The experience with these individual products is provided in the respective Investigator Brochures and/or product labelling. Some of the experience with FF/VI is described in the table above, as this provides relevant background information for FF/UMEC/VI.

4.6.2. Benefit Assessment

The addition of UMEC to FF/VI in asthma has the potential to improve lung function, reduce moderate/severe exacerbations and improve quality of life in patients whose asthma is inadequately controlled on ICS/LABA alone. Current asthma treatment guidelines recommend the addition of a LAMA (tiotropium) for patients that are uncontrolled on ICS/LABA (GINA 2016 Steps 4 and 5); the availability of the FF/UMEC/VI combination would therefore be consistent with this approach. The combination in a closed triple combination would provide the convenience of once daily dosing and reduce the need for multiple inhalers. Furthermore, the availability of two doses of FF would allow the prescriber to select an appropriate inhaled corticosteroid dose based on the severity of asthma.

4.6.3. Overall Benefit: Risk Conclusion

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

The current experience with FF, UMEC and VI and the lack of significant safety concerns relevant to the asthma population provides reassurance that the potential risks associated with the known pharmacology of these compounds is offset by the potential significant benefits that are afforded to patients inadequately controlled on ICS/LABA therapy.

The ICS/LABAs used as run-in (FSC) and stabilization/comparator arms (FF/VI) are both marketed for the treatment of asthma and have favourable benefit-risk profiles.

5. 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 IB.

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.

In order to confirm eligibility, a review of each subject's medical records must be performed prior to a subject entering the run-in period. To be enrolled into the study, subjects will be required to meet the additional enrolment criteria (see Section 5.3); to be

randomised into the study, subjects will be required to meet the additional randomization criteria (see Section 5.4).

5.1. Inclusion Criteria

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

AGE
1. **18 years of age or older** at the time of signing the informed consent.

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
2. **Diagnosis:** Subjects with a diagnosis of asthma as defined by the National Institutes of Health [NIH 2007] at least one year prior to Visit 0. 3. **Symptomatic:** Subjects with inadequately controlled asthma (ACQ-6 score ≥1.5) despite ICS/LABA maintenance therapy at Visit 1. 4. **Asthma Control:** *Note: please refer to the SRM for guidance on the following:* In the 1 year prior to Visit 1: • A documented healthcare contact for acute asthma symptoms OR • A documented temporary change in asthma therapy for acute asthma symptoms, according to a pre-specified asthma action plan (or equivalent) 5. **Current Asthma Maintenance Therapy**: Subjects are eligible if they have required daily ICS/LABA for at least 12 weeks prior to Visit 0 with no changes to maintenance asthma medications during the 6 weeks immediately prior to Visit 0 (including no changes to a stable total dose of ICS of >250 mcg/day fluticasone proprionate [FP, or equivalent]). Examples of acceptable doses of commonly prescribed ICS medication are provided in the GINA guidelines [GINA 2016], [BTS/SIGN 2016], [Japanese guidelines for adult asthma 2017]. Dosing regimen (once or twice daily to equal the total daily dose) should be restricted to the current local product labels/treatment guidelines. 6. **Spirometry:** A best pre-bronchodilator morning (AM) FEV_1 ≥30% and <85% of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer 2012]. 7. **Reversibility of Disease:** airway reversibility defined as ≥12% and ≥200 mL increase in FEV_1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1. *Note: If the subject does not meet the above reversibility criteria at Visit 1 then the reversibility assessment may be repeated once within 7 days of Visit 1 if either criteria a) or b) are met:*

a) ≥9% increase in FEV_1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.

b) *Documented evidence of a reversibility assessment within 1 year prior to Visit 1 which demonstrated a post-bronchodilator increase in FEV_1 of ≥12% and ≥200 mL.*

Should the subject successfully demonstrate airway reversibility (defined as ≥12% and ≥200 mL increase in FEV_1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol) at the second attempt then, provided that all other eligibility criteria assessed at Visit 1 are met, the subject may enter the 3-week run-in period (see Section 7.3.4.1).

8. **Short-Acting β_2 Agonists (SABAs):** All subjects must be able to replace their current SABA inhaler with albuterol/salbutamol aerosol inhaler at Visit 1 as needed for the duration of the study. Subjects must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

SEX

9. **Male or Eligible Female**, defined as having documentation of non-reproductive potential or reproductive potential as follows:

   A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test), not lactating, is not planning on becoming pregnant during the study and at least one of the following conditions applies:

   a. Non-reproductive potential defined as:

   - Pre-menopausal females with one of the following:
     - Documented tubal ligation
     - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
     - Hysterectomy
     - Documented Bilateral Oophorectomy
   - Postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile (e.g., age appropriate, >45 years, in the absence of hormone replacement therapy). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory. Females under 60 years of age, who are on hormone replacement therapy (HRT) and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following

confirmation of their post-menopausal status, subjects can resume use of HRT during the study without use of a highly effective method to avoid pregnancy.

b. Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Appendix 5) from the screening visit until after the last dose of study medication and completion of the follow-up visit.

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

INFORMED CONSENT
10. **Informed Consent:** Able to give written informed consent prior to participation in the study, which will include the ability to comply with the requirements and restrictions listed in the consent form and in this protocol. Subjects must be able to read, comprehend, and write at a level sufficient to complete study related materials.

5.2. Exclusion Criteria

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

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

CONCURRENT CONDITIONS/MEDICAL HISTORY (INCLUDES LIVER FUNCTION AND QTc INTERVAL)
1. **Pneumonia:** Chest X-ray documented pneumonia in the 6 weeks prior to Visit 1. 2. **Asthma Exacerbation:** Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1. *Note: Subjects requiring a temporary change in asthma therapy (e.g., oral corticosteroids or increased dose of ICS) to treat an exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's discretion, the subject's condition is stable after they have resumed their pre-exacerbation maintenance asthma therapy (without modification) and they are considered appropriate for enrolment into this study of up to 12 months' duration.* **3. Chronic Obstructive Pulmonary Disease:** Subjects with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD 2016) guidelines, including all of the following: • History of exposure to risk factors (i.e., especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels). For personal tobacco use, see exclusion criterion number 14: **Tobacco Use**;

AND

- A post-albuterol/salbutamol FEV_1/Forced Vital Capacity (FVC) ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≤70% of predicted normal values;

  AND

- Onset of disease ≥40 years of age

4. **Concurrent respiratory disorders**: Subjects with current evidence of pneumonia, active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases or abnormalities other than asthma.
5. **Risk Factors for Pneumonia**: immune suppression (e.g., HIV, Lupus) or other risk factors for pneumonia (e.g., neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis).
   Patients at potentially high risk (e.g., very low BMI, severely malnourished, or very low FEV_1) will only be included at the discretion of the Investigator.
6. **Other diseases/abnormalities**: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
7. **Unstable liver disease** as defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, esophageal or gastric varices or persistent jaundice, cirrhosis, known biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones). **Note:** *Chronic stable hepatitis B and C are acceptable if the subject otherwise meets entry criteria*
8. **Clinically significant ECG abnormality:** Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening. The Investigator will determine the clinical significance of each abnormal ECG finding in relation to the subject's medical history and exclude subjects who would be at undue risk by participating in the trial. An abnormal and clinically significant finding is defined as a 12-lead tracing that is interpreted as, but not limited to, any of the following:
   - Atrial Fibrillation (AF) with rapid ventricular rate >120 beats per minute (BPM);
   - Sustained or nonsustained ventricular tachycardia (VT);
   - Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted);
   - QTcF ≥500 msec in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥120 msec
9. **Unstable or life threatening cardiac disease:** subjects with any of the following at Screening (Visit 1) would be excluded:
   - Myocardial infarction or unstable angina in the last 6 months
   - Unstable or life threatening cardiac arrhythmia requiring intervention in the

last 3 months

- New York Heart Association (NYHA) Class IV Heart failure [American Heart Association 2016]

10. **Antimuscarinic effects:** Subjects with a medical condition such as narrow-angle glaucoma, urinary retention, prostatic hypertrophy or bladder neck obstruction should only be included if in the opinion of the Investigator the benefit outweighs the risk and that the condition would not contraindicate study participation.
11. **Cancer**: Subjects with carcinoma that has not been in complete remission for at least 5 years. Subjects who have had carcinoma *in situ* of the cervix, squamous cell carcinoma and basal cell carcinoma of the skin would not be excluded based on the 5 year waiting period if the subject has been considered cured by treatment.
12. **Questionable validity of consent**: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation or other conditions that will limit the validity of informed consent to participate in the study.

CONCOMITANT MEDICATIONS/TREATMENTS

13. **Medication prior to spirometry**: Subjects who are medically unable to withhold their albuterol/salbutamol for the 6-hour period required prior to spirometry testing at each study visit.

RELEVANT HABITS

14. **Tobacco Use:** Subjects who are:
    - Current smokers (defined as subjects who have used inhaled tobacco products within the 12 months prior to Visit 1 [i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco]).
    - Former smokers with a smoking history of ≥10 pack years (e.g., ≥20 cigarettes/day for 10 years).

    Note: Refer to the SRM for the formula for calculating pack years.
15. **Drug/alcohol abuse**: Subjects with a known or suspected history of alcohol or drug abuse within the last 2 years.

CONTRAINDICATIONS

16. **Allergy or Hypersensitivity:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta$_2$-agonist, lactose/milk protein or magnesium stearate.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA

17. **Non-compliance**: Subjects at risk of non-compliance, or unable to comply with the study procedures. Any infirmity, disability, or geographic location that would limit compliance for scheduled visits.
18. **Affiliation with Investigator site**: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or study site, or immediate family members of the aforementioned that is involved with this study.

19. **Inability to read**: In the opinion of the Investigator, any subject who is unable to read and/or would not be able to complete study related materials.

5.3. Enrolment Criteria

Those subjects who meet the enrolment criteria will be enrolled into the study until the target of approximately 2250 randomised subjects is reached.

At the end of the run-in period, study subjects must fulfil the following additional criteria in order to be enrolled in the study and enter the 2-week stabilization period:

5.3.1. Inclusion Criteria for Enrolment

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
1. **Inadequately controlled asthma:** Subjects with inadequately controlled asthma (ACQ-6 score ≥1.5) at Visit 2.
2. **Percent-predicted FEV_1:** A best pre-bronchodilator morning (AM) FEV_1 ≥30% and <90% of the predicted normal value at Visit 2. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer 2012].

CONCURRENT CONDITIONS/MEDICAL HISTORY
3. **Liver function tests at Visit 1**: • alanine aminotransferase (ALT) <2 x upper limit of normal (ULN) • alkaline phosphatase ≤1.5 x ULN • bilirubin ≤1.5 x ULN (isolated bilirubin >1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

eDIARY
4. **Compliance** with completion of the Daily eDiary reporting defined as completion of all questions/assessments on ≥4 of the last 7 days during the run-in period.

5.3.2. Exclusion Criteria for Enrolment

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. **Respiratory Infection:** 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.
2. **Severe asthma exacerbation:** Evidence of a severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days[1] or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

[1] *For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.*

CONCOMITANT MEDICATIONS/TREATMENTS
3. **Asthma medication:** Changes in asthma medication (excluding run-in medication and albuterol/salbutamol inhalation aerosol provided at Visit 1).

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
4. **Laboratory test abnormalities:** Evidence of clinically significant abnormal laboratory tests during screening or run-in which are still abnormal upon repeat analysis and are not believed to be due to disease(s) present. Each Investigator will use his/her own discretion in determining the clinical significance of the abnormality.

5.4. Randomization Criteria

Those subjects who meet the randomization criteria will be randomised into the study until the target of approximately 2250 randomised subjects is reached.

At the end of the stabilization period, study subjects must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

5.4.1. Inclusion Criteria for Randomization

eDIARY
1. **Compliance** with completion of the Daily eDiary reporting defined as completion of all questions/assessments on ≥4 of the last 7 days during the stabilization period.

5.4.2. Exclusion Criteria for Randomization

CONCURRENT CONDITIONS/MEDICAL HISTORY
1. **Respiratory Infection:** Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the stabilization 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. 2. **Severe asthma exacerbation:** Evidence of a severe exacerbation during enrolment or the stabilization period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days[1] or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. [1] *For subjects on maintenance systemic corticosteroids, at least double the existing maintenance dose for at least 3 days is required.*
CONCOMITANT MEDICATIONS/TREATMENTS
3. **Asthma medication:** Changes in asthma medication (excluding stabilization period medication provided at Visit 2 and albuterol/salbutamol inhalation aerosol provided at

Visit 1).

5.5. Pre-Screening/Screening/Run-in Failures

A subject will be assigned a subject number at the time the informed consent is signed.

The study interactive response technology (IRT) system (RAMOS NG) will be contacted to report pre-screen failures. The following information will be collected in the eCRF for subjects who are pre-screen failures:

- Date of informed consent form (ICF) signature
- Demographic information including race, age and gender
- Subject number
- Serious Adverse Event information only for any SAE considered as related to study participation
- Investigator signature page

For the purposes of this study pre-screen failures, screening failures, run-in failures and stabilization failures will be defined as follows:

- **Pre-screening failures:** those subjects that sign the informed consent document but do not have a Visit 1 (Screening) procedure.
- **Screening failures:** those subjects that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period.

  A subject who completes Visit 1 assessments and is dispensed the study medication for the run-in period is considered to have entered the run-in period.
- **Run-in failures:** those subjects that enter the run-in period but do not subsequently enter the stabilization period.

  Any subject who completes the run-in period and then meets the eligibility criteria and is dispensed the stabilization period study medication at Visit 2 is considered to have entered the stabilization period.
- **Stabilization failures:** those enrolled subjects that enter the stabilization period but are not subsequently randomised at Visit 3.

RAMOS NG will be contacted to report pre-screening, screening, run-in and stabilization failures.

In order to ensure transparent reporting of screen/run-in failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen/run-in/stabilization failure information is required including demography, screen/run-in/stabilization failure details, eligibility criteria, and any SAEs (see Section 7.5.1.7 and Appendix 4). Further details are provided in the study-specific eCRF completion guidelines document.

Re-screening of subjects will be permitted; however, advance written approval to proceed with re-screening a subject must be obtained from the Medical Monitor (for contact details, see the medical monitor/Sponsor Information Page at the beginning of this protocol).

5.6. Withdrawal/Stopping Criteria

5.6.1. Withdrawal from Study Treatment

Subjects who withdraw from double-blind study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the Safety Follow-up assessments (Section 7.1; refer to the SRM for further details). If this is not possible, the Investigator must encourage the subject to participate in as much of the study as they are willing (or able) to.

A subject may be withdrawn from study treatment at any time. A reason for premature discontinuation of study treatment (e.g., AE, lack of efficacy [including acute moderate or severe asthma exacerbation], protocol deviation, Investigator discretion, consent withdrawn etc.) must be captured in the eCRF.

A subject must be withdrawn from study treatment if any of the following stopping criteria are met:

- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria (see Section 5.6.3 and Appendix 2)
- QTc: Meets any of the protocol-defined stopping criteria (see Section 5.6.4)
- Pregnancy: Positive pregnancy test (see Section 7.5.3 and Appendix 5)

5.6.2. Withdrawal from the Study

A subject may withdraw from the study at any time at his/her own request; if a subject withdraws from the study, he/she may request destruction of any samples taken, and the Investigator must document this in the site study records.

A reason for the withdrawal from the study must be captured in the eCRF.

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".

In the event of early withdrawal from the study, every effort should be made to have the subject to return to the clinic for an Early Withdrawal Visit and Safety Follow-up, and to return all study related materials. Assessments to be performed during the Early Withdrawal Visit and the Safety Follow-up contact are described in the Time and Events table (Section 7.1).

5.6.3. Liver Chemistry Stopping Criteria

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

Liver chemistry stopping criteria 1-5 are defined in Appendix 2.

5.6.3.1. Study Treatment Restart or Rechallenge

Study treatment restart or rechallenge after liver chemistry stopping criteria are met by any subject participating in this study is not allowed.

5.6.4. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 7.5.6.

- The QT interval corrected for heart rate by Fredericia's formula (QTcF) *must* be used for *each individual subject* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted for the duration of the study.
  - *QTcF* must continue to be used for all subjects *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception.
- The QTcF should be based on single or averaged QTcF values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period.
- For this study, the following QTc stopping criteria will apply:
  - QTcF>500 msec or uncorrected QT>600 msec
  - Bundle branch block: QTcF≥ 530 msec
  - Change from baseline: QTcF> 60msec

5.7. Subject and Study Completion

The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date.

To determine when the final treatment/EOS visit will occur for each randomized subject in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a date henceforth referred to as the transition date will be communicated to the study sites by GSK. GSK will communicate a *provisional* transition date to all study sites on an ongoing basis during the study, until a fixed *actual* transition date is communicated at least 20 weeks in advance of the selected date (unless extenuating circumstances dictate otherwise). The date selected by GSK as the actual transition date will always be more than 12 days prior to the study completion date. At the Investigator's discretion, subjects should be informed of the transition date (provisional and actual) on an ongoing basis during the study so that their expected final treatment/EOS visit can be planned using the provisional transition date and then confirmed once the actual transition date is known.

Subjects who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit.

After the actual transition date is communicated, subjects must adhere to their study visit schedule and complete a minimum of 24 weeks of study treatment. A subject's final treatment/EOS visit will be defined as follows:

- Subjects whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at their Week 24 clinic assessment visit.
- Subjects who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time-windows).

The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.

A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the subject completes all of the protocol-defined procedures for Visit 8/EOS or, if applicable, the Early Withdrawal Visit. A subject will be considered to have completed the study upon completion of all assessments and procedures for Visit 8/EOS and including a successful follow-up contact/visit.

6. STUDY TREATMENT

6.1. 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.

The DISKUS device will be used during the 3-week run-in period of the study. The DISKUS is a plastic inhalation delivery system containing a single-foil blister strip of a powder formulation of FSC intended for oral inhalation only. Each blister on the single-foil strip within the device contains 250 mcg of microfine FP and 72.5 mcg of microfine salmeterol xinafoate salt, equivalent to 50 mcg of salmeterol base, in 12.5 mg of formulation containing lactose (see Table 2). Each blister contains 1 complete dose of both medications. FSC will be sourced from local commercial stock. If not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements.

Table 2 Description of FSC Inhalation Powder in DISKUS

Formulation	Single strip FP and salmeterol blended with lactose
Dosage Form	DPI with 60 doses (1 strip with 60 blisters)
Unit Dose Strengths	250 mcg FP and 50 mcg salmeterol per blister
Physical description	Dry white powder
Route of Administration	Inhaled

The ELLIPTA device will be used during the stabilization period and the treatment period. The ELLIPTA DPI is a moulded plastic two-sided device that can hold two individual blister strips. Descriptions of the study treatments administered via the ELLIPTA are provided in Table 3.

Table 3 Description of Study Treatment Inhalation Powder in ELLIPTA

FF/UMEC/VI	First strip	Second strip
	FF blended with lactose	UMEC and VI blended with lactose and magnesium stearate
Dosage Form	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100 or 200 mcg per blister	UMEC 31.25 or 62.5 mcg per blister, VI 25 mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	
	First strip	Second strip
FF/VI	FF blended with lactose	VI blended with lactose and magnesium stearate
Dosage Form	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	100 or 200 mcg per blister	25 mcg per blister
Physical description	Dry white powder	Dry white powder
Route of Administration	Inhaled	

Each subject will be instructed on the proper use of the ELLIPTA and will inhale once from the ELLIPTA each morning for the duration of the 2-week stabilization period and the subsequent treatment period.

Subjects will self-administer their first dose of stabilization-period study treatment (FF/VI 100/25 mcg) in the clinic during the enrolment visit (Visit 2) and will continue to administer FF/VI at approximately the same time each morning for the duration of the stabilization period.

At Visit 3, the stabilization period ELLIPTA device will be collected from all subjects and an ELLIPTA device containing one of the double-blind study treatments (see Section 6.2) will be provided; subjects will self-administer their first dose of double-blind study treatment in the clinic during Visit 3 and will continue to administer double-blind study treatment at approximately the same time each morning for the duration of the treatment period. Subjects will take their last dose of study treatment in the clinic during Visit 8/EOS (or at the Early Withdrawal Visit, if applicable) and a safety follow-up will be conducted approximately one week later.

On the morning of all study clinic visits after Visit 1 (i.e. the day of Visit 2 onwards), subjects will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel.

Albuterol/salbutamol via metered-dose inhaler (MDI) will be issued for reversibility testing at Visit 1. An albuterol/salbutamol MDI for as needed (prn) use throughout the study will be provided starting at Visit 1; at the Investigator's discretion, more than one MDI may be provided at any one time. Albuterol/salbutamol will be sourced from local commercial stock. If not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements.

Ipratropium via MDI will be issued for reversibility testing at Visit 2. Ipratropium will be sourced from local commercial stock. The contents of the label will be in accordance with all applicable regulatory requirements.

At the Investigator's discretion, provision will be made from Visit 1[1] onwards for subjects to temporarily receive inhaled fluticasone propionate (FP) to treat the symptoms of a moderate asthma exacerbation (see Section 6.9.1.1 and Section 7.3.6.1). Treatment start and stop dates will be recorded in the eCRF.
[1]*Note: Should the subject use the provided FP prior to randomization at Visit 3, the enrolment or randomization concomitant medication exclusion criteria would be met (see Section 5.3.2 and Section 5.4.2).*

FP will be sourced from local commercial stock; if not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements. A record of the number of FP-containing inhalers dispensed to each subject must be maintained and reconciled with study treatment records.

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. Notify the monitor of any unintentional occupational exposure. A Material Safety Data Sheet (MSDS) describing the occupational hazards and recommended handling precautions will be provided to site staff if required by local laws or will otherwise be available from GSK upon request.

Study treatment must be stored in a secure area under the appropriate physical conditions for the product. Access to the investigational product will be limited to the Investigator and authorized site staff. Investigational product must be dispensed to or administered by only those subjects enrolled in the study and in accordance with the protocol.

6.1.1. Study Treatment, albuterol/salbutamol, ipratropium and FP Return

All used and unused study treatment, albuterol/salbutamol, ipratropium and FP will be returned to GSK at the end of the study to be available for disposal. In some instances for sites outside the US, study supplies will be disposed of locally either by the site, the country medical department or third-party vendor. Detailed instructions for the return of the study drug can be found in the SRM.

If any DISKUS or ELLIPTA fails to function properly, the subject should return to the clinic as soon as possible to obtain a new inhaler. The site will use the IRT system (RAMOS NG) to obtain a new treatment pack number for the subject and dispense a new study treatment kit from the site's study treatment supply as instructed by the IRT system.

In addition, any DPI or MDI that fails to function properly must be identified and returned to GSK for testing. Details of the failure will be documented in the eCRF.

6.2. Treatment Assignment

Subjects will be assigned to study treatment in accordance with the randomization schedule. The randomization code will be generated by GSK using a validated computerized system. Subjects will be randomized using an IRT system (RAMOS NG). The study will use central-based randomization to allocate treatments(see Appendix 7 for country-specific requirements). Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study.

Following the 2-week stabilization period and subject to satisfying all eligibility criteria, subjects will be stratified by pre-study ICS treatment dosage strength (mid, high) at screening and randomized 1:1:1:1:1:1 to one of the following six double-blind treatments for the duration of the treatment period:

- FF/UMEC/VI 100/62.5/25 mcg QD
- FF/UMEC/VI 200/62.5/25 mcg QD
- FF/UMEC/VI 100/31.25/25 mcg QD
- FF/UMEC/VI 200/31.25/25 mcg QD
- FF/VI 100/25 mcg QD
- FF/VI 200/25 mcg QD

The duration of double-blind treatment for each subject is a minimum of 24 weeks and a maximum of 52 weeks (see Section 4.2); on the morning of each scheduled clinic study visit, subjects will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. Study treatment will be taken at the clinic at approximately the same time of day as taken at the Enrolment Visit (Visit 2). On the other days during the treatment period (i.e. "non-clinic days"), subjects will be instructed to take their study treatment each morning at approximately the same time. Each Investigator will be provided with sufficient supplies to conduct the trial. Additional

treatment packs will be supplied as needed to the sites. Details of how to use the IRT system (RAMOS NG) to randomize subjects and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IRT manual and SRM.

6.3. Blinding

This will be a double-blind 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 an 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. Subjects will not be withdrawn from the study.

6.4. Packaging and Labeling

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

6.5. Preparation/Handling/Storage/Accountability

- Only subjects enrolled in the study may receive study treatment and only authorized site staff may supply 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 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.

6.6. Compliance with Study Treatment Administration

When subjects are dosed at the study site, they will receive study treatment under medical supervision. The date and time of each dose administered in the clinic will be recorded in the eCRF. The dose of study treatment and study subject identification will be confirmed at the time of dosing by a member of the study site staff.

At scheduled clinic visits, subject compliance with study treatment administration since the previous scheduled clinic visit will be assessed by recording the number of doses remaining in the DISKUS or ELLIPTA, as applicable, in the eCRF (see the SRM for details), by reviewing the eDiary (see Section 7.3.5) and by querying the subject, as necessary. Subjects should be ≥80% to ≤120% compliant on taking study treatment between each pair of scheduled and consecutive on-treatment clinic visits. Subjects who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the subject's source document.

When subjects self-administer study treatment(s) at home (i.e. not at the study site), compliance with study treatment administration should be monitored by the Investigator (or designee) by reviewing the transmitted eDiary data via the vendor-provided portal (see Section 7.3.5); subjects should be immediately contacted for re-education on treatment compliance if non-compliance (as assessed by the Investigator or designee) is observed. This re-education should be documented in the subject's source document.

A record of the number of DISKUSs and ELLIPTAs dispensed to each subject must be maintained and reconciled with study treatment and compliance records. Study treatment start and stop dates will be recorded in the eCRF.

6.7. Treatment of Study Treatment Overdose

An overdose is defined as a dose greater than the total doses described above which results in clinical signs and symptoms. These should be recorded by the Investigator on the AE/SAE pages. In the event of an overdose of study treatment, the Investigator should use clinical judgment in treating the overdose and contact the GSK medical monitor.

GSK is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator is advised to refer to the relevant document(s) for detailed

information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by GSK.

6.8. Treatment after the End of the Study

Subjects will not receive any additional treatment from GSK after completion of the study because other treatment options are available.

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.

6.9. Concomitant Medications and Non-Drug Therapies

All asthma medications used within approximately 6 weeks prior to pre-screening (Visit 0) and during the study (including the post-treatment period) should be recorded in the eCRF.

All non-asthma medications taken during the study (after randomization including post-treatment) and any changes to concomitant medications will be recorded in the eCRF. *Note: Study provided albuterol/salbutamol and ipratropium should not be recorded in the eCRF; however non-study supplied albuterol/salbutamol or ipratropium will be recorded in the eCRF. The use of study provided and non-study provided FP and additional asthma medications added temporarily for moderate asthma exacerbations will be recorded in the eCRF.*

The minimum requirement is that the drug name, dose, route and the dates of administration are to be recorded.

Medications initiated after completion of the assessments at Visit 8/EOS or the Early Withdrawal Visit will not be recorded in the eCRF unless taken to treat an AE or asthma exacerbation. Detailed information of permitted and prohibited medications is included in the SRM for your reference. Subjects who have completed the Early Withdrawal Visit are allowed to use any medications prescribed by the Investigator or primary care physician.

6.9.1. Permitted Medications and Non-Drug Therapies

6.9.1.1. Permitted Asthma Medications

In addition to study treatment, the following medications are permitted during this study:

- Study-provided albuterol/salbutamol will be dispensed at Visit 1 for use as relief medication throughout the duration of the study. Subjects must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.
- Systemic corticosteroids (≤5 milligrams (mg)/day of prednisone [or an equivalent dose of an alternative systemic corticosteroid]) will be permitted provided that treatment was initiated at least 12 weeks prior to Visit 1, remains stable for the 8

weeks prior to Visit 1 and the subject remains in the maintenance phase (i.e., it is not weaned) throughout the study (the only exception being the treatment of moderate/severe asthma exacerbations [see below]).

- Anti-immunoglobulin E (IgE) (e.g. omalizumab) treatment will be permitted provided that treatment was initiated at least 16 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study.
- Anti-interleukin (IL)-5 (e.g. mepolizumab) treatment will be permitted provided that treatment was initiated at least 16 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study.

Temporary additions in medications are permitted for the treatment of moderate asthma exacerbations (see Section 7.3.6.1) at the Investigator's/treating physician's discretion. Asthma exacerbations should be treated in line with national and international recommendations and local medical standards. Asthma medications permitted on a temporary basis to treat a moderate asthma exacerbation include but are not limited to the following (the Medical Monitor may be contacted for additional guidance, see the medical monitor/Sponsor Information Page):

- An increase in ICS dose (including but not limited to the use of study-provided FP which may be used by the subject at a total daily dose deemed appropriate by the Investigator/treating physician).
- Systemic corticosteroids (tablets, suspension or injection) for no more than 2 days (or an increase in systemic corticosteroid dose for those subjects receiving maintenance systemic corticosteroids for no more than 2 days).
- An Investigator-advised change in SABA use (i.e., routinely scheduled versus as needed use).
- Leukotriene receptor antagonists (LTRAs) and leukotriene modifiers.
- Oral theophylline.
- By definition, a severe asthma exacerbation will be treated with systemic corticosteroid (tablets, suspension or injection) for at least 3 consecutive days (or at least double the existing maintenance dose of systemic corticosteroid, if applicable, for at least 3 consecutive days). See Section 7.3.6.2.

6.9.1.2. Permitted Non-Asthma Medications

The following medications are permitted during this study:

- Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines [including ocular and intranasal], cromolyn, nedocromil, nasal decongestants)

  Note: Use of these medications should be captured on the concomitant medication pages of the eCRF prior to ECG measurements.
- Antibiotics for short term treatment of acute infections. Long term treatment with topical or ophthalmic antibiotics are permitted.

- Decongestants: Subjects may take decongestants during the study, but these are disallowed for 24 hours prior to ECG measurements.
- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated 4 weeks prior to Visit 1 and subjects remain in the maintenance phase for the duration of the study.
- Topical and ophthalmic corticosteroids.
- Systemic and ophthalmic beta-blockers: Administer with caution as systemic beta-blockers block the pulmonary effect of beta-agonists and may produce severe bronchospasm in patients with reversible obstructive airways disease. Cardioselective beta-blockers should be considered, although they also should be administered with caution.
- Localized corticosteroid injections (e.g. intra-articular and epidural).
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs). (Administer with extreme caution as they may potentiate the effects of beta-agonists on the cardiovascular system, including QTc prolongation)
- Diuretics. (Caution is advised in the co-administration of beta-agonists with non-potassium sparing diuretics as this may result in ECG changes and/or hypokalemia)
- Cytochrome P450 3A4 (CYP3A4) inhibitors (Caution should be exercised when considering the coadministration of long-term ketoconazole and other known strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) because increased systemic corticosteroid and increased cardiovascular adverse effects may occur)
- Vaccinations (Influenza vaccine, Pneumonia vaccine, Shingles vaccine, etc.) (Administration of influenza and pneumonia vaccines should be considered based on clinical discretion of the Investigator and local/national guidelines. Current influenza vaccines and pneumonia vaccines will be captured on the concomitant medication pages of the eCRF)

All medications for other disorders may be continued throughout the study provided their use would not be expected to affect the subjects' lung function or safety assessments (e.g., cardiac measurements). However, no systemic corticosteroids for other conditions will be permitted.

6.9.1.3. Permitted Non-Drug Therapies

Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnea is permitted if initiated at least 6 weeks prior to the Screening Visit (Visit 1) and the subject continues CPAP treatment throughout the study. This treatment must be captured in the eCRF.

6.9.2. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 4 is not permitted during the study.

Table 4 Concomitant Medications

Medication	No use during the study and/or within the following time interval before Visit 1
Inhaled short-acting anticholinergics	6 hours
Inhaled short-acting anticholinergics+ Short-acting beta agonist combination	6 hours
Inhaled long-acting anticholinergics other than study treatment	2 days. Temporary use during the study is also prohibited.
Immunosuppressive medications including immunomodulators	12 weeks
Inhaled long-acting beta$_2$-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta$_2$-agonists (e.g., Seretide, Symbicort) Inhaled very long-acting beta2-agonists, (Indacaterol, Olodaterol) Oral long-acting beta$_2$-agonists (e.g., bambuterol)	These must be withheld at least 24h prior to Visit 1; other than the study treatment, they will not be permitted during the study (including for temporary use). 10 days prior to Visit 1 for Indacaterol and Olodaterol component. Temporary use during the study is also prohibited.
Inhaled short-acting beta$_2$-agonist (rescue albuterol/salbutamol will be provided and is permitted during the study)	6 hours (including all study visits)
Theophyllines, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Anti-leukotrienes	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Medical marijuana	6 months. Medical marijuana administered via the inhaled route is strictly prohibited. Other routes of administration of medical marijuana are also prohibited UNLESS written permission is obtained from the Medical Monitor prior to Visit 1.
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

7. 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 Section 7.1.

7.1. Time and Events Table

Protocol Activity	**Pre-Screen[1]**	**Screen Run-in**	**Enrolment Stabilization**	**Treatment Period**						**Follow-up**	
				Fixed Treatment Period				**Variable Treatment Period**			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window					**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Written Informed Consent[5]	x										
Genetic Informed Consent[6]	x										
Demography	x										
Medical history		x									
Asthma History[7]		x									
Exacerbation History		x									
Concomitant Medication Assessment	x	x	x	x	x	x	x	x	x	x	x
Inclusion/Exclusion criteria		x	x								
Smoking History and status		x									
Randomization[8]				x							
Register visit in IRT (RAMOS NG)[9]	x	x	x	x	x	x	x	x	x	x	x
Efficacy Assessments											
Global Assessment of Severity[10]				x	x	x	x	x	x	x	

Protocol Activity	**Pre-Screen[1]**	**Screen Run-in**	**Enrolment Stabilization**	**Treatment Period**						**Follow-up**	
				Fixed Treatment Period				**Variable Treatment Period**			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
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Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window					**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Global Assessment of Response to Treatment[10]					x	x	x	x	x	x	
ACQ[10]		x	x	x	x	x	x	x	x	x	
SGRQ[10]				x		x	x	x	x	x	
AQLQ[10]				x	x	x	x	x	x	x	
Healthcare Resource Utilization[10]				x	x	x	x	x	x	x	
E-RS + asthma symptoms + PEF + home FEV1[10, 11]		x									
eDiary/device training and registration		x									
Dispense eDiary		x									
Collect eDiary									x	x	
eDiary review			x	x	x	x	x	x	x	x	
Dispense paper Medical Problems/Medications Taken worksheet	x	x	x	x	x	x	x	x	x	x	

Protocol Activity	**Pre-Screen**[1]	**Screen Run-in**	**Enrolment Stabilization**	**Treatment Period**						**Follow-up**	
				Fixed Treatment Period				**Variable Treatment Period**			
Visit	**0**	**1**[1]	**2**[2]	**3**[3] **Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)**[4]	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window					**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Review paper Medical Problems/Medications Taken worksheet		x	x	x	x	x	x	x	x	x	x
Pre-dose spirometry (clinic)		x[12]	x[12]	x[13]	x[12]	x[12]	x[13]	x[12]	x[13]	x[13, 14]	
Post-dose spirometry (clinic)				x[13]			x[13]		x[13]	x[13, 14]	
Reversibility test		x[15]	x[16]								
Exacerbation assessment			x	x	x	x	x	x	x	x	x
Health Outcomes											
WPAI-SHP[10]				x		x	x		x	x	
Safety Assessments											
Physical Examination		x					x		x	x	
Vital Signs		x[17]	x	x	x	x	x	x	x	x	
ECG[18]		x			x		x		x	x	
Adverse Events		x	x	x	x	x	x	x	x	x	x

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window					**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Serious Adverse Events	x	x	x	x	x	x	x	x	x	x	x
FeNO[19]				x							
Laboratory Assessments											
Hematology and clinical chemistry		x				x	x		x	x	
Total Serum IgE		x									
Urinalysis		x				x	x		x	x	
Pharmacogenetic sample[20]				x							
Serum pregnancy test		X[21]					x[21]		x[21]	x[21]	
Urine pregnancy test[21]			x	x	x	x		x			
PK samples						x[22]	x[23]		x[23, 24]	x[23]	
Study Treatment											
Dispense ICS/LABA run-in medication		x[25]									

Protocol Activity	**Pre-Screen[1]**	**Screen Run-in**	**Enrolment Stabilization**	**Treatment Period**						**Follow-up**	
				Fixed Treatment Period				**Variable Treatment Period**			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
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Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window					**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Assess run-in medication compliance			x								
Collect ICS/LABA run-in medication			x								
Dispense ICS/LABA stabilization medication			x								
Assess stabilization medication compliance				x							
Collect ICS/LABA stabilization medication				x							
Administer double-blind study treatment[26]				x	x	x	x	x	x	x[27]	
Dispense double-blind study treatment (Scheduled)				x	x	x	x	x			
Dispense double-blind study treatment (Unscheduled)				x[28]							
Assess double-blind study treatment compliance					x	x	x	x	x	x	

Protocol Activity	**Pre-Screen[1]**	**Screen Run-in**	**Enrolment Stabilization**	**Treatment Period**						**Follow-up**	
				Fixed Treatment Period				**Variable Treatment Period**			
Visit	**0**	**1[1]**	**2[2]**	**3[3] Random-ization**	**4**	**5**	**6**	**7**	**8 End of Study (EOS)**	**Early Withdrawal (EW)[4]**	**Safety Follow-up Contact**
Study Day	**-49 to -36**	**-35**	**-14**	**1**	**29**	**85**	**169**	**253**	**365**		
Week	**-6 to -7**	**-5**	**-2**	**0**	**4**	**12**	**24**	**36**	**52**		**1 week after Visit 8/EOS or EW Visit**
Window					**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Collect double-blind study treatment (Scheduled)					x	x	x	x	x	x	
Collect double-blind study treatment (Unscheduled)				x[29]							
Dispense albuterol/salbutamol, as required		x	x	x	x	x	x	x			
Collect albuterol/salbutamol, as required			x	x	x	x	x	x	x	x	
Dispense FP, as required[30]		x	x	x	x	x	x	x			
Collect FP, as required			x	x	x	x	x	x	x	x	

Notes:

1. Visit 1 should be completed ≥1 day but ≤14 days after Visit 0; however, if it is local and routine medical practice to request that a subject withhold their ICS/LABA medication for at least 24 hours prior to a clinic visit then, provided that the subject has complied with the request, Visit 0 and Visit 1 can occur on the same day.
2. Visit 2 may be conducted up to 3 days before the scheduled date of Visit 2. The duration of the run-in period (i.e. the time period between Visits 1 and 2) must be ≥18 days but ≤26 days.
3. Visit 3 must always be conducted ≥14 days but ≤17 days after Visit 2.
4. EW Visit should be conducted if double-blind study treatment is discontinued AND the subject discontinues from participating in the study.
5. The ICF must be signed before any study procedures, including protocol-specified medication cessation.
6. Genetics research consent may be obtained at the same time as the study IC and must be obtained prior to obtaining a genetic blood sample.

7. The assessment of asthma history will include: the age of the subject when they were first provided with an inhaler for asthma; completion of an asthma medical history questionnaire (a copy of this questionnaire and instructions for its use can be found in the SRM).
8. Subjects must not be randomised prior to confirming their eligibility to participate in the study.
9. The IRT will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOS NG IRT manual and SRM for more information).
10. Assessment(s) to be completed prior to the administration of study treatment.
11. To be completed using the provided combined spirometer/eDiary device. Assessments should be completed in the morning upon wakening and in the evening immediately prior to going to bed.
12. Spirometry to be performed between 6am and 11am after withholding rescue medication for at least 6 hours and prior to taking the morning dose of study treatment. Pre-dose spirometry assessments should be performed at the same time of day at each applicable visit.
13. Pre-dose spirometry to be performed between 6am and 11am, prior to taking the morning dose of study treatment. Post-dose spirometry is to be performed 3 hours (±15 minutes) after taking the morning dose of study treatment. Rescue medication should be withheld for at least 6 hours prior to the pre-dose spirometry assessments until after completion of the 3-hour post-dose spirometry assessments. Pre- and post-dose spirometry assessments should be performed at the same time of day at each applicable visit.
14. In the event that double-blind study treatment is not administered at this visit, spirometry assessments should be performed at the same time of day as the pre- and post-dose spirometry assessments at the preceding on-treatment clinic visits.
15. Following completion of the pre-dose spirometry assessments, the reversibility test will be conducted between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol. If airway reversibility is not demonstrated at Visit 1 then the assessment may be repeated within 7 days of Visit 1 (see Section 7.3.4.1.1 for details of the criteria to be met before a repeat of the reversibility assessment is permitted). If airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are met then the subject may commence the 3-week run-in period (starting on the date that airway reversibility was successfully demonstrated at the second attempt).
16. Following completion of the pre-dose spirometry assessments, the reversibility test will be conducted between 60 and 90 minutes following 4 inhalations of ipratropium aerosol (see Section 7.3.4.1)
17. The vital signs assessment will include the measurement of height and weight at this visit only.
18. At the Screening Visit (Visit 1), the ECG is to be obtained after the vital signs assessment but prior to performing the pre-bronchodilator spirometry assessment (see Section 7.5.6). At all post-randomization visits the ECG is to be obtained 15 minutes to 45 minutes after the administration of study treatment.
19. Exhaled Nitric Oxide is widely accepted as a non-invasive marker for airway inflammation and will be assessed to characterise the study subject population. Details on performing the FeNO assessment, including information on the equipment provided and its use, are documented in the SRM and the third-party vendor manual.
20. Pharmacogenetic sample may be drawn any time from Visit 3 onwards.
21. Assessments only to be conducted in females of reproductive potential.
22. Pharmacokinetic (PK) subset: In a subset of approximately 20% of all randomized subjects, PK samples will be obtained at pre-dose on the visit day, and 1 sample in each of the following three time windows: 5min-30min, 45min-90min, and 2-3h post dose on the visit day. NOTE: the date and time of study treatment administration on the day prior to the visit must be recorded in the eCRF.
23. PK sample to be obtained at pre-dose on the visit day (This PK sample is to be obtained from ALL study subjects). NOTE: the date and time of study treatment administration on the day prior to the visit must be recorded in the eCRF.
24. PK sample to be obtained at this visit ONLY in the event that Visit 8/EOS assessments are conducted at Week 24.
25. In the event that the reversibility assessment needs to be repeated within 7 days of Visit 1 (see Section 7.3.4.1.1) then the medication for the 3-week run-in period must not be dispensed until airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are confirmed as met.
26. Study treatment should be administered at the same time of day at each applicable clinic visit.

27. The administration of study treatment at this visit is optional. If study treatment is not administered at this visit then those assessments which are scheduled based on the time of study treatment administration should be performed at approximately the same time of day as performed at the preceding post-randomization visits.
28. Between scheduled visits, unscheduled visits to the study clinic to re-supply the subject with double-blind study treatment is permitted after Visit 3 but before Visit 8/EOS. The IRT will be used for study treatment supply management (Please refer to the RAMOS NG IRT manual and SRM for more information).
29. In the event that the subject attends the study clinic for the unscheduled dispensing of double-blind study treatment, previously dispensed study treatment should be collected for drug accountability purposes.
30. FP may be used temporarily to treat the symptoms of a moderate asthma exacerbation, at the Investigator's discretion. However, please note that a subject's use of the provided FP prior to randomization at Visit 3 would meet the enrolment or randomization concomitant medication exclusion criteria (see Section 5.3.2 and Section 5.4.2)

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7.2. Screening and Critical Baseline Assessments

No study related procedures may be performed until the informed consent form has been signed by the subject. A Pre-Screening visit (Visit 0) is required in order to administer the informed consent before any changes are made to the subject's current medical regimen. Selection and modification of the subject's medications prior to study participation is based on the physician's judgment according to sound medical practice, principles, and each subject's needs. A subject's treatment must not be changed merely for the purpose of enabling the subject's participation in the study.

During the Pre-Screening visit (Visit 0) the following information will be captured in the eCRF for each subject:

- Date of ICF signature
- Demographic information including race, age and gender
- Subject number
- Serious Adverse Event information only for any SAE considered as related to study participation
- Investigator signature page

The additional following critical baseline assessments will be conducted at Screening (Visit 1):

- Weight and height
- Asthma diagnosis history including:
  - The age of the subject when they were first provided with an inhaler for asthma
  - Completion of an asthma medical history questionnaire: a copy of this questionnaire and instructions for its use can be found in the SRM
- Smoking history and status
- Exacerbation history
- Asthma and other concurrent medications
- Medical History including previous and/or concurrent medical conditions, detailed cardiovascular risk factor history, pneumonia, and pneumonia vaccine status
- Reason for screen failure (if applicable)
- Vital signs
- ACQ
- Pre-and post-albuterol/salbutamol lung function
- Inclusion/Exclusion criteria assessment

- Physical examination
- 12-lead ECG
- Child bearing status assessment for all potential female subjects
- Clinical laboratory tests (including hematology, chemistry, urinalysis and serum pregnancy test)
- SAE assessment

In addition, the following procedures must be completed at Screening (Visit 1):

- Electronic device training / dispense eDiary
- Review/dispense Medical Problems/Medication Taken worksheet
- Dispense albuterol/salbutamol
- Dispense FSC run-in medication
- Dispense FP (as applicable, per Investigator discretion)

7.3. Efficacy

For a definition of baseline for each of the endpoints listed below, please refer to Section 9.4.

7.3.1. Efficacy Endpoints

7.3.1.1. Primary Efficacy Endpoint

Mean change from baseline in clinic trough FEV_1 at Week 24

7.3.1.2. Key Secondary Efficacy Endpoint

Annualized rate of moderate/severe asthma exacerbations.

7.3.1.3. Other Secondary Efficacy Endpoints

- Mean change from baseline in clinic FEV1 at 3 hours post study treatment at Week 24
- Mean change from baseline in ACQ-7 total score at Week 24
- Mean change from baseline in SGRQ total score at Week 24
- Mean change from baseline in E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period

7.3.1.4. Other Efficacy Endpoints

- Mean change from baseline in clinic trough FEV_1 over the first 24 weeks of the treatment period
- Mean change from baseline in daily home trough FEV_1 over the first 24 weeks of the treatment period

- Annualized rate of severe asthma exacerbations
- Time to first severe asthma exacerbation
- Time to first moderate/severe asthma exacerbation
- Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-7 at Week 24
- Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-6 at Week 24
- Percent of patients meeting a responder threshold of ≥0.5 points improvement (decrease) from baseline for the ACQ-5 at Week 24
- Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤0.75) at both Week 12 and Week 24
- Mean change from baseline in SGRQ domain scores at Week 24
- Percent of patients meeting a responder threshold of ≥ 4 points improvement (decrease) from baseline for the SGRQ total score at Week 24
- Mean change from baseline in E-RS domain scores over Weeks 21 to 24 (inclusive) of the treatment period
- Percent of patients meeting a responder threshold of ≥ 2 points improvement (decrease) from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period
- Mean change from baseline in AQLQ total score at Week 24
- Percent of patients meeting a responder threshold of ≥ 0.5 points improvement (increase) from baseline for the AQLQ total score at Week 24
- Mean change from baseline in morning (AM) pre-dose PEF over the first 24 weeks of the treatment period
- Mean change from baseline in evening (PM) PEF over the first 24 weeks of the treatment period
- Mean change from baseline in the percentage of symptom-free days over the first 24 weeks of the treatment period

  Note: this endpoint will be assessed using eDiary data (excluding E-RS total/domain scores and supplemental asthma questions); see Section 7.3.5.1.3 and Appendix 6. A symptom-free day is defined as subjects having on that day: a daytime asthma symptom score of 0 (i.e. no asthma symptoms) AND a physical limitation score of 0 (i.e. not at all limited) AND no nocturnal awakenings due to asthma symptoms.

- Mean change from baseline in the percentage of rescue medication-free days over the first 24 weeks of the treatment period
- Mean change from baseline in daily rescue medication use over the first 24 weeks of the treatment period
- Unscheduled asthma-related healthcare resource utilization over the first 24 weeks of the treatment period

7.3.2. Efficacy Assessments

The timings of all efficacy assessments are documented in the Time and Events table (see Section 7.1).

7.3.3. Questionnaires

The questionnaires should be completed before any procedures are performed on the subject to avoid influencing the subject's response. To avoid biasing responses, the subjects should not be told the results of diagnostic tests prior to completing the questionnaires and it is recommended that the questionnaires be administered at the same time of day during each visit (as applicable) using the provided electronic device (unless otherwise specified). Adequate time must be allowed to complete all items on the questionnaires; the questionnaires must be reviewed for completeness and, if necessary, the subject must be encouraged to complete any missing assessments or items.

Instructions for completing the questionnaires can be found in the SRM.

7.3.3.1. Global Assessment of Severity and Response to Treatment

The subject will be asked to complete the Global Assessment of Severity and Response to Treatment at the visits specified in the Time and Events table (Section 7.1). The Global Assessment of Severity is a single item questionnaire; subjects are asked to rate their asthma symptoms at the study visit using a five-point scale (none, mild, moderate, severe, very severe). The Response to Treatment is a single question of the patient's overall evaluation of response to treatment, using a seven-point rating scale with the following definitions: 1 = significantly improved; 2 = moderately improved; 3 = mildly improved; 4 = no change; 5 = mildly worse; 6 = moderately worse; and 7 = significantly worse.

7.3.3.2. Asthma Control Questionnaire (ACQ)

The ACQ measures seven attributes of asthma control [Juniper 1999]. Six attributes are measured with a patient-completed questionnaire, and the questions are designed to be self-completed by the subject. Subjects will complete the ACQ at specified study visits. The six questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath, wheeze and rescue medication use) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall period is the past week. The seventh attribute of the ACQ-7 is lung function (FEV1%-predicted) which will be included via study visit spirometry.

Two shortened versions of the ACQ exist. The two shortened versions include the ACQ-5 (a five-item measure using only the symptoms items) and the ACQ-6 (six-item measures and rescue bronchodilator use). The measurement properties were very similar for all versions of the ACQ (original 7-item ACQ and shortened versions) [Juniper 2005; Wyrwich 2011]. For all versions, a score of ≤0.75 indicates well-controlled asthma and a score ≥1.5 indicates poorly controlled asthma [Juniper 2006]. A change of 0.5 in score suggests a clinically important change in score [Juniper 2005].

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

The St. George's Respiratory Questionnaire is a well established instrument, comprising 50 questions designed to measure Quality of Life in patients with diseases of airway obstruction, measuring symptoms, impact, and activity. The questions are designed to be self-completed by the subject [Jones 1992] with a recall over the past 3 months. Higher scores indicate worse health status, and a change of 4 points is considered a clinically relevant change [Jones 2005].

7.3.3.4. Asthma Quality of Life Questionnaire (AQLQ)

The Asthma Quality of Life Questionnaire (AQLQ) was developed to measure the functional impairments related to asthma experienced by adults 17+ years old. The AQLQ (+12), is a modified version of the original AQLQ and validated for use in asthma patients between the ages of 12 and 70 [Juniper 2005]. The response scale ranges from 1 (totally impaired) to 7 (not at all impaired). The questions are designed to be self-completed by the subject with a recall over the past 2 weeks. Higher scores indicate better asthma-related HR-QoL, and a change of 0.5 is considered clinically important [Juniper 1994].

7.3.3.5. Healthcare Resource Utilization

All unscheduled asthma-related healthcare utilization will be recorded in the eCRF at the time points specified in the Time and Events table (Section 7.1). Unscheduled asthma-related healthcare utilization includes telephone contacts, specialist nurse visits, visits to a physician's office, home visits (day and night time), outpatient visits, visits to urgent care, visits to the emergency department, and hospitalizations associated with the subject's worsening of symptoms. The Medical Problems/Medication Taken worksheet (see Section 7.5.8) used by the subject to record all healthcare contacts experienced since the last visit will be presented to the Investigator (or designee) at the clinic visits. Subjects will be asked to bring their worksheet to every study site visit as it will be used to assist subject recall in discussions with the Investigator, for site staff to then enter as appropriate in the eCRF. The Investigator (or designee) should ask the subject if any of the healthcare contacts that are recorded on the worksheet were due to a worsening of asthma symptoms. The Investigator can refer to his/her records to verify or supplement information given by the subject, if necessary.

7.3.4. Pulmonary Function Tests

Spirometry will be performed at the study site to assess FEV_1 and FVC. At least 3 acceptable spirometry manoeuvres (from a maximum of 8 attempts) should be achieved

on each occasion that spirometry assessments are performed, in accordance with the ATS/ERS standards [Miller 2005]. The highest of 3 technically acceptable measurements will be recorded at each visit:

- **Pre-dose Spirometry:** At Visits 3 through 8/EOS (and the Early Withdrawal Visit, if applicable), subjects should withhold short-acting beta-2-agonists (SABAs) for ≥ 6 hours prior to the clinic visit, if possible. Spirometry assessments must be performed:
  - Between 6am and 11am on the day of the visit.
  - At the same time of day (± 1 hour) as the assessment performed at Visit 3 (the baseline assessment).
  - At least 24 hours after the subject's last morning dose of study treatment on the day prior to the visit.
  - Before the subject's morning dose of study treatment on the day of the visit.
- **Post-dose Spirometry:** At Visits 3, 6 and 8/EOS (and the Early Withdrawal Visit, if applicable), spirometry assessments must be performed 3 hours after the subject's morning dose of study treatment; the assessment performed at Visits 6 and 8/EOS should be performed at the same time of day (± 1 hour) as the assessment performed at Visit 3 (the baseline assessment). At each visit, subjects should withhold short-acting beta-2-agonists (SABAs) between receiving their morning dose of study treatment and completing the spirometry assessments, if possible.

Spirometry equipment will be provided to all sites by a third-party vendor; the same third-party vendor will also centrally analyse the spirometry data from this study. Details on performing the spirometry assessments, including information on the equipment provided and its use as well as specific instructions on performing the spirometry manoeuvres, are documented in the SRM and the third-party vendor manual.

7.3.4.1. Reversibility

All reversibility evaluations should follow the recommendations of the ATS/ERS Task force: Standardization of Lung Function Testing [Miller 2005]. A pre-bronchodilator spirometry assessment should be performed after a washout period of at least 6 hours for short-acting β_2- agonists.

Percent reversibility will be calculated as follows:

$$\frac{(\text{Post-bronchodilator } FEV_1 - \text{Pre-bronchodilator } FEV_1)}{\text{Pre-bronchodilator } FEV_1} \times 100$$

7.3.4.1.1. Albuterol/Salbutamol

The reversibility requirement for eligibility must be assessed at Visit 1. Subjects must demonstrate a ≥12% and ≥200 mL increase in FEV_1 to be eligible for the study. If these reversibility criteria are not met at Visit 1 then the subject may not enter the 3-week run-in period; however, the reversibility assessment may be repeated once within 7 days of Visit 1 if either criteria a) or b) are met:

a) ≥9% increase in FEV_1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.

b) Documented evidence of a reversibility assessment within 1 year prior to Visit 1 which demonstrated a post-bronchodilator increase in FEV_1 of ≥12% and ≥200 mL.

Should the subject successfully demonstrate airway reversibility (defined as ≥12% and ≥200 mL increase in FEV_1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol) at the second attempt then, provided that all other eligibility criteria assessed at Visit 1 are met, the subject may enter the 3-week run-in period.

To perform the reversibility assessment, 4 puffs of the provided salbutamol/albuterol is administered (a spacer device may be used, if required). Following completion of the pre-bronchodilator assessment, a second spirometry assessment is performed within 20 to 60 minutes after administration of the salbutamol/albuterol.

7.3.4.1.2. Ipratropium

At Visit 2, subjects will perform a reversibility assessment using ipratropium as the bronchodilator. As the aim of this assessment is to aid the characterisation of the study population, subjects are not required to demonstrate a ≥12% and ≥200 mL increase in FEV_1 to ipratropium to be eligible for the study.

To perform the reversibility assessment, 4 puffs (approximately 80 mcg total) of the provided ipratropium is administered (a spacer device may be used, if required). Following completion of the pre-bronchodilator assessment at Visit 2, a second spirometry assessment is performed within 60 to 90 minutes after administration of the ipratropium.

For a list of countries whose study subjects may not perform this assessment, please refer to the SRM.

7.3.5. Daily Diaries

Subjects will be issued with a combination spirometer and eDiary device at Visit 1 for twice daily use (in the morning upon waking and in the evening just before going to bed) throughout the study. The eDiary device will be provided by a third-party vendor. Information on the device and its use are documented in the SRM and the third-party vendor manual. Subjects will be instructed on how to use the device in order to record results for the following in the eDiary each day from Visit 1 onwards:

- Daily symptom assessment (E-RS and supplemental asthma items; night-time awakening, asthma symptom and physical activity questions)
- The number of inhalations of rescue albuterol/salbutamol used during the day and night.
- Morning and evening FEV_1
- Morning and Evening Peak Expiratory Flow (PEF)

- Morning and evening FSC medication use (during the run-in period only)
- Morning FF/VI medication use (during the stabilization period only)
- Morning double-blind study medication use (during the treatment period only)

Section 7.3.5.1 describes the assessments and questionnaires recorded on the eDiary device, as well as the alerts that can be triggered based on recorded results. The data from the eDiary device will be automatically transmitted to a centralised server on a daily basis. The Investigator and designee(s) will be provided with access to the transmitted eDiary data via a vendor-provided portal and should review the data on an ongoing basis to check for the incidence of alerts (see Section 7.3.5.1.6) as well as subject compliance with eDiary use and study treatment administration.

Subjects will also be issued with a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study (please refer to the SRM for further details). Subjects must also use this paper worksheet to record all healthcare contacts that occur during their participation in the study. This paper worksheet will be used to assist subject recall in discussions with the Investigator, for site staff to then enter as appropriate in the eCRF.

7.3.5.1. eDiary Questionnaires, Assessments and Alerts

For information on the eDiary questions, please refer to Appendix 6.

7.3.5.1.1. E-RS

The Evaluating Respiratory Symptoms (E-RS) in COPD consists of 11 items from the 14 item Exacerbations of COPD (EXACT-PRO) instrument. E-RS is intended to capture information related to respiratory symptoms, i.e. breathlessness, cough, sputum production, chest congestion and chest tightness. The E-RS was developed for use in patients with COPD but symptom experience of patients with asthma may be appropriately measured with the E-RS. The daily recording of information allows an assessment of the underlying day to day variability of a patient's symptoms. The instrument is to be completed daily each night prior to going to bed. The 11-items are scored on a 5-point scale of "not at all" to "extreme". The E-RS has a scoring range of 0-40.

7.3.5.1.2. Supplemental Asthma Items

To ensure that asthma symptoms are completely evaluated, two additional questions will be asked. A question on wheeze, a symptom of importance in asthma will also be asked within the context of the daily diary. An item on breathlessness activities will evaluate shortness of breath associated with strenuous activities. Subjects will be asked to respond to the question 'Did you wheeze today?' with response options of: Not at all, Rarely, Occasionally, Frequently, Almost constantly. Subjects will be asked to respond to the question "Were you short of breath today when performing strenuous activities such climbing stairs, running, or participating in sports activity with a response scale of not at all, slightly, moderately, severely, extremely or too breathless to do these.

7.3.5.1.3. Night-time Awakening, Asthma Symptom and Physical Activity Questions

Every morning upon waking (from the morning after Visit 1 onwards), subjects will answer a question on the occurrence of night-time awakenings due to asthma symptoms. The subject's response to the question on the occurrence of night-time awakenings will be either 'Yes' (i.e. Did you wake up due to asthma symptoms (i.e. wheezing, coughing, shortness of breath, or chest tightness) or 'No' (i.e. they did not experience at least one night-time awakening due to asthma symptoms). If 'Yes', subjects will be asked to respond either 'Yes' or 'No' to the question on rescue medication (i.e. when you woke up due to your asthma symptoms did you use any rescue bronchodilator?).

On the evening of Visit 1 (just before going to bed) and every evening there-after, subjects will answer a question on daytime asthma symptoms and daytime physical activity limitation. These questions will be answered on a 5-point scale (0 to 4) with '0' representing no daytime asthma symptoms/physical activity limitations and '4' representing very severe daytime asthma symptoms or total daytime activity limitation. (Please describe the severity of your asthma symptoms today (i.e. cough, wheeze, chest tightness, shortness of breath) today [0=no asthma symptoms, 1=mild asthma symptoms, 2= moderate asthma symptoms, 3=severe asthma symptoms, 4= very severe asthma symptoms. How limited were you in your activities today because of your asthma (0=not at all limited, 1=a little limited, 2=moderately limited, 3=severely limited, 4=totally limited).

7.3.5.1.4. Rescue Albuterol/Salbutamol Use

The number of puffs of albuterol/salbutamol self-administered by the subject each day for the relief of asthma symptoms will be recorded morning and evening in the eDiary. Upon awakening in the morning, subjects should record the number of puffs of albuterol/salbutamol taken since completing the eDiary assessments on the evening of the previous day. Each evening, before going to bed, subjects should record the number of puffs of albuterol/salbutamol taken since completing the eDiary that morning (except on the day of Visit 1 when the number of puffs of albuterol/salbutamol taken since being provided with the albuterol/salbutamol MDI should be recorded). Subjects should be instructed that study-provided albuterol/salbutamol should be used on an "as needed" basis only.

Any use of non-study-provided rescue medication should be recorded as a concomitant medication in the eCRF. Use of study-provided rescue albuterol/salbutamol should not be recorded as a concomitant medication in the eCRF; however, the use of study-provided albuterol/salbutamol prior to exercise as a preventative measure should be recorded as a concomitant medication in the eCRF.

7.3.5.1.5. Morning and Evening Home Spirometry

An electronic home spirometer/eDiary device will be issued to subjects at Visit 1 for daily monitoring of their lung function (i.e. FEV_1 and PEF). The home Spirometer/eDiary device will be provided by a third-party vendor. Information on the device and its use are documented in the SRM and the third-party vendor manual. Subjects will conduct

spirometry maneuvers each morning, prior to study medication dosing, and each evening. Three measurements for each session will be performed by the subjects using the spirometer/eDiary device; the highest value from the three FEV_1 and PEF measurements will be recorded. Assessments will be performed:

- After completing all other eDiary assessments
- Prior to albuterol/salbutamol use
- Prior to study medication dosing

Data from the home FEV_1 assessments will be used to determine the time to maximal effect of the assigned double-blind study treatment.

7.3.5.1.6. Alerts

The following alerts for a change from baseline in asthma symptoms, lung function, and/or rescue medication use that may indicate the onset of a moderate/severe asthma exacerbation, will be programmed into the eDiary:

- Nocturnal awakening(s) due to asthma requiring albuterol/salbutamol use for 2 consecutive nights.
- An increase of ≥1.0 (on a 5-point scale) from baseline in daytime asthma symptom score on 2 consecutive days.
- An increase from baseline of ≥ 4 puffs /day of albuterol/salbutamol use on 2 consecutive days.
- A ≥20% decrease in AM PEF from baseline on 2 consecutive mornings.
- A ≥20% decrease in PM PEF from baseline on 2 consecutive evenings
- A ≥20% decrease in AM FEV1 from baseline on 2 consecutive mornings.
- A ≥20% decrease in PM FEV1 from baseline on 2 consecutive evenings.

The baseline value, for the purpose of alerts, is defined as the average value over the last 7 days prior to randomization. Subjects will be instructed to contact the Investigator if any of the above alert criteria are met (either by telephone and/or by visiting the study clinic).

The data from the home spirometer/eDiary device will be automatically transmitted to a centralised server on a daily basis. The Investigator and designee(s) will be provided with access to the transmitted eDiary data via a vendor-provided portal and should review the data on an ongoing basis to check for the incidence of alerts as well as subject compliance with eDiary use. The Investigator or designee(s) is instructed to evaluate subjects who meet eDiary alert criteria for signs or symptoms of an asthma exacerbation and to provide appropriate medical care (see Section 7.3.6).

7.3.6. Asthma Exacerbations

For the purposes of this study, moderate/severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page from the start of randomized double blinded treatment until Visit 8/EOS Visit or the Early Withdrawal Visit for those subjects

that withdraw from participation in the study (see Section 5.6). Moderate/severe asthma exacerbations should not be recorded as an adverse event unless:

- They meet the definition of an Adverse Event (see Appendix 4) and occur:
  - After the start of study treatment until the start of double blinded study treatment or;
  - After completion of the Visit 8/EOS Visit (or Early Withdrawal Visit) assessments until the follow-up contact.

OR

- They meet the definition of a Serious Adverse Event (see Appendix 4).
  Note: The SAE page of the eCRF should be completed in addition to the asthma exacerbation eCRF page if the exacerbation occurs after the start of double blinded treatment but before completion of the Visit 8/EOS Visit or Early Withdrawal Visit assessments.

For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Alerts will be programmed into the eDiary to instruct the subject to contact the Investigator immediately for a medical assessment (see Section 7.3.5.1.6). The notification of decreasing asthma control from the eDiary will assist the Investigator in the identification of new asthma exacerbations.

Subjects will also complete a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study, as well as all emergency department visits and/or hospitalizations that occur during their participation in the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist the Investigator in the identification of new asthma exacerbations.

All moderate/severe asthma exacerbations will be recorded in the eCRF by the Investigator (or designee).

7.3.6.1. Moderate Asthma Exacerbation

All eDiary alerts will be evaluated by the Investigator (or appropriately trained designee). The Investigator will utilize clinical discretion and available objective evidence (including eDiary data) to determine if the patient is experiencing a moderate asthma exacerbation. Examples of key considerations include subject's past medical history, severity and duration of current symptoms, and known asthma triggers. Guidance for identifying moderate exacerbations includes the following [Reddel 2009, Virchow 2015]:

- A moderate asthma exacerbation is considered to be a deterioration in asthma symptoms, deterioration in lung function, or increased rescue bronchodilator use lasting for at least 2 days or more, but will not be severe enough to warrant systemic corticosteroid use (or a doubling or more of the maintenance systemic corticosteroid dose, if applicable) for 3 days or more and/or hospitalisation.

- A moderate asthma exacerbation is an event that, when recognized, should result in a temporary change in treatment, in an effort to prevent the exacerbation from becoming severe.

As eDiary alerts are triggered on the second day of a change from baseline in asthma symptoms, lung function, and/or rescue medication, subjects and Investigators are asked to investigate eDiary alerts at the time they are received. Subjects are also instructed to contact the Investigator for signs of worsening asthma that may not be triggered by eDiary data. The paper Medical Problems/Medications Taken worksheet must also be reviewed by the Investigator (or appropriately trained designee) at each visit to the study site to assist the Investigator in the identification of new asthma exacerbations. At the Investigator's discretion, a temporary change in background asthma medication will be permitted in order to treat the symptoms of a moderate asthma exacerbation (see Section 6.9.1.1 for details). If a subject experiences a second moderate asthma exacerbation requiring a change in therapy, the Investigator may choose to continue the additional therapy for as long as medically appropriate.

7.3.6.2. Severe Asthma Exacerbation

A severe asthma exacerbation is defined as:

The deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection), or an increase from a stable maintenance dose[1], for at least 3 days.

[1] *For subjects receiving maintenance systemic corticosteroids, at least double the maintenance systemic corticosteroid dose for at least 3 days is required.*

OR

An inpatient hospitalization or emergency department visit because of asthma, requiring systemic corticosteroids.

7.4. Health Outcomes

7.4.1. Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP)

The WPAI-SHP (version 2) is a self administered tool comprised of 6 questions which address absenteeism, presenteeism (reduced effectiveness while working), overall work productivity loss (absenteeism plus presenteeism), and activity impairment. This validated tool captures data from the past 7 days. WPAI-SHP (asthma) outcomes are scored as impairment percentages, with a higher percentage indicating greater impairment and less productivity [Reilly 1993].

The WPAI-SHP will be completed at specific study visits as defined in the Time and Events table (see Section 7.1).

7.5. Safety

Planned time points for all safety assessments are listed in the Time and Events table (Section 7.1).

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

The definitions of an AE or SAE can be found in Appendix 4.

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

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

- 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.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.5.1.3), at the timepoints specified in the Time and Events table (Section 7.1).
- 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.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- 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 4

7.5.1.2. 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?”

Subjects will be issued with a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study (please refer to the SRM for further details). This paper worksheet will be used to assist subject recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the eCRF.

7.5.1.3. 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 7.5.2) 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 5.6.2). Further information on follow-up procedures is given in Appendix 4.

7.5.1.4. Cardiovascular and Death Events

7.5.1.4.1. Cardiovascular Events

Cardiovascular-related AEs and SAEs that will require the Investigator to complete event specific pages in the eCRF are listed in Appendix 4.

Cardiovascular events information should be recorded on the corresponding eCRF pages within one week of when the AE/SAE(s) are first reported. Please refer to Appendix 4 for timelines for reporting AE/SAEs.

7.5.1.4.2. Death Events

In addition, all deaths will require completion of a specific death data collection page in the eCRF. The death data collection page in the eCRF includes questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

Death information should be recorded on the death eCRF page within one week of when the death is first reported.

Please refer to Appendix 4 for timelines for reporting SAEs.

7.5.1.5. Pneumonia

Medical history will also be taken for pneumonia in previous 12 months, including recording of any episodes resulting in hospitalisation. Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a subject has a suspected pneumonia. Suspected pneumonias will require confirmation as defined by the presence of new infiltrate(s) on chest x-ray AND at least 2 of the following signs and symptoms:

- Increased cough
- Increased sputum purulence (color) or production
- Auscultatory findings of adventitious sounds (e.g., egophony, bronchial breath sounds, rales, etc.)

- Dyspnea or tachypnea
- Fever (oral temperature > 37.5 degrees centigrade [°C])
- Elevated white blood cells (WBC) (>10,000/millimetres cubed [mm^3] or >15% immature forms)
- Hypoxemia (Oxyhemoglobin (HbO2) saturation <88% or at least 2% lower than baseline value)

All pneumonias must be captured on the AE/SAE page of the eCRF and on the pneumonia page of the eCRF.

For all suspected cases of pneumonia, investigators are strongly encouraged to confirm the diagnosis (this includes obtaining a chest x-ray) and to initiate appropriate therapy as promptly as possible. All diagnoses of pneumonia (radiographically confirmed or unconfirmed) must be reported as an AE or SAE (if applicable).

7.5.1.6. Radiography (Chest X-Rays)

Confirmation by chest x-ray (posteroanterior and lateral) should be performed as soon as possible and preferably within 48 hours of suspected pneumonia. In all cases, the signs and symptoms that were used to identify the pneumonia must be documented in the source documents and eCRF. Diagnoses of pneumonia must be recorded as adverse events in the eCRF.

7.5.1.7. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to GSK of SAEs 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.

7.5.2. Adverse Events of Special Interest (AESIs)

AE groups of special interest have been defined as AEs which have specified areas of interest for one or more of class of drugs (ICS, LAMA, LABA). Some AE groups may have subgroups defined.

The following table presents the current special interest AE groups and subgroups. These may be updated prior to conclusion of the study reporting. The final list, including the preferred terms which contribute to each of the groups will be documented *a priori* in the study Reporting and Analysis Plan (RAP).

Special interest AE group	Special interest AE subgroup
Cardiovascular effects	Cardiac arrhythmia
	Cardiac failure
	Cardiac ischemia
	Stroke
Anticholinergic syndrome	-
Urinary retention	-
Dry mouth / drying of airway secretions	-
Gastrointestinal obstruction	-
Antimuscarinic ocular effects / Corticosteroids associated eye disorders	Glaucoma (antimuscarinic/corticosteroid)
	Cataracts (corticosteroid)
Pneumonia and LRTI	Pneumonia
	LRTI excluding pneumonia
Adrenal suppression	-
Decreased bone mineral density and associated fractures	-
Effects on glucose	-
Effects on potassium	-

Special interest AE group	Special interest AE subgroup
Tremor	-
Asthma intubations, and deaths	-
Hypersensitivity	-
Local steroid effects	-

7.5.3. Pregnancy

- Details of all pregnancies in female subjects will be collected after the start of dosing and until the safety follow-up contact/visit.
- 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 Appendix 5.

7.5.4. Physical Exams

Physical exams will be performed at the time points specified in the Time and Events table (Section 7.1).

- A complete physical examination will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- Height and weight will be measured at Visit 1.

7.5.5. Vital Signs

Vital signs will be performed at the time points specified in the Time and Events table (Section 7.1) prior to conducting spirometry and prior to taking the morning dose of study treatment. Blood pressure (systolic and diastolic) and pulse rate will be measured in the sitting position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

7.5.6. Electrocardiogram (ECG)

All sites will use standardised ECG equipment provided by a centralized external vendor. At the Screening Visit (Visit 1), a single 12-lead ECG and rhythm strip will be recorded after the measurement of vital signs but before performing the pre-bronchodilator spirometry assessment. At the post-randomization visits, a single 12-lead ECG and rhythm strip will be recorded 15 to 45 minutes after the administration of study treatment. Recordings will be made at the time-points defined in the Time and Events table (Section 7.1). All ECG measurements will be made with the subject in a supine position having rested in this position for approximately 5 minutes before each reading.

For subjects who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 5.6.4).

The Investigator, a designated sub-Investigator or other appropriately trained site personnel will be responsible for performing each 12-lead ECG. The Investigator must provide his/her dated signature on the original paper tracing, attesting to the authenticity of the ECG machine interpretation.

All ECGs will be electronically transmitted to an independent cardiologist and evaluated. The independent cardiologist, blinded to treatment assignment, will be responsible for providing measurements of heart rate, QT intervals and an interpretation of all ECGs collected in this study. A hard copy of these results will be sent to the Investigator. The Investigator must provide his/her dated signature on the confirmed report, attesting to his/her review of the independent cardiologist's assessment.

Details of the cardiac monitoring procedures will be provided by the centralized cardiology service provider.

7.5.7. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol Time and Events table (Section 7.1). Laboratory requisition forms must be completed and samples must be clearly labelled with the subject number, protocol number, site/centre number, and visit date. Details for the preparation and shipment of samples will be provided by the laboratory and are detailed in the Laboratory Manual. Reference ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

All blood samples which will be taken pre-dose, will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). Standard reference ranges will be used.

If additional non-protocol specified laboratory assessments are performed at the institution's local laboratory and result in a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification) the results must be recorded in the eCRF.

Refer to the Laboratory Manual for appropriate processing and handling of samples to avoid duplicate and/or additional blood draws.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 5.

Table 5 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count; Red Blood Cell (RBC) Count; Hemoglobin; Hematocrit; RBC Indices: MCV, MCH; WBC count with Differential: Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
Clinical Chemistry [1]	Blood Urea Nitrogen (BUN); Creatinine; Glucose; Total Serum IgE[2]; Potassium; Sodium; Calcium; AST (SGOT); ALT (SGPT); Alkaline phosphatise; Total and direct bilirubin; Total Protein; Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• FSH and estradiol (as needed in females of non-reproductive potential only) • Serum/urine hCG Pregnancy test (as specified in the Time and Events table [Section 7.1])

NOTES:

1. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 5.6.3 and Appendix 2.
2. Total Serum IgE is required at Visit 1 only.

All laboratory tests with values that are considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline. If such values do not return to normal within a period judged reasonable by the Investigator, the etiology should be identified and the sponsor notified.

7.5.8. Paper Medical Problems/Medications Taken Worksheet

Subjects will be issued with a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study (please refer to the SRM for further details). Subjects must also use this paper worksheet to record all emergency department visits and/or hospitalizations that occur during their participation in the study. Subjects will be asked to bring their paper worksheet to every study site visit

as it will be used to assist subject recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the eCRF.

7.6. Pharmacokinetics (PK)

Concentrations of FF, UMEC and VI in plasma will be determined using currently approved assay methodology under the control of GSK. A population PK approach will be employed in this study; the PK samples will be collected at the time points specified in Section 7.1.

The actual date and time of each blood sample collection will be recorded in the eCRF. The date and time of study treatment administration on the day prior to the clinic visit will be recorded in the eCRF. This is to ensure appropriate usage of the pre-dose PK data.

Details of PK blood sample collection (including volume to be collected), processing, storage and shipping procedures are provided in the SRM.

The following points must be noted:

- If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order (as applicable):
    1. Vital signs
    2. 12-lead ECG
    3. blood draws.

  Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.
- The change in timing or addition of time points for any planned study assessments must be documented in a Note to File which is approved by the relevant GSK study team member and then archived in the study sponsor and site study files, but this will not constitute a protocol amendment.
- The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the Informed Consent Form.
- No more than 500 mL of blood will be collected over the duration of the study, including any extra assessments that may be required.

7.6.1. Blood Sample Collection

Blood samples for PK analysis of FF, UMEC and VI will be collected pre-dose from ALL subjects at Visit 6 (or Visit 8/EOS [if this visit occurs at Week 24] or, if applicable, the Early Withdrawal Visit [see Section 7.1]).

7.6.1.1. Pharmacokinetic Sub-study

At Visit 3, consenting subjects who are randomised to participate in the main study will be entered into the PK sub-study.

In a subset of approximately 20% of the subjects randomised to participate in the main study, PK samples will be obtained at pre-dose on the day of Visit 5, and 1 sample in each of the following three time windows: 5min-30min, 45min-90min, and 2-3h post dose on the day of Visit 5.

The methodology for inclusion of consenting subjects into the PK sub-study is provided in the SRM.

7.6.2. Sample Analysis

Plasma analysis will be performed under the management of Bioanalytical Science and Toxicokinetics (BST), Drug Metabolism and Pharmacokinetics (DMPK), GSK. Concentrations of UMEC, VI and FF will be determined in plasma samples using the currently approved analytical methodology.

Personnel involved in the bioanalysis of PK samples will be unblinded as per GSK policy. Samples will be analyzed only for relevant analyte, e.g. (FF/VI) treatment samples will not be analyzed for UMEC concentrations.

Raw data will be stored in the Good Laboratory Practice (GLP) Archives, GSK or at a designated contract laboratory. Once the plasma has been analyzed for UMEC, VI and FF any remaining plasma may be analyzed qualitatively for other circulating metabolites and the results reported under a separate DMPK protocol.

7.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 3. The IEC/IRB and, where required, the applicable regulatory agency must approve the PGx and genetic assessments before these can be conducted at the site. The approval(s) must be in writing and will clearly specify approval of the PGx and genetic assessments (i.e., approval of Appendix 3). In some cases, approval of the PGx and genetic assessments can occur after approval is obtained for the rest of the study. If so, then the written approval will clearly indicate approval of the PGx and genetic assessments is being deferred and the study, except for PGx and genetic assessments, can be initiated. When PGx and genetic assessments will not be approved, then the approval for the rest of the study will clearly indicate this and therefore, PGx and genetic assessments will not be conducted.

8. DATA MANAGEMENT

- For this study subject data will be entered into GSK defined eCRFs, 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.
- eCRFs (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 will not be collected or transmitted to GSK according to GSK policy.

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to evaluate the efficacy and safety of UMEC in combination with FF/VI in subjects with asthma over a 24 week treatment period. This is a superiority study to demonstrate the add-on benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg in a single inhaler when compare to FF/VI. The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at the end of the 24-week treatment period.

For each test on each efficacy endpoint, the null hypothesis is that there is no difference between treatment groups.

H_0: $T_1 - T_2 = 0$

The alternative hypothesis is that there is a difference between treatment groups.

H_1: $T_1 - T_2 \neq 0$

For the primary endpoint and other lung function related efficacy endpoints, the primary treatment comparisons of interest are the comparisons for each triple therapy and the respective dual therapy FF/VI without the UMEC component as follows:

UMEC 62.5 mcg:

- FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/62.5/25 mcg vs. FF/ VI 200/25 mcg

UMEC 31.25 mcg:

- FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/31.25/25 mcg vs. FF/ VI 200/25 mcg

Therefore T_1 and T_2 for these endpoints are the mean changes from baseline for the individual triple therapy and dual therapy, respectively, as listed above.

For the key secondary endpoint and all other non-lung function efficacy endpoints, the primary treatment comparisons of interest are the comparisons between triple therapy and dual therapy for a fixed dose of UMEC:

- (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)
- (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25)

For example, T_1 and T_2 in the hypothesis associated with the key secondary efficacy endpoint are the averages of the mean annualized rate of moderate/severe exacerbations for the triple therapies over two FF doses at a given UMEC dose, and for the dual therapies over two FF doses, respectively.

Details on all pairwise treatment comparisons of interest are provided in Section 9.3.3.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

Sample size calculation is based on the primary efficacy endpoint of mean change from baseline in trough FEV1 at the end of the 24-week treatment period.

A total of 2250 randomized subjects are required for this study, with 375 subjects in each of the six double-blind treatment groups:

- FF/VI 100/25 mcg
- FF/VI 200/25 mcg
- FF/UMEC/VI 100/31.25/25 mcg
- FF/UMEC/VI 200/31.25/25 mcg
- FF/UMEC/VI 100/62.5/25 mcg
- FF/UMEC/VI 200/62.5/25 mcg

Assuming 10% missing data on spirometry at the end of the 24-week treatment period, due to early withdrawal from study, approximately 337 subjects per treatment group should have trough FEV_1 data available for the analysis.

The standard deviation for the mean change from baseline in trough FEV_1 at the end of the 24-week treatment period is estimated to be 400 mL based on previous asthma studies. The proposed sample size of n=337 per treatment group should provide 90% power, assuming a difference of 100 mL, based on a two sample t-test with a two sided significance level of 0.05 for each of the two primary comparisons of interest for each UMEC dose.

For the target population, it is assumed that the mean exacerbation rate is 2 per year for the control group FF/VI; this was based on a review of previous FF/VI asthma exacerbation study conducted by GSK and Tio asthma studies conducted by Boehringer Ingelheim. The proposed sample size of 750 randomzed subject per arm (based on the treatment comparison of combined triple therapies and combined dual therapies with both FF doses) should have approximately 95% power if the true reduction in exacerbation

rate for triple therapy vs. dual therapy is 20%. The calculation assumes the number of exacerbations per year follows a negative binomial distribution [Keene 2007], with a dispersion parameter k=0.7 based on a previous FF/VI asthma exacerbation study, and assumes the following accelerative recruitment rate per week over a period of 39 weeks:

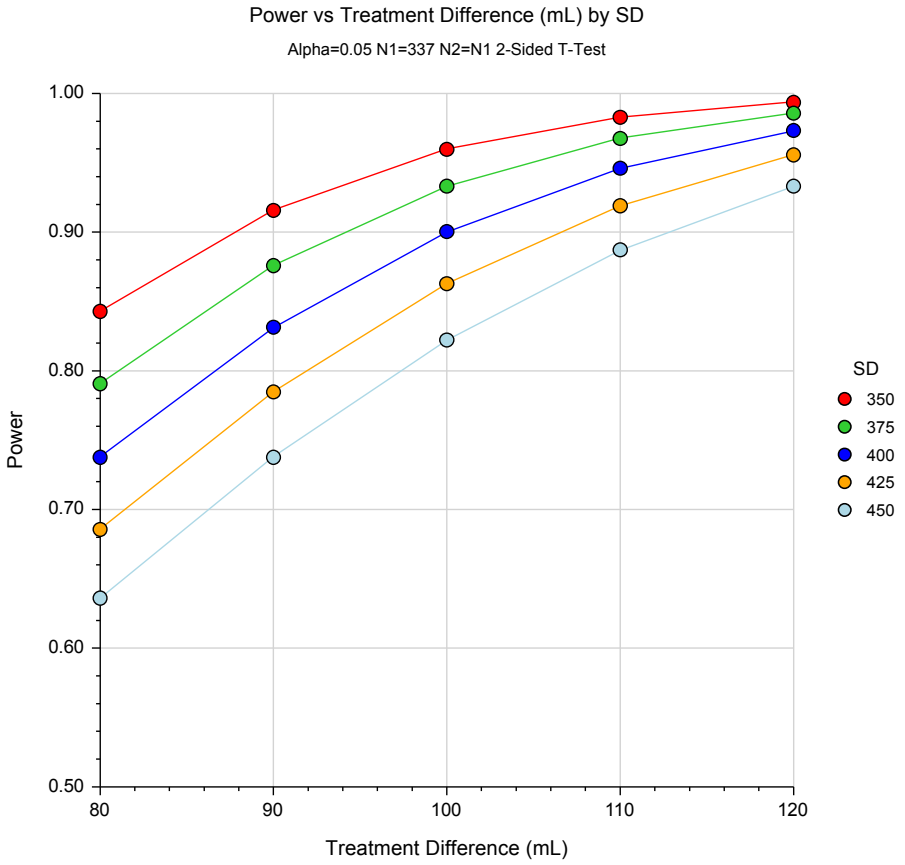
- 3.5 weeks at 15 patients/week
- 4.5 weeks at 25 patients/week
- 4.5 weeks at 35 patients/week
- 4.5 weeks at 45 patients/week
- 4.5 weeks at 55 patients/week
- 4.5 weeks at 70 patients/week
- 13 weeks at 90 patients/week

The duration of the treatment period is variable but will be at least 24 weeks and up to a maximum of 52 weeks, with the end of study date being established once the last subject has been randomized.

9.2.2. Sample Size Sensitivity

To demonstrate the sensitivity of the sample size calculation for this study, the following table and graph show the power function for a fixed sample size of n=337 per arm in the ITT population for the primary efficacy analysis, varying the observed treatment difference and estimated standard deviation on the change from baseline in trough FEV_1 at the end of the 24-week treatment period.

	Treatment difference (mL)				
Standard Deviation	80	90	100	110	120
350	0.84	0.92	0.96	0.98	0.99
375	0.79	0.88	0.93	0.97	0.99
400	0.74	0.83	0.90	0.95	0.97
425	0.69	0.78	0.86	0.92	0.96
450	0.64	0.74	0.82	0.89	0.93

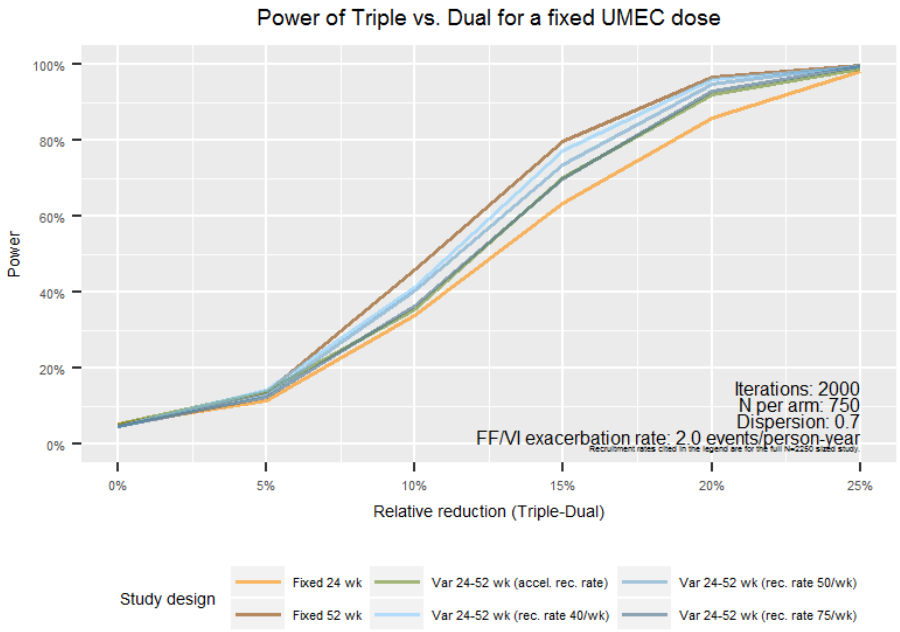


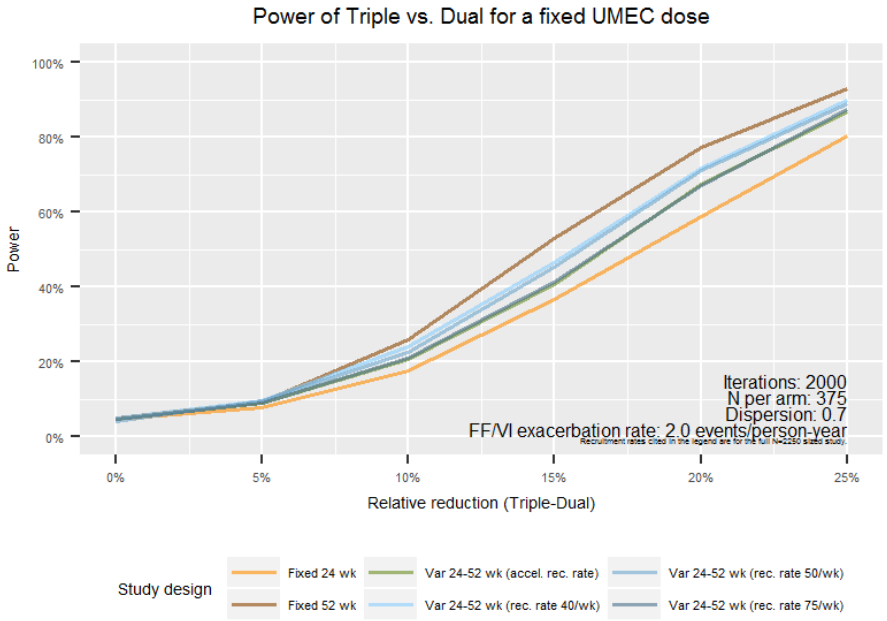
For the key secondary endpoint, the following table shows the power function for a fixed sample size of n=750 per arm (combining two FF containing triple arms or dual arms for a fixed UMEC dose) or for a fixed sample size of n=375 per arm (individual treatment group) in the ITT population, varying the mean annualized rate of exacerbations in the control group, the true treatment effect (relative reduction in moderate/severe exacerbations) and the dispersion assumption in a variable duration study, assuming an

accelerative recruitment rate per week over a period of 39 weeks as given in Section 9.2.1.

dispersion	FF/VI rate	FF/UMEC/VI rate	Relative Reduction	power	
				n=750/arm	n=375/arm
0.7	1.50	1.275	15%	0.62	0.37
	1.50	1.200	20%	0.87	0.59
	1.50	1.125	25%	0.98	0.81
	2.00	1.700	15%	0.70	0.41
	2.00	1.600	20%	0.92	0.67
	2.00	1.500	25%	0.99	0.87
	2.50	2.125	15%	0.75	0.49
	2.50	2.000	20%	0.95	0.72
	2.50	1.875	25%	>0.99	0.90
0.8	1.50	1.275	15%	0.61	0.36
	1.50	1.200	20%	0.86	0.56
	1.50	1.125	25%	0.97	0.77
	2.00	1.700	15%	0.65	0.41
	2.00	1.600	20%	0.91	0.66
	2.00	1.500	25%	0.99	0.85
	2.50	2.125	15%	0.73	0.44
	2.50	2.000	20%	0.94	0.69
	2.50	1.875	25%	>0.99	0.88

The power for the statistical test on the key secondary efficacy endpoint was further evaluated for a fixed UMEC dose, assuming a constant rate of recruitment at 40, 50, or 75 subjects per week throughout the enrolment period. The power functions were illustrated below for n=750/arm and n=375/arm, respecitvely, assuming dispersion=0.7 and a mean annualized rate of moderate/severe exacerbations of 2 for FF/VI group.





9.2.3. Sample Size Re-estimation or Adjustment

No sample size re-estimation is planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

The following subject populations will be identified:

All Subjects Enrolled Population: This population will comprise all subjects for whom a record exists on the study database, including pre-screened subjects that sign the informed consent document but do not complete a Visit 1 (screening) procedure (i.e., pre-screening failures), or subjects that complete at least one Visit 1 procedure but do not enter the run-in period (i.e., screening failures). This population will be used for the summary of subject disposition.

All Subjects Screened Population: This population contains all subjects that complete at least one Visit 1 (Screening) procedure. This population will be used for the summary of subject disposition (including reasons for screening failures, run-in failures, and stabilization failures) and for the listing of AEs and SAEs for non-randomized subjects.

Intent-to-Treat (ITT) Population: This population will comprise all randomized subjects, excluding those who were randomized in error. A subject who is recorded as a screen failure, run-in failure, or stabilization failure, but is randomized and does not receive a dose of study treatment, is considered to be randomized in error. Any other subject who receives a randomization number will be considered to have been randomized. This will constitute the primary population for all efficacy and safety analyses.

Pharmacokinetic (PK) population: This population will comprise all subjects in the ITT Population for whom a PK sample was obtained and analyzed.

9.3.2. Interim Analysis

No interim analysis is planned for this study.

9.3.3. Treatment Comparisons

To demonstrate the benefit of UMEC when added to FF/VI treatment arms with the same FF dose, the primary comparisons of interest for the primary efficacy endpoint are:

- The replicate efficacy for UMEC 62.5 mcg dosage:
  - FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg
  - FF/UMEC/VI 200/62.5/25 mcg vs. FF/ VI 200/25 mcg

- The replicate efficacy for UMEC 31.25 mcg dosage:
  - FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg
  - FF/UMEC/VI 200/31.25/25 mcg vs. FF/ VI 200/25 mcg

For the multiple comparisons and multiplicity adjustment, see Section 9.3.4 .

To allow evaluation of the effect of FF/UMEC/VI on non-lung function efficacy endpoints, including the key secondary efficacy endpoint on moderate/severe

exacerbations, for each fixed UMEC dose, the data from the two FF/UMEC/VI arms will be pooled and compared to the pooled data from the two FF/VI arms.

- FF/UMEC/VI (100/62.5/25 and 200/62.5/25) vs. FF/VI (100/25 and 200/25)
- FF/UMEC/VI (100/31.25/25 and 200/31.25/25) vs. FF/VI (100/25 and 200/25).

The integrated analyses will provide a more precise overall estimate for the treatment effect size of the addition of UMEC to FF/VI.

Other pairwise treatment comparisons of interest consist of the following assessments for all efficacy endpoints:

1) Triple therapy with low dose FF vs. dual therapy with high dose FF:

   - FF/UMEC/VI 100/62.5/25 vs. FF/VI 200/25
   - FF/UMEC/VI 100/31.25/25 vs. FF/VI 200/25

2) The benefit of increase FF dose in triple therapy:

   - FF/UMEC/VI 200/62.5/25 vs. FF/UMEC/VI 100/62.5/25
   - FF/UMEC/VI 200/31.25/25 vs. FF/UMEC/VI 100/31.25/25

3) The benefit of increasing UMEC dose in triple therapy:

   - FF/UMEC/VI 100/62.5/25 vs. FF/UMEC/VI 100/31.25/25
   - FF/UMEC/VI 200/62.5/25 vs. FF/UMEC/VI 200/31.25/25

9.3.4. Multiple Comparisons and Multiplicity

In order to account for multiple tests involving two UMEC doses and across multiple efficacy endpoints, a step-down testing procedure will be applied whereby inference for a test in the pre-defined hierarchy is dependent upon statistical significance having been achieved for the previous tests in the hierarchy.

A step-down closed testing approach will be applied for the primary efficacy endpoint, the key secondary efficacy endpoint, and the secondary efficacy endpoints SGRQ, ACQ-7, and E-RS. Specifically, if the defined treatment comparisons for the primary efficacy endpoint between triple therapy and dual therapy at the high dose of UMEC 62.5 mcg are statistically significant at the 0.05 level for both fixed FF doses (100 and 200mcg), then the replicate efficacy of UMEC 62.5mcg is demonstrated, and the defined treatment comparison between triple therapy and dual therapy will be tested for the key secondary efficacy endpoint of moderate/severe asthma exacerbations based on the combined data of both FF doses for UMEC 62.5mcg. If the test for the key secondary efficacy endpoint is statistically significant at the 0.05 level, then the secondary efficacy endpoints for SGRQ (Mean change from baseline in SGRQ at Week 24) and ACQ-7 (Mean change from baseline in ACQ-7 at Week 24) will be tested sequentially based on the combined data of both FF doses for UMEC 62.5mcg at significance level 0.05.

If all tests mentioned above for UMEC 62.5 mcg are statistically significant at the 0.05 level, the above testing hierarchy for the primary efficacy endpoint, the key secondary efficacy endpoint, and the secondary efficacy endpoints SGRQ and ACQ-7 will be repeated for the low dose of UMEC 31.25 mcg.

If all tests for the primary, the key secondary, and the secondary efficacy endpoints for SGRQ and ACQ-7 are statistically significant at the 0.05 level for both UMEC 62.5mcg and 31.25mcg, the secondary endpoint for E-RS (Mean change from baseline in E-RS score over the Weeks 21-24 (inclusive) of the treatment period) will be tested at the significance level 0.05 for UMEC 62.5 and UMEC 31.25 in sequence.

The family-wise Type I Error is strongly controlled at 0.05 level for both UMEC 62.5mcg and UMEC 31.25mcg on the primary endpoint (trough FEV1), the key secondary endpoint (moderate/severe asthma exacerbations), and the secondary endpoints on SGRQ, ACQ-7, and E-RS.

All secondary non-lung function efficacy endpoints will be tested for triple vs. dual using the combined data of both FF doses, at a given UMEC dose. The full testing hierarchy is provided below:

Multiplicity Adjustment Plan

Level 1: Primary endpoint, UMEC 62.5 mcg: Mean change from baseline in trough FEV1 at Week 24,

Two comparisons:

FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25

FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25

Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 62.5 mcg in order to move to Level 2 test.

Level 2: Key secondary endpoint, UMEC 62.5 mcg: Annualized rate of moderate/severe asthma exacerbations,

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 3 test.

Level 3: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in SGRQ at Week 24,

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 4 test.

Level 4: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in ACQ-7 at Week 24,

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 5 tests.

Level 5: Primary endpoint, UMEC 31.25mcg: Mean change from baseline in trough FEV1 at Week 24,

Two comparisons:

FF/UMEC/VI 100/31.25/25 vs. FF/VI 100/25

FF/UMEC/VI 200/31.25/25 vs. FF/VI 200/25

Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 31.25mcg and move to Level 6 test.

Level 6: Key secondary endpoint, UMEC 31.25 mcg: Annualized rate of moderate/severe asthma exacerbations,

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 7 test.

Level 7: Secondary endpoints, UMEC 31.25 mcg: Mean change from baseline in SGRQ at Week 24.

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/ 31.25/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 8 test.

Level 8: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in ACQ-7 at Week 24.

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/ 31.25/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 9 test.

Level 9: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in E-RS score over Weeks 21-24 (inclusive) of the treatment period.

One comparison based on pooled data:

(FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Test needs to be significant at 0.05 level in order to move to Level 10 test.

Level 10: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in E-RS score over Weeks 21-24 (inclusive) of the treatment period.

One comparison based on pooled data:

(FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25)

For all non-lung function secondary efficacy endpoints and all other efficacy endpoints, the following treatment comparisons of triple therapy vs. dual therapy at a fixed FF dose, for each given UMEC dose, will also be made without adjusting for multiplicity:

- FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/31.25/25 mcg vs. FF/ VI 200/25 mcg
- FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/62.5/25 mcg vs. FF/ VI 200/25 mcg

For all efficacy endpoints (primary, secondary, and other), treatment comparisons between triple therapy at low dose FF vs. dual therapy with high dose FF, or the benefit of increasing FF dose in a triple therapy, or the benefit of increasing UMEC dose in a triple therapy as outlined in 1) to 3) of Section 9.3.3 , respectively, will also be made without adjusting for multiplicity.

9.4. Key Elements of Analysis Plan

Where possible, data from subjects who withdraw prematurely from the study treatment or the study will be included in any relevant analyses. Specific details for inclusion will be detailed in the Reporting and Analysis Plan (RAP).

In general, the baseline value is the last assessment value prior to randomization at Visit 3 for the efficacy endpoints based on assessments at clinic visits, and the average value over the last 14 days prior to randomization during the stabilization period for the efficacy endpoints based on subjects' diary data. The covariates to be considered in the efficacy analyses include age, sex, the randomization stratification variable, and the baseline value, if relevant. For the pooled analyses of triple therapy vs. dual on non-lung function efficacy endpoints using combined data from both FF doses, the FF dosage will also be included in the analysis model as a categorical covariate to account for possible heterogeneity and/or data variability resulted from different ICS doses. Other covariates, if appropriate, may be considered. Specific details will be provided in the RAP.

9.4.1. Primary Analyses

The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at the end of the 24-week treatment period. For each subject, the baseline value of clinic FEV_1 is the last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomization (either from Visit 3 pre-dose or from Visit 2 pre-bronchodilator).

The primary efficacy analysis will evaluate the "de facto" type estimand in the Intent-to-Treat population, using a mixed-model repeated measures (MMRM) analysis, including all trough FEV_1 recorded post randomization. Analyses will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, sex, randomization stratification by pre-study ICS treatment dosage strength (mid, high) at screening, as well as the continuous, fixed covariates of age, baseline value, and baseline value by visit interaction. Point estimates and 95% confidence intervals will be calculated for the following primary comparisons of interest.

There are two treatment comparisons to demonstrate the replicate efficacy for the UMEC 62.5 mcg dose:

- FF/UMEC/VI 100/62.5/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/62.5/25 mcg vs. FF/ VI 200/25 mcg

Additionally, there will be two treatment comparisons for the UMEC 31.25 mcg dose to demonstrate the replicate efficacy for the UMEC 31.25 mcg dose:

- FF/UMEC/VI 100/31.25/25 mcg vs. FF/VI 100/25 mcg
- FF/UMEC/VI 200/31.25/25 mcg vs. FF/ VI 200/25 mcg

In addition, a de jure estimand, including data collected over the randomized double-blind treatment period, will be analyzed using a MMRM model. Sensitivity analyses to assess the impact of missing data will be detailed in the RAP.

Other pairwise treatment comparisons of interest as outlined in Section 9.3.3 will also be provided for the primary efficacy endpoint.

9.4.2. Secondary Analyses

The key secondary efficacy endpoint is the annualized rate of moderate/severe asthma exacerbations. Moderate/severe asthma exacerbations from the start to the end of double-blinded study period will be used in the analysis, regardless of subject's IP completion status. Exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

The exacerbation rate will be analysed using a generalised linear model, assuming the number of exacerbations has a negative binomial probability distribution and that its mean is related to covariate factors with a 'log link' function. The logarithm of time (year) on study will be used as an offset variable. The model will include covariates for age, sex, treatment group, randomization stratification by pre-study ICS treatment dosage strength (mid, high) at screening, and the FF dosage (categorical).

For each given UMEC dose, there is one treatment comparison of interest to demonstrate the efficacy of UMEC for the key secondary endpoint, based on the pooled data from both FF doses for triple therapy and dual therapy, respectively:

- FF/UMEC/VI (100/62.5/25 and 200/62.5/25) vs. FF/VI (100/25 and 200/25)
- FF/UMEC/VI (100/31.25/25 and 200/31.25/25) vs. FF/VI (100/25 and 200/25).

All pairwise treatment comparisons of interest as outlined in Section 9.3.3 will also be provided for the key secondary efficacy endpoint.

9.4.3. Other Analyses

Full details of the analyses to be performed on all efficacy endpoints, as well as details of time points to be analyzed, will be given in the RAP.

9.4.4. Examination of Subgroups and Phenotypic Characteristics

To explore differential responses and the phenotypic characteristics, subgroup and exploratory analyses may be considered. Of particular interest are the following phenotypic variables: age, sex, baseline lung function, reversibility to albuterol and ipratropium, asthma disease history, atopic status, exacerbation history, and biomarkers (blood and FeNO). The details of these exploratory analyses will be provided in the RAP.

9.4.5. Pharmacokinetic Analyses

The purpose of PK sampling in this study is for characterisation of PK of FF, UMEC and VI in the target asthma patients following FF/UMEC/VI administration. Plasma concentration-time data for FF, UMEC and VI will be subjected separately to nonlinear mixed effects modelling using NONMEM or other programs to develop the population PK models. Full details of the analyses for PK endpoints will be provided in the RAP.

9.4.6. Exploratory Analysis

The psychometric properties of the E-RS (see Section 7.3.5.1.1) and Supplemental asthma items (see Section 7.3.5.1.2) will be evaluated to support qualification of the E-RS as an endpoint for asthma. These exploratory analyses may be provided in a separate RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. 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.

10.2. 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 International Conference on Harmonisation (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.

10.3. 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 the eCRF 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.

10.4. 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.

10.5. 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.

10.6. 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.

10.7. Provision of Study Results to Investigators, Posting of Information on Publically 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.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
ACT	Asthma Control Test
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AM	Morning
AQLQ	Asthma Quality of Life Questionnaire
AST	Aspartate Transaminase
ATS	American Thoracic Society
AUC	Area Under the Curve
BID	Twice daily
BMI	Body Mass Index
BPM	Beats Per Minute
BST	Bioanalytical Science and Toxicokinetics
BTS/SIGN	British Thoracic Society / Scottish Intercollegiate Guidelines Network
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic acid
DMPK	Drug Metabolism and Pharmacokinetics
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
eDiary	Electronic Diary
EMA	European Medicines Agency
EOS	End of study
E-RS	Evaluating Respiratory Symptoms
ERS	European Respiratory Society
EU	European Union
EW	Early Withdrawal
FDA	Food and Drug Administration
FeNO	Fractional Exhaled Nitric Oxide
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FRP	Female of Reproductive Potential
FSC	Fluticasone Salmeterol Combination

FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GLP	Good Laboratory Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Axis
HR-QoL	Health-Related Quality of Life
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
kg	Kilogram
L/min	Liters per minute
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LOCS III	Lens Opacities Classification System III
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
MACE	Major Adverse Cardiac Event
MAOI	Monoamine Oxidase Inhibitors
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg (μg)	Microgram
MDI	Metered Dose Inhaler
mg	Milligram
min	Minute
mL	Milliliter
MMRM	Mixed-Model Repeated Measures
MSDS	Material Safety Data Sheet
msec	Millisecond
NIH	National Institutes of Health
NYHA	New York Heart Association
OCS	Oral Corticosteroids

PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PM	Afternoon
prn	As needed
QD	Once daily
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RAP	Reporting and Analysis Plan
RBC	Red Blood Cell
RNA	Ribonucleic acid
SABA	Short-Acting Beta-2-Agonists
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire
SPC	Summary of Product Characteristics
SRM	Study Reference Manual
TQT	Thorough QT
ULN	Upper Limit of Normal
UMEC	Umeclidinium
US	United States
VI	Vilanterol
VT	Ventricular Tachycardia
WBC	White Blood Cell
WPAI-SHP	Work Productivity and Activity Impairment-Specific Health Problem

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
DISKUS
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
NONMEM

12.2. Appendix 2 Liver Safety Required Actions and Follow up Assessments

Liver chemistry stopping and follow up criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance [Food and Drug Administration 2009]).

Liver chemistry stopping criteria 1-5 are defined below:

1. ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin) (or ALT ≥ 3xULN and INR>1.5, if INR measured)

NOTE: If serum bilirubin fractionation is not immediately available, withdraw study drug if ALT ≥ 3xULN and bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

2. ALT ≥ 8xULN.
3. ALT ≥ 5xULN but <8 xULN persists for ≥2 weeks
4. ALT ≥ 3xULN if associated with symptoms (new or worsening) believed to be related to hepatitis (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).
5. ALT ≥ 5xULN but <8 xULN and cannot be monitored weekly for ≥2 weeks

When any of the liver chemistry stopping criteria 1-5 is met, do the following:

- **Immediately** withdraw investigational product
- Report the event to GSK **within 24 hours** of learning its occurrence
- Complete the liver event CRF and SAE data collection tool if the event also meets the criteria for an SAE. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct) (or ALT ≥ 3xULN **and** INR>1.5, if INR measured); INR measurement is not required and the threshold value stated will not apply to patients receiving anticoagulants), termed 'Hy's Law', **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**.

NOTE: if serum bilirubin fractionation is not immediately available, withdraw study drug if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN. Serum bilirubin fractionation should be performed if testing is available. If testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.

- Complete the liver imaging and/or liver biopsy CRFs if these tests are performed
- Perform liver event follow up assessments, and monitor the subject until liver chemistries resolve, stabilize, or return to baseline values as described below.

- Withdraw the subject from the **study** (unless further safety follow up is required) after completion of the liver chemistry monitoring as described below.
- Do not re-challenge with investigational product.

In addition, for criterion 1:

- Make every reasonable attempt to have subjects return to clinic within **24 hours** for repeat liver chemistries, liver event follow up assessments (see below), and close monitoring
- A specialist or hepatology consultation is recommended
- Monitor subjects twice weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values

For criteria 2, 3, 4 and 5:

- Make every reasonable attempt to have subjects return to clinic **within 24-72 hrs** for repeat liver chemistries and liver event follow up assessments (see below)
- Monitor subjects weekly until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values; criterion 5 subjects should be monitored as frequently as possible.

Subjects with ALT ≥5xULN and <8xULN which exhibit a decrease to ALT x≥3xULN, but <5xULN and bilirubin <2xULN without hepatitis symptoms or rash, and who can be monitored weekly for 4 weeks:

- Notify the GSK medical monitor within 24 hours of learning of the abnormality to discuss subject safety
- Can continue investigational product
- Must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilize or return to within baseline
- If at any time these subjects meet the liver chemistry stopping criteria, proceed as described above
- If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor subjects twice monthly until liver chemistries normalize or return to within baseline values.

For criteria 1-5, make every attempt to carry out the **liver event follow up assessments** described below:

- Viral hepatitis serology including:
  - Hepatitis A IgM antibody;
  - Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM);
  - Hepatitis C RNA;
  - Cytomegalovirus IgM antibody;

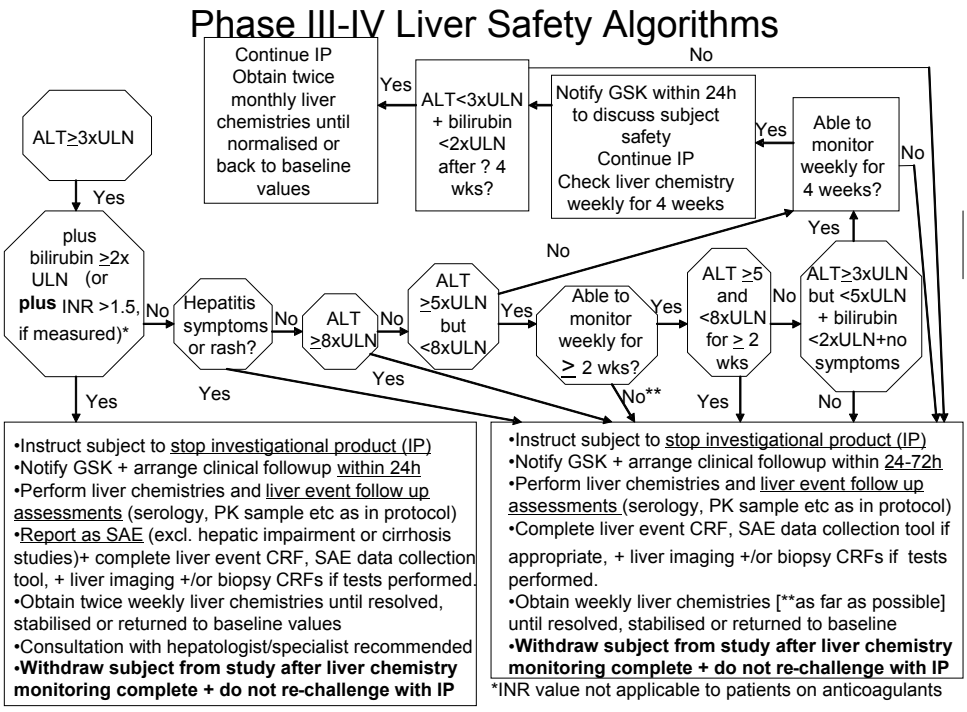
- Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing);
- Hepatitis E IgM antibody

- Blood sample for PK analysis, obtained within 72 hours of last dose. Record the date/time of the PK blood sample draw and the date/time of the last dose of investigational product 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.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥2xULN
- Obtain complete blood count with differential to assess eosinophilia
- Record the appearance or worsening of clinical symptoms of hepatitis or hypersensitivity, such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever rash or eosinophilia as relevant on the AE report form
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins, on the concomitant medications report form.
- Record alcohol use on the liver event alcohol intake case report form

The following are required for subjects with ALT ≥3xULN and bilirubin ≥2xULN (>35% direct) but are optional for other abnormal liver chemistries:

- Anti-nuclear antibody, anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Serum acetaminophen adduct assay (quantifies potential acetaminophen contribution to liver injury, detectable by HPLC assay more than 1 week following acetaminophen use) [James 2009].
- 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 antibody.
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

Figure 1 Phase III-IV Liver Safety Algorithms



12.3. Appendix 3 Genetic Research

Genetics – Background

Naturally occurring genetic variation may contribute to inter-individual variability in response to medicines, as well as an individual's risk of developing specific diseases. Genetic factors associated with disease characteristics may also be associated with response to therapy, and could help to explain some clinical study outcomes. For example, genetic variants associated with age-related macular degeneration (AMD) are reported to account for much of the risk for the condition [Gorin 2012] with certain variants reported to influence treatment response [Chen 2012]. Thus, knowledge of the genetic etiology of disease may better inform understanding of disease and the development of medicines. Additionally, genetic variability may impact the pharmacokinetics (absorption, distribution, metabolism, and elimination), or pharmacodynamics (relationship between concentration and pharmacologic effects or the time course of pharmacologic effects) of a specific medicine and/or clinical outcomes (efficacy and/or safety) observed in a clinical study.

Genetic Research Objectives and Analyses

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

- Response to medicine 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 6ml blood sample will be taken for Deoxyribonucleic acid (DNA) extraction. A blood sample is collected at the baseline 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 blood 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 blood 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 blood 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.

References

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12.4. Appendix 4 Definition of and Procedures for Recording, Evaluating, Follow-Up and Reporting of Adverse Events

12.4.1. Definition of Adverse Events

Adverse Event Definition:
• 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:
• 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.

Events <u>NOT</u> meeting definition of an AE include:
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the 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.

12.4.2. 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

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 <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 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 ≥ 3xULN and total bilirubin ≥ 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.

12.4.3. 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

12.4.4. 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.

12.4.5. 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.

12.4.6. 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 assigned SAE contact (see the Medical Monitor/Sponsor Information page at the beginning of this protocol) • 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 assigned SAE contact by telephone. • Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5 Reproduction

12.5.1. Females of Non-Reproductive Potential and Females of Reproductive Potential

A female subject is eligible to participate if she is not pregnant (as confirmed by a negative serum human chorionic gonadotrophin (hCG) test), not lactating, is not planning on becoming pregnant during the study and at least one of the following conditions applies:

- Non-reproductive potential defined as:
  - Pre-menopausal females with one of the following:
    - Documented tubal ligation
    - Documented hysteroscopic tubal occlusion procedure with follow-up confirmation of bilateral tubal occlusion
    - Hysterectomy
    - Documented Bilateral Oophorectomy
  - Postmenopausal defined as 12 months of spontaneous amenorrhea with an appropriate clinical profile (e.g., age appropriate, >45 years, in the absence of hormone replacement therapy). In questionable cases for women <60 years of age, a blood sample with simultaneous follicle stimulating hormone and estradiol falling into the central laboratory's postmenopausal reference range is confirmatory. Females under 60 years of age, who are on HRT and whose menopausal status is in doubt, are required to use a highly effective method to avoid pregnancy if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of post-menopausal status prior to study enrolment. For most forms of HRT, at least 2 to 4 weeks will elapse between the cessation of therapy and the blood draw; this interval depends on the type and dosage of HRT. Following confirmation of their post-menopausal status, subjects can resume use of HRT during the study without use of a highly effective method to avoid pregnancy.
- Reproductive potential and agrees to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 12.5.2) from the screening visit until after the last dose of study medication and completion of the follow-up visit.

12.5.2. List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP)

The list does not apply to FRP with same sex partners or for subjects who are and will continue to be abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

1. Contraceptive subdermal implant
2. Intrauterine device or intrauterine system
3. Combined estrogen and progestogen oral contraceptive [Hatcher 2011])
4. Injectable progestogen [Hatcher 2011]
5. Contraceptive vaginal ring [Hatcher 2011]
6. Percutaneous contraceptive patches [Hatcher 2011]
7. 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 2011]. The documentation on male sterility can come from the site personnel's: review of subject's medical records, medical examination and/or semen analysis, or medical history interview provided by her or her partner.

These allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label. The Investigator is responsible for ensuring that subjects understand how to properly use these methods of contraception.

12.5.3. 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 4. 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 in the study will immediately discontinue study medication.

12.5.4. References

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12.6. Appendix 6 Daily eDiary Questions

12.6.1. Morning Questions

The subject should complete the morning eDiary questions upon wakening and prior to the administration of study treatment.

Night-time Awakening

1.	Did you wake up due to asthma symptoms (i.e. wheezing, coughing, shortness of breath, or chest tightness).	No Yes
2.	If Yes; when you woke up due to your asthma symptoms did you use any rescue inhaler?	No Yes

12.6.2. Evening Questions

The subject should complete the evening eDiary questions just before going to bed.

E-RS

1.	Did your chest feel congested today?	Not at all Slightly Moderately Severely Extremely
2.	How often did you cough today?	Not at all Rarely Occasionally Frequently Almost constantly
3.	How much mucus (phlegm) did you bring up when coughing today?	None at all A little Some A great deal A very great deal
4.	How difficult was it to bring up mucus (phlegm) today?	Not at all Slightly Moderately

		Quite a bit Extremely
5.	Did you have chest discomfort today?	Not at all Slight Moderate Severe Extreme
6.	Did your chest feel tight today?	Not at all Slightly Moderately Severely Extremely
7.	Were you breathless today?	Not at all Slightly Moderately Severely Extremely
8.	Describe how breathless you were today:	Unaware of breathlessness Breathless during strenuous activity Breathless during light activity Breathless when washing or dressing Present when resting
9.	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Not at all Slightly Moderately Severely Extremely Too breathless to do these
10.	Were you short of breath today when performing your usual indoor activities like cleaning or household work?	Not at all Slightly Moderately Severely Extremely Too breathless to do these
11.	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Not at all Slightly Moderately Severely Extremely Too breathless to do these

Supplemental Asthma Items

1. Did you wheeze today?'	Not at all Rarely Occasionally Frequently Almost constantly
2. Were you short of breath today when performing strenuous activities such climbing stairs, running, or participating in sports activity.	Not at all Slightly Moderately Severely Extremely

Asthma Symptom and Physical Activity Questions

1. Please describe the severity of your asthma symptoms today (i.e. cough, wheeze, chest tightness, shortness of breath	No asthma symptoms Mild asthma symptoms Moderate asthma symptoms Severe asthma symptoms Very severe asthma symptoms
2. How limited were you in your activities today because of your asthma	Not at all limited A little limited Moderately limited Severely limited Totally limited

12.7. Appendix 7 Country Specific Requirements

12.7.1. Country Specific Requirement for the Randomization of Subjects

Japan Only: Subjects will be stratified by pre-study ICS treatment dosage strength (mid, high) at screening and will be assigned to study treatment in accordance with a country-specific randomization schedule (to ensure treatment balance within each stratum (mid- or high-dose pre-study ICS treatment dosage strength). The randomization code will be generated by GSK using a validated computerized system. Subjects will be randomized using an IRT system (RAMOS NG). Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study.

12.8. Appendix 8 Protocol Changes

12.8.1. Protocol Amendment 01

This amendment applies to all sites.

List of protocol changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

Change **Section, Text affected, and Rationale**

1. Medical Monitor/SAE Contact Information:

Changed from:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD	PPD	PPD	709 Swedeland Road, UW2531, King of Prussia, PA 19406
Secondary Medical Monitor	PPD	PPD	PPD	Gunnels Wood Rd, Stevenage SG1 2NY
SAE contact information	Medical monitor as above			

Change	Section, Text affected, and Rationale

Changed to:

Role	Name	Day Time Phone Number and email address	After-hours Phone/Cell/ Pager Number	Site Address
Primary Medical Monitor	PPD	PPD ***Please refer to the Study Reference Manual (SRM) for phone number details.***	PPD ***Please refer to the SRM.***	~~709 Swedeland Road, UW2531, King of Prussia, PA 19406~~
Secondary Medical Monitor	PPD	PPD ***Please refer to the SRM for phone number details.***	PPD ***Please refer to the SRM.***	~~Gunnels Wood Rd, Stevenage SG1 2NY~~
SAE contact information	Medical monitor as above			

Rationale: To capture a change in the assigned Medical Monitors as well as to provide a means to readily update the Medical Monitor contact details.

2. Section 1 Protocol Synopsis: Rationale, second paragraph, first sentence:

Changed from:

The GINA guidelines recommend a long-acting muscarinic antagonist (LAMA) as add-on treatment for adults with asthma that are currently taking medium to high dose inhaled corticosteroid/long-acting beta$_2$ agonist (ICS/ LABA) treatment and have a history of exacerbations.

Change	Section, Text affected, and Rationale
	Changed to: The GINA guidelines recommend a long-acting muscarinic antagonist (LAMA) as ***an*** add-on treatment ***option*** for adults with asthma that are currently taking medium to high dose inhaled corticosteroid/long-acting beta$_2$ agonist (ICS/ LABA) treatment and have a history of exacerbations. **Rationale:** To clarify the recommendation in the GINA guidelines.
3.	Section 1 Protocol Synopsis: Objective(s)/Endpoint(s) table, other secondary, endpoints column, fourth bullet-point AND Section 3 Objective(s) and Endpoint(s) table: other secondary, endpoints column, fourth bullet-point AND Section 7.3.1.3 Other Secondary Efficacy Endpoints: fourth bullet-point: ***Changed from:*** • Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over the first 24 weeks of the treatment period ***Changed to:*** • Mean change from baseline in Evaluating Respiratory Symptoms (E-RS) total score over ***Weeks 21 to 24 (inclusive)*** ~~the first 24 weeks~~ of the treatment period **Rationale:** To align with the primary endpoint and Patient Reported Outcome/Quality of Life related secondary endpoints on the assessment time period and the statistical analysis methodology.
4.	Section 1 Protocol Synopsis: Treatment Arms and Duration, first paragraph, second bullet-point (Screening / run-in), second sentence: ***Changed from:*** Subjects will take the last dose of their usual (i.e. pre-study) ICS/LABA asthma medication the morning prior to Visit 1 (i.e. ≥ 24 hours prior to the Screening Visit). ***Changed to:*** Subjects will take the last dose of their usual (i.e. pre-study) ICS/LABA asthma

Change	Section, Text affected, and Rationale
	medication ~~the morning prior to Visit 1 (i.e.~~ ≥ 24 hours prior to the Screening Visit~~)~~. **Rationale:** To clarify that an Investigator is able to request that a subject withhold their ICS/LABA asthma medication for longer than the morning prior to Visit 1.
5.	Section 2.1 Study Rationale: first paragraph, first sentence: ***Changed from:*** The Global Initiative for Asthma guidelines [GINA 2016] recommend a long-acting muscarinic antagonist (LAMA) as add-on treatment for adults (≥18 years) with asthma that are currently taking medium-to-high dose inhaled corticosteroid and long-acting beta$_2$ agonist (ICS/LABA) maintenance therapy and have a history of exacerbations. ***Changed to:*** The Global Initiative for Asthma guidelines [GINA 2016] recommend a long-acting muscarinic antagonist (LAMA) as ***an*** add-on treatment ***option*** for adults (≥18 years) with asthma that are currently taking medium-to-high dose inhaled corticosteroid and long-acting beta$_2$ agonist (ICS/LABA) maintenance therapy and have a history of exacerbations. **Rationale:** To clarify the recommendation in the GINA guidelines.
6.	Section 3 Objective(s) and Endpoint(s): other objectives, endpoints column, ninth, tenth, eleventh, fourteenth and fifteenth bullet-points AND Section 7.3.1.4 Other Efficacy Endpoints: ninth, tenth, eleventh, fourteenth and fifteenth bullet-points: ***Changed from:*** • Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score <0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score <0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score <0.75) at both Week 12 and Week 24 • Mean change from baseline in E-RS domain scores over the first 24 weeks of the treatment period

Change	Section, Text affected, and Rationale
	• Percent of patients meeting a responder threshold of ≥ 2 points improvement from baseline for the E-RS total score at Week 24 ***Changed to:*** • Percentage of patients that have achieved asthma control based on ACQ-7 (i.e. a total score ≤~~<~~0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-6 (i.e. a total score ≤~~<~~0.75) at both Week 12 and Week 24 • Percentage of patients that have achieved asthma control based on ACQ-5 (i.e. a total score ≤~~<~~0.75) at both Week 12 and Week 24 • Mean change from baseline in E-RS domain scores over ***Weeks 21 to 24 (inclusive)*** ~~the first 24 weeks~~ of the treatment period • Percent of patients meeting a responder threshold of ≥ 2 points improvement from baseline for the E-RS total score ***over Weeks 21 to 24 (inclusive) of the treatment period*** ~~at Week 24~~ **Rationale:** To clarify: • The Asthma Control Questionnaire (ACQ) total score that denotes controlled asthma. • The endpoints "Mean change from baseline in E-RS domain scores" and "Percent of patients meeting a responder threshold of ≥ 2 points improvement from baseline for the E-RS total score" will be assessed over Weeks 21 to 24 (inclusive) of the treatment period (rather than 'over the first 24 weeks of the treatment period' and 'at Week 24', respectively) to align with the secondary E-RS endpoint (i.e. mean change from baseline in E-RS total score).
7.	Section 4.2 Treatment Arms and Duration: Table 1, Phase 2 (Screening / Run-in), description column, second sentence: ***Changed from:*** Subjects will take the last dose of their regular (i.e. pre-study) ICS/LABA asthma medication the morning prior to Visit 1 (i.e. ≥ 24 hours prior to the Screening Visit). ***Changed to:*** Subjects will take the last dose of their regular (i.e. pre-study) ICS/LABA asthma medication ***≥ 24 hours*** ~~the morning~~ prior to Visit 1 (i.e. ≥ 24 hours prior to the Screening Visit).

Change	Section, Text affected, and Rationale
	Rationale: To clarify that an Investigator is able to request that a subject withhold their ICS/LABA asthma medication for longer than the morning prior to Visit 1.
8.	Section 4.6.1 Risk Assessment (table): Systemic ICS effects row, Summary of Data/Rationale for Risk column, first paragraph: ***Changed from:*** • No studies have shown a clinically relevant effect of FF/VI or FF on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), which assessed the effects of FF/VI 100/25 and 200/25 on serum cortisol and 24 hour serum cortisol excretion, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. ***Changed to:*** • No studies have shown a clinically relevant effect of FF/VI or FF on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), which assessed the effects of FF/VI 100/25 and 200/25 on serum cortisol and 24 hour ~~serum~~ ***urinary*** cortisol excretion, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. **Rationale:** To clarify that study HZA106851 assessed the effect of Investigational Product on 24 hour urinary (rather than serum) cortisol excretion.
9.	Section 5.1 Inclusion Criteria: inclusion criterion number 4: ***Changed from:*** **Asthma Control:** A documented non-routine healthcare visit due to acute asthma symptoms in the 1 year prior to Visit 1. ***Changed to:*** **Asthma Control:** ~~A documented non-routine healthcare visit due to acute asthma symptoms in the 1 year prior to Visit 1.~~ ***Note: please refer to the SRM for guidance on the following:*** ***In the 1 year prior to Visit 1:*** • ***A documented healthcare contact for acute asthma symptoms*** ***OR*** • ***A documented temporary change in asthma therapy for acute asthma symptoms, according to a pre-specified asthma action plan (or equivalent)***

Change	Section, Text affected, and Rationale
	Rationale: To align the criteria with the 'real-world' reporting/treatment of acute asthma symptoms.
10.	Section 5.1 Inclusion Criteria: inclusion criterion number 5: ***Changed from:*** **Current Asthma Maintenance Therapy**: Subjects are eligible if they have required daily ICS/LABA for at least 12 weeks prior to Visit 0 with no changes to maintenance asthma medications during the 6 weeks immediately prior to Visit 0 (including no changes to a stable total dose of ICS of >250 mcg/day fluticasone proprionate [FP, or equivalent]). Examples of acceptable doses of commonly prescribed ICS and LABA or ICS/LABA combination medication is provided in the Study Reference Manual (SRM). Dosing regimen (once or twice daily to equal the total daily dose) should be restricted to the current local product labels. ***Changed to:*** **Current Asthma Maintenance Therapy**: Subjects are eligible if they have required daily ICS/LABA for at least 12 weeks prior to Visit 0 with no changes to maintenance asthma medications during the 6 weeks immediately prior to Visit 0 (including no changes to a stable total dose of ICS of >250 mcg/day fluticasone proprionate [FP, or equivalent]). Examples of acceptable doses of commonly prescribed ICS ~~and LABA or ICS/LABA combination~~ medication ~~is~~ ***are*** provided in the ***GINA guidelines [GINA 2016]*** ~~Study Reference Manual (SRM)~~. Dosing regimen (once or twice daily to equal the total daily dose) should be restricted to the current local product labels***/treatment guidelines***. **Rationale:** The criteria requires that, in the 6 weeks immediately prior to Visit 0, there be no change to a stable total dose of ICS of >250 mcg/day FP (or equivalent) but there is no minimum total daily dose of LABA specified; therefore, only acceptable doses of commonly prescribed ICS (not LABA) need to be provided. The SRM references the GINA 2016 guidelines for acceptable doses of commonly prescribed ICS medication so a direct reference to the GINA 2016 guidelines has been provided in the protocol.
11.	Section 5.2 Exclusion Criteria: exclusion criterion number 2: ***Changed from:*** **Asthma Exacerbation:** Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1. *Note: Subjects who experience an asthma exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's*

Change	Section, Text affected, and Rationale
	discretion, the subject's condition is stable and they are considered appropriate for enrolment into this study of up to 12 months' duration. ***Changed to:*** **Asthma Exacerbation:** Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1. *Note: ~~Subjects who experience an asthma exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's discretion, the subject's condition is stable and they are considered appropriate for enrolment into this study of up to 12 months' duration.~~* ***Subjects requiring a temporary change in asthma therapy (e.g., oral corticosteroids or increased dose of ICS) to treat an exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's discretion, the subject's condition is stable after they have resumed their pre-exacerbation maintenance asthma therapy (without modification) and they are considered appropriate for enrolment into this study of up to 12 months' duration.*** **Rationale:** To clarify which subjects may not be excluded from the study in the event that they experience an asthma exacerbation in the 6 weeks prior to Visit 1.
12.	Section 5.2 Exclusion Criteria: exclusion criterion number 3: ***Changed from:*** **Chronic Obstructive Pulmonary Disease:** Subjects with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD 2016) guidelines, including all of the following: • History of exposure to risk factors (i.e., especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels); AND • A post-albuterol/salbutamol FEV_1/Forced Vital Capacity (FVC) ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≤70% of predicted normal values; AND • Onset of disease ≥40 years of age ***Changed to:*** **Chronic Obstructive Pulmonary Disease:** Subjects with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic

Change	Section, Text affected, and Rationale
	Obstructive Lung Disease (GOLD 2016) guidelines, including all of the following: • History of exposure to risk factors (i.e., especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels). ***For personal tobacco use, see exclusion criterion number 14: Tobacco Use***; AND • A post-albuterol/salbutamol FEV_1/Forced Vital Capacity (FVC) ratio of <0.70 and a post-albuterol/salbutamol FEV_1 of ≤70% of predicted normal values; AND • Onset of disease ≥40 years of age **Rationale:** To clarify that although the Investigator should consider exposure to tobacco smoke as a risk factor, the exclusion criteria concerning personal tobacco use are documented in exclusion criterion number 14.
13.	Section 5.2 Exclusion Criteria: exclusion criterion number 14: ***Changed from:*** **Tobacco Use:** Current smoker or a smoking history of ≥10 pack years (e.g., ≥20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products within the past 12 months (i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco). *Note: Refer to the SRM for the formula for calculating pack years.* ***Changed to:*** **Tobacco Use:** ~~Current smoker or a smoking history of ≥10 pack years (e.g., ≥20 cigarettes/day for 10 years). A subject may not have used inhaled tobacco products within the past 12 months (i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco).~~***Subjects who are:*** • ***Current smokers (defined as subjects who have used inhaled tobacco products within the 12 months prior to Visit 1 [i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco]).*** • ***Former smokers with a smoking history of ≥10 pack years (e.g., ≥20 cigarettes/day for 10 years).*** *Note: Refer to the SRM for the formula for calculating pack years.* **Rationale:** To clarify the definition of a 'current smoker' and, therefore, the definition of a 'former smoker'.
14.	Section 5.6.1 Withdrawal from Study Treatment: third paragraph, fourth bullet-

Change	**Section, Text affected, and Rationale**
	point: ***Changed from:*** • Study treatment unblinded: Unblinding of the study treatment assigned to a subject (see Section 6.3). ***Changed to:*** • ~~Study treatment unblinded: Unblinding of the study treatment assigned to a subject (see Section 6.3).~~ **Rationale:** It is not necessary to mandate that a subject must be withdrawn from study treatment for the sole reason that the treatment assigned to a subject is unblinded; however, the reason for the unblinding must still be captured in the eCRF.

15.	Section 5.6.4 QTc Stopping Criteria:
	
	Changed from:
	
	Details on performing ECG assessments can be found in Section 7.5.6.
	
	• 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 (QT interval corrected for heart rate by Bazett's formula), 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.
	• For this study, the following QTc stopping criteria will apply:
	  • QTcF>500 msec or uncorrected QT>600 msec
	  • Bundle branch block: QTcF≥ 530 msec
	  • Change from baseline: QTcF> 60msec

Change	**Section, Text affected, and Rationale**
	Changed to: Details on performing ECG assessments can be found in Section 7.5.6. • The ***QT interval corrected for heart rate by Fredericia's formula (QTcF)*** ~~*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 ***for the duration of the study***~~once the subject has been enrolled~~. ~~• For example, if a subject is eligible for the protocol based on QTcB (QT interval corrected for heart rate by Bazett's formula), 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*~~***QTcF*** must continue to be used for ***all*** ~~that~~ subject***s*** *for all QTc data being collected for data analysis*. Safety ECGs and other non-protocol specified ECGs are an exception. • The QTc***F*** should be based on single or averaged QTc***F*** values of triplicate electrocardiograms obtained over a brief (e.g., 5-10 minute) recording period. • For this study, the following QT c stopping criteria will apply: • QTcF>500 msec or uncorrected QT>600 msec • Bundle branch block: QTcF≥ 530 msec • Change from baseline: QTcF> 60msec **Rationale:** The QT interval corrected for heart rate by Fredericia's formula (QTcF) will be used throughout the study. The QT interval corrected for heart rate by Bazett's formula (QTcB) will not be used (safety ECGs and other non-protocol specified ECGs are an exception).
16.	Section 6.1 Investigational Product and Other Study Treatment: tenth paragraph: ***Changed from:*** At the Investigator's discretion, provision will be made from Visit 1 onwards for subjects to temporarily receive fluticasone propionate (FP; 100 mcg BID or equivalent) via the DISKUS DPI to treat the symptoms of a moderate asthma exacerbation (see Section 7.3.6.1); treatment start and stop dates will be recorded in the eCRF. FP will be sourced from local commercial stock; if not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements. A record of the number of FP-containing DISKUS DPIs dispensed to each subject must be maintained and reconciled with study treatment records.

Change	**Section, Text affected, and Rationale**
	Changed to: At the Investigator's discretion, provision will be made from Visit 1***[1]*** onwards for subjects to temporarily receive fluticasone propionate (FP~~;~~ 100 mcg ~~BID~~ ***[***or equivalent***]***) via the DISKUS DPI to treat the symptoms of a moderate asthma exacerbation (see ***Section 6.9.1.1 and Section 7.3.6.1***)~~.~~; ***T***~~t~~reatment start and stop dates will be recorded in the eCRF. ***[1]Note: Should the subject use the provided FP prior to randomization at Visit 3, the enrolment or randomization concomitant medication exclusion criteria would be met (see Section 5.3.2 and Section 5.4.2).*** FP will be sourced from local commercial stock; if not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements. A record of the number of FP-containing DISKUS DPIs dispensed to each subject must be maintained and reconciled with study treatment records. **Rationale:** The total daily dose of the study-provided FP (to be used temporarily to treat the symptoms of a moderate asthma exacerbation) is at the Investigator's discretion; therefore it is not appropriate to specify that FP should be administered twice daily (i.e. BID). In addition, a statement has been included to indicate that although FP will be provided to the subject at Visit 1, its use by the subject prior to randomization at Visit 3 will meet the study exclusion criteria.
17.	Section 6.3 Blinding: second paragraph: ***Changed from:*** A subject will be withdrawn from the study if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF. ***Changed to:*** ~~A subject will be withdrawn from the study if the subject's treatment code is unblinded by the Investigator or treating physician. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the eCRF.~~ **Rationale:** It is not necessary to mandate that a subject must be withdrawn from the study for the sole reason that the treatment assigned to a subject is unblinded.
18.	Section 6.6 Compliance with Study Treatment Administration: fourth paragraph, first sentence:

Change	**Section, Text affected, and Rationale**
	Changed from: If the double-blind study treatment is prematurely discontinued during the course of the study or treatment compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study. ***Changed to:*** ~~If the double-blind study treatment is prematurely discontinued during the course of the study or treatment compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss subject eligibility for continued participation in the study.~~ **Rationale:** Subjects should continue to be followed-up as per protocol until the completion of the Safety Follow-up assessments.
19.	Section 6.9 Concomitant Medications and Non-Drug Therapies: first paragraph, first sentence: ***Changed from:*** All asthma medications used within approximately 6 weeks prior to screening and during the study (including the post-treatment period) should be recorded in the eCRF. ***Changed to:*** All asthma medications used within approximately 6 weeks prior to ***pre-***screening ***(Visit 0)*** and during the study (including the post-treatment period) should be recorded in the eCRF. **Rationale:** To align with Inclusion Criterion number 5 which requires no changes to maintenance asthma medications during the 6 weeks immediately prior to Visit 0.
20.	Section 6.9.1.1 Permitted Asthma Medications: first paragraph, second bullet-point: ***Changed from:*** • Systemic corticosteroids (≤5 milligrams (mg)/day) will be permitted provided that treatment was initiated at least 12 weeks prior to Visit 1, remains stable for the 8 weeks prior to Visit 1 and the subject remains in the maintenance phase (i.e., it is not weaned) throughout the study (the only exception being the treatment of moderate/severe asthma exacerbations [see below]).

Change	Section, Text affected, and Rationale
	Changed to: • Systemic corticosteroids (≤5 milligrams (mg)/day ***of prednisone [or an equivalent dose of an alternative systemic corticosteroid]***) will be permitted provided that treatment was initiated at least 12 weeks prior to Visit 1, remains stable for the 8 weeks prior to Visit 1 and the subject remains in the maintenance phase (i.e., it is not weaned) throughout the study (the only exception being the treatment of moderate/severe asthma exacerbations [see below]). **Rationale:** To clarify the permitted daily dose of systemic corticosteroids.
21.	Section 6.9.1.1 Permitted Asthma Medications: second paragraph (including first bullet-point): ***Changed from:*** Temporary changes in medications are permitted for the treatment of moderate asthma exacerbations (see Section 7.3.6.1) at the Investigator's/treating physician's discretion. Asthma exacerbations should be treated in line with national and international recommendations and local medical standards. Asthma medications permitted on a temporary basis to treat a moderate asthma exacerbation include but are not limited to the following (the Medical Monitor may be contacted for additional guidance, see the medical monitor/Sponsor Information Page): • An increase in ICS dose (including but not limited to fluticasone propionate [FP; 100 mcg BID or equivalent] which will be provided for this purpose). ***Changed to:*** Temporary ***additions*** ~~changes~~ in medications are permitted for the treatment of moderate asthma exacerbations (see Section 7.3.6.1) at the Investigator's/treating physician's discretion. Asthma exacerbations should be treated in line with national and international recommendations and local medical standards. Asthma medications permitted on a temporary basis to treat a moderate asthma exacerbation include but are not limited to the following (the Medical Monitor may be contacted for additional guidance, see the medical monitor/Sponsor Information Page): • An increase in ICS dose (including but not limited to ***the use of study-provided*** ~~fluticasone propionate [~~FP~~; 100 mcg BID or equivalent]~~ which ***may be used by the subject at a total daily dose deemed appropriate by the Investigator/treating physician*** ~~will be provided for this purpose~~). **Rationale:** To clarify that: • Medications used temporarily for the treatment of moderate asthma

Change Section, Text affected, and Rationale

exacerbations are in addition to the protocol-defined study treatment (rather than a change in study treatment).

- The total daily dose of study-provided FP used to treat a moderate asthma exacerbation is at the discretion of the Investigator/treating physician.

22. Section 6.9.1 Permitted Medications and Non-Drug Therapies

Added as Section 6.9.1.3 Permitted Non-Drug Therapies:

Continuous Positive Airway Pressure (CPAP) for the treatment of obstructive sleep apnea is permitted if initiated at least 6 weeks prior to the Screening Visit (Visit 1) and the subject continues CPAP treatment throughout the study. This treatment must be captured in the eCRF.

Rationale: To allow subjects to continue pre-study initiated CPAP for the treatment of obstructive sleep apnea.

23. Section 6.9.2 Prohibited Medications and Non-Drug Therapies; Table 4 Concomitant Medications

Changed from:

Medication	No use during the study and/or within the following time interval before Visit 1
Inhaled short-acting anticholinergics	6 hours
Inhaled short-acting anticholinergics+ Short-acting beta agonist combination	6 hours
Inhaled long-acting anticholinergics other than study treatment	2 days
Immunosuppressive medications including immunomodulators	12 weeks
Inhaled long-acting beta$_2$-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta$_2$-agonists (e.g., Seretide, Symbicort) Inhaled very long-acting beta2-agonists, (Indacaterol, Olodaterol) Oral long-acting beta$_2$-agonists (e.g., bambuterol)	These must be withheld after the regular dose on the morning of the day before Visit 1 (at least 24h prior to Visit 1); other than the study treatment, they will not be permitted during the study. 10 days prior to Visit 1 for Indacaterol and Olodaterol component.
Inhaled short-acting beta$_2$-agonist (rescue albuterol/salbutamol will be provided and is permitted during the study)	6 hours (including all study visits)
Theophyllines, slow-release bronchodilators, ketotifen, nedocromil sodium,	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations

Change Section, Text affected, and Rationale

sodium cromoglycate, roflumilast	
Anti-leukotrienes	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

Changed to:

Medication	No use during the study and/or within the following time interval before Visit 1
Inhaled short-acting anticholinergics	6 hours
Inhaled short-acting anticholinergics+ Short-acting beta agonist combination	6 hours
Inhaled long-acting anticholinergics other than study treatment	2 days***. Temporary use during the study is also prohibited.***
Immunosuppressive medications including immunomodulators	12 weeks
Inhaled long-acting beta$_2$-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta$_2$-agonists (e.g., Seretide, Symbicort) Inhaled very long-acting beta2-agonists, (Indacaterol, Olodaterol) Oral long-acting beta$_2$-agonists (e.g., bambuterol)	These must be withheld ~~after the regular dose on the morning of the day before Visit 1 (~~at least 24h prior to Visit 1~~)~~; other than the study treatment, they will not be permitted during the study ***(including for temporary use)***. 10 days prior to Visit 1 for Indacaterol and Olodaterol component. ***Temporary use during the study is also prohibited.***
Inhaled short-acting beta$_2$-agonist (rescue albuterol/salbutamol will be provided and is permitted during the study)	6 hours (including all study visits)
Theophyllines, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Anti-leukotrienes	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Medical marijuana	***6 months. Medical marijuana administered via the inhaled route is strictly prohibited. Other routes of administration of medical marijuana are also prohibited UNLESS written permission is obtained from the Medical***

Change Section, Text affected, and Rationale

	Monitor prior to Visit 1.
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

Rationale:

- To clarify that the temporary use of LABAs and LAMAs during the study is prohibited.
- To clarify the time-period prior to Visit 1 that LABA medication must be withheld.
- To address the possible use of medical marijuana during the study.

Change	Section, Text affected, and Rationale

24. Section 7.1 Time and Events Table

Changed from:

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	0	1[1]	2	3[2] Random-ization	4	5	6	7	8 End of Study (EOS)	Early Withdrawal (EW)[3]	Safety Follow-up Contact
Study Day	-49 to -36	-35	-14	1	29	85	169	253	365		
Week	-6 to -7	-5	-2	0	4	12	24	36	52		1 week after Visit 8/EOS or EW Visit
Window			-3/+5d[4]		-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d		-1/+4d

Notes:

1. Visit 1 must be completed ≥1 day but ≤14 days after Visit 0.
2. Visit 3 must always be conducted ≥14 days after Visit 2.
3. EW Visit should be conducted if double-blind study treatment is discontinued AND the subject discontinues from participating in the study.
4. The time window for this visit means that Visit 2 may be conducted up to 3 days before or up to 5 days after the scheduled date of Visit 2.
5. The ICF must be signed before any study procedures, including medication cessation.

15. Following completion of the pre-dose spirometry assessments, the reversibility test will be conducted between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol. If airway reversibility is not demonstrated at Visit 1 then the assessment may be repeated within 7 days of Visit 1 (see Section 7.3.4.1.1 for details of the criteria to be met before a repeat of the reversibility assessment is permitted). If airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are met then the subject may enter the 3-week run-in period.

18. ECG to be obtained 15 minutes to 45 minutes after the administration of study treatment.

27. The administration of study treatment at this visit is optional.

30. FP 100 mcg BID (or equivalent) may be used temporarily to treat the symptoms of a moderate asthma exacerbation, at the Investigator's discretion.

Change Section, Text affected, and Rationale

Changed to:

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period						Follow-up	
				Fixed Treatment Period				Variable Treatment Period			
Visit	0	1[1]	2[2]	3[23] Random-ization	4	5	6	7	8 End of Study (EOS)	Early Withdrawal (EW)[34]	Safety Follow-up Contact
Study Day	-49 to -36	-35	-14	1	29	85	169	253	365		
Week	-6 to -7	-5	-2	0	4	12	24	36	52		1 week after Visit 8/EOS or EW Visit
Window			~~-3/+5d~~[4]		-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d		-1/+4d

Notes:

1. Visit 1 ***should*** ~~must~~ be completed ≥1 day but ≤14 days after Visit 0***; however, if it is local and routine medical practice to request that a subject withhold their ICS/LABA medication for at least 24 hours prior to a clinic visit then, provided that the subject has complied with the request, Visit 0 and Visit 1 can occur on the same day***.
2. ~~Visit 3 must always be conducted ≥14 days after Visit 2.~~ ***Visit 2 may be conducted up to 3 days before the scheduled date of Visit 2. The duration of the run-in period (i.e. the time period between Visits 1 and 2) must be ≥18 days but ≤26 days.***
3. ~~EW Visit should be conducted if double-blind study treatment is discontinued AND the subject discontinues from participating in the study.~~ Visit 3 must always be conducted ≥14 days ***but ≤17 days*** after Visit 2.
4. ~~The time window for this visit means that Visit 2 may be conducted up to 3 days before or up to 5 days after the scheduled date of Visit 2.~~ EW Visit should be conducted if double-blind study treatment is discontinued AND the subject discontinues from participating in the study.
5. The ICF must be signed before any study procedures, including ***protocol-specified*** medication cessation.

15. Following completion of the pre-dose spirometry assessments, the reversibility test will be conducted between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol. If airway reversibility is not demonstrated at Visit 1 then the assessment may be repeated within 7 days of Visit 1 (see Section 7.3.4.1.1 for details of the criteria to be met before a repeat of the reversibility assessment is permitted). If airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are met then the subject may ***commence*** ~~enter~~ the 3-week run-in period ***(starting on the date that airway reversibility was successfully demonstrated at the second attempt)***.

18. ***At the Screening Visit (Visit 1), the ECG is to be obtained after the vital signs assessment but prior to performing the pre-bronchodilator spirometry assessment (see Section 7.5.6). At all post-randomization visits the*** ECG ***is*** to be obtained 15 minutes to 45 minutes after the administration of study treatment.

27. The administration of study treatment at this visit is optional. ***If study treatment is not administered at this visit then those assessments which are scheduled based on the time of study treatment administration should be performed at approximately the same time of day as performed at the preceding post-***

Change	Section, Text affected, and Rationale

randomization visits.

30. FP ~~100 mcg BID (or equivalent)~~ may be used temporarily to treat the symptoms of a moderate asthma exacerbation, at the Investigator's discretion. ***However, please note that a subject's use of the provided FP prior to randomization at Visit 3 would meet the enrolment or randomization concomitant medication exclusion criteria (see Section 5.3.2 and Section 5.4.2).***

Rationale:

- In the table header, the footnote numbers have been amended to align with the order of the amended footnotes.
- The Visit 2 time window has been deleted (along with the associated footnote); the explanation of the time window is now captured in footnote 2 in order to clarify the possible length of the run-in period when the time windows are applied.
- The maximum duration of the stabilization period (i.e. the time period between Visits 2 and 3) has been included to clarify the possible length of the stabilization period.
- Footnote number 5 has been amended to align with the amended wording of footnote number 1.
- In the event that it is necessary to repeat the airway reversibility assessment, footnote number 15 has been amended to clarify that if airway reversibility is successfully demonstrated at the second attempt then the run-in period will commence on the date that the this repeat reversibility assessment was conducted.
- Footnote number 18 has been amended to clarify that the ECG assessment conducted at the Screening Visit should be done prior to the pre-bronchodilator spirometry assessment in order to mitigate any effect that albuterol/salbutamol administration may have on the ECG assessment.
- Footnote 27 has been amended to clarify when the Early Withdrawal Visit assessments should be conducted in the event that study treatment is not administered at this visit (the administration of study treatment at this visit is optional).

Change	Section, Text affected, and Rationale
	• Footnote 30 has been amended to clarify that a subject's pre-randomization use of the study-provided FP will meet the exclusion criteria for the study.

Change	Section, Text affected, and Rationale
25.	Section 7.3.4.1 Reversibility: first paragraph, second sentence: ***Changed from:*** A pre-bronchodilator spirometry assessment should be performed after a washout period of at least 4 hours for short-acting β_2- agonists. ***Changed to:*** A pre-bronchodilator spirometry assessment should be performed after a washout period of at least ~~4~~ ***6*** hours for short-acting β_2- agonists. **Rationale:** Correction of a typographical error.
26.	Section 7.3.5 Daily Diaries: third paragraph, first sentence ***Changed from:*** Subjects will also be issued with a paper Medical Problems/Medications Taken worksheet to record any medical problems and non-study specific medications used during the study. ***Changed to:*** ***Subjects will also be issued with a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study (please refer to the SRM for further details).*** ~~Subjects will also be issued with a paper Medical Problems/Medications Taken worksheet to record any medical problems and non-study specific medications used during the study.~~ **Rationale:** The paper Medical Problems/Medications Taken worksheet will be used to record study specific and non-study specific medications used during the study.
27.	Section 7.3.6 Asthma Exacerbations: ***Changed from:*** Moderate/severe asthma exacerbation data will be collected from the start of randomized double blinded treatment until Visit 8/EOS Visit or the Early Withdrawal Visit for those subjects that withdraw from participation in the study (see Section 5.6). For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. Alerts will be programmed into the eDiary to instruct the subject to contact the Investigator immediately for a medical assessment (see Section 7.3.5.1.6). The notification of decreasing asthma control from the eDiary will assist the

Change	Section, Text affected, and Rationale
	Investigator in the identification of new asthma exacerbations. Subjects will also complete a paper Medical Problems/Medications Taken worksheet to record any medical problems and non-study specific medications used during the study, as well as all emergency department visits and/or hospitalizations that occur during their participation in the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist the Investigator in the identification of new asthma exacerbations. All moderate/severe asthma exacerbations will be recorded in the eCRF by the Investigator (or designee). ***Changed to:*** ~~Moderate/severe asthma exacerbation data will be collected~~ ***For the purposes of this study, moderate/severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page*** from the start of randomized double blinded treatment until Visit 8/EOS Visit or the Early Withdrawal Visit for those subjects that withdraw from participation in the study (see Section 5.6). ***Moderate/severe asthma exacerbations should not be recorded as an adverse event unless:*** • ***They meet the definition of an Adverse Event (see Appendix 4) and occur:*** o ***After the start of study treatment until the start of double blinded study treatment or;*** o ***After completion of the Visit 8/EOS Visit (or Early Withdrawal Visit) assessments until the follow-up contact.*** ***OR*** • ***They meet the definition of a Serious Adverse Event (see Appendix 4). Note: The SAE page of the eCRF should be completed in addition to the asthma exacerbation eCRF page if the exacerbation occurs after the start of double blinded treatment but before completion of the Visit 8/EOS Visit or Early Withdrawal Visit assessments.*** For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation. Alerts will be programmed into the eDiary to instruct the subject to contact the Investigator immediately for a medical assessment (see Section 7.3.5.1.6). The notification of decreasing asthma control from the eDiary will assist the

Change	Section, Text affected, and Rationale
	Investigator in the identification of new asthma exacerbations. ***Subjects will also complete a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study***~~Subjects will also complete a paper Medical Problems/Medications Taken worksheet to record any medical problems and non-study specific medications used during the study~~, as well as all emergency department visits and/or hospitalizations that occur during their participation in the study. This paper worksheet must be reviewed by the Investigator (or designee) at each visit to the study site to assist the Investigator in the identification of new asthma exacerbations. All moderate/severe asthma exacerbations will be recorded in the eCRF by the Investigator (or designee). **Rationale:** • To clarify how asthma exacerbations should be recorded in the eCRF. • The paper Medical Problems/Medications Taken worksheet will be used to record study specific and non-study specific medications used during the study.
28.	Section 7.5.1.2 Method of Detecting AEs and SAEs: second paragraph, first sentence: AND Section 7.5.8 Paper Medical Problems/Medications Taken Worksheet: first paragraph, first sentence: ***Changed from:*** Subjects will be issued with a paper Medical Problems/Medications Taken worksheet to record any medical problems and non-study specific medications used during the study. ***Changed to:*** ***Subjects will be issued with a paper Medical Problems/Medications Taken worksheet to record medical problems experienced and medications used during the study (please refer to the SRM for further details).***~~Subjects will be issued with a paper Medical Problems/Medications Taken worksheet to record any medical problems and non-study specific medications used during the study.~~ **Rationale:** The paper Medical Problems/Medications Taken worksheet will be used to record study specific and non-study specific medications used during the study.

Change	**Section, Text affected, and Rationale**
29.	Section 7.5.6 Electrocardiogram (ECG): first paragraph: ***Changed from:*** All sites will use standardised ECG equipment provided by a centralized external vendor. A single 12-lead ECG and rhythm strip will be recorded after measurement of vital signs and spirometry. Recordings will be made at the time-points defined in the Time and Events table (Section 7.1). All ECG measurements will be made with the subject in a supine position having rested in this position for approximately 5 minutes before each reading. ***Changed to:*** All sites will use standardised ECG equipment provided by a centralized external vendor. A***t the Screening Visit (Visit 1), a*** single 12-lead ECG and rhythm strip will be recorded after ***the*** measurement of vital signs ***but before*** ~~and~~ ***performing the pre-bronchodilator*** spirometry ***assessment***. ***At the post-randomization visits, a single 12-lead ECG and rhythm strip will be recorded 15 to 45 minutes after the administration of study treatment.*** Recordings will be made at the time-points defined in the Time and Events table (Section 7.1). All ECG measurements will be made with the subject in a supine position having rested in this position for approximately 5 minutes before each reading. **Rationale:** To clarify the timing of the pre- and post-randomization ECG assessments.
30.	Section 7.6 Pharmacokinetics (PK): fourth paragraph, first bullet-point: ***Changed from:*** The following points must be noted: • If assessments are scheduled for the same nominal time, THEN the assessments should occur in the following order: 1. 12-lead ECG 2. vital signs 3. blood draws. Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time. ***Changed to:*** The following points must be noted: • If assessments are scheduled for the same nominal time, THEN the

Change Section, Text affected, and Rationale

assessments should occur in the following order ***(as applicable)***:

1. ***Vital signs***~~12-lead ECG~~
2. ***12-lead ECG***~~vital signs~~
3. blood draws.

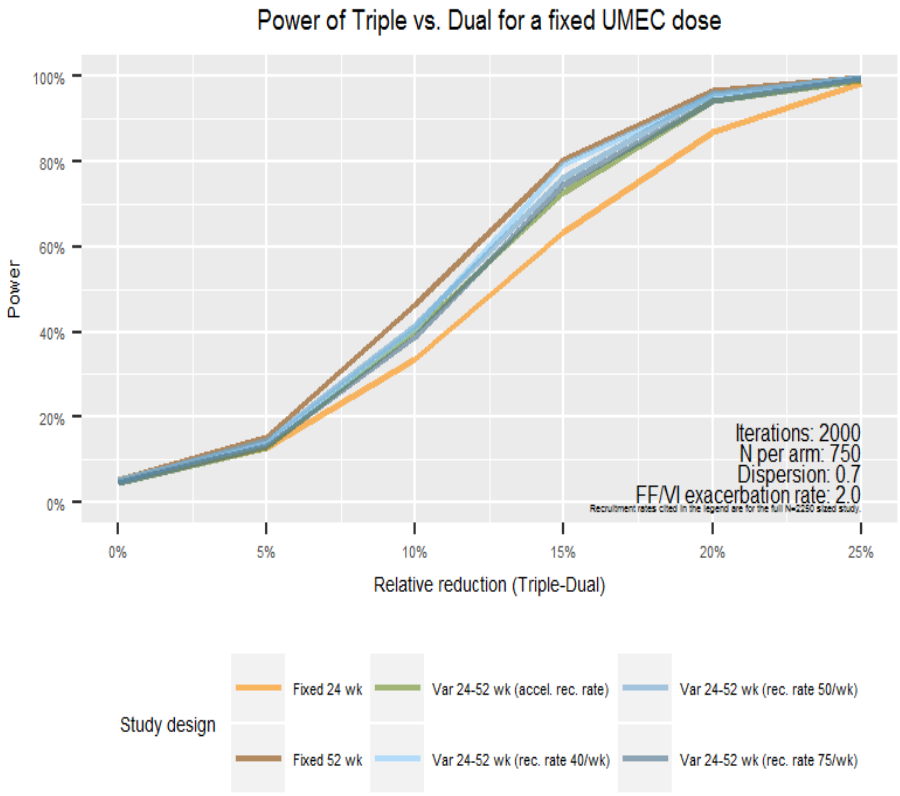
Note: The timing of the assessments should allow the blood draw to occur at the exact nominal time.

Rationale: To clarify the order of assessments.

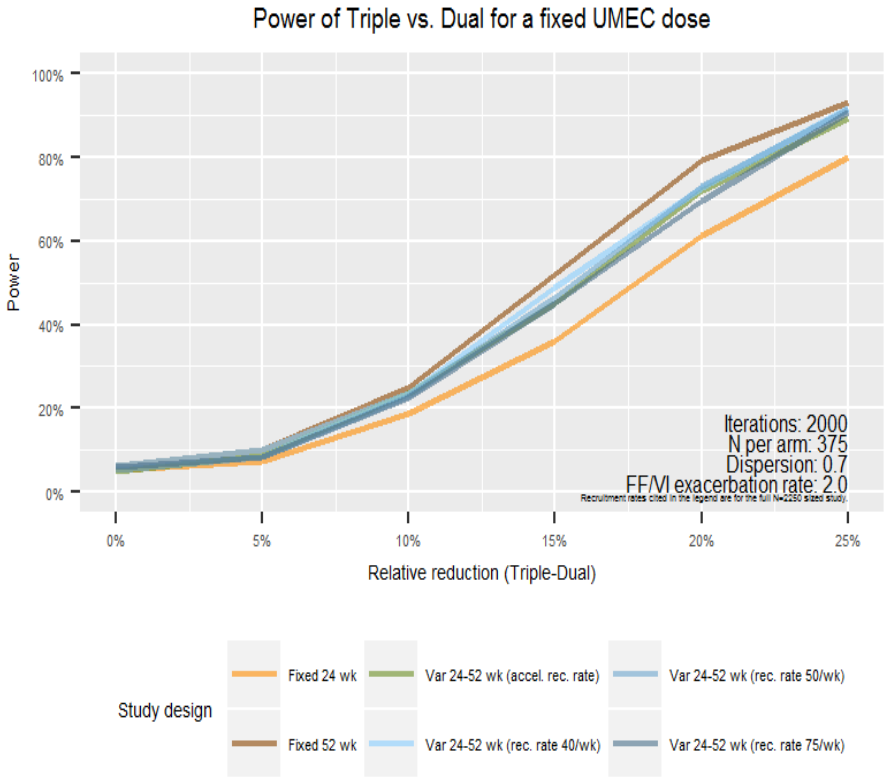
31. Section 9.2.2 Sample Size Sensitivity: power function table AND power of triple vs. dual for a fixed UMEC dose graphs:

Changed from:

dispersion	FF/VI rate	FF/UMEC/VI rate	Relative Reduction	power	
				n=750/arm	n=375/arm
0.7	1.50	1.275	15%	0.66	0.40
	1.50	1.200	20%	0.90	0.63
	1.50	1.125	25%	0.98	0.84
	2.00	1.700	15%	0.73	0.45
	2.00	1.600	20%	0.94	0.72
	2.00	1.500	25%	>0.99	0.89
	2.50	2.125	15%	0.77	0.50
	2.50	2.000	20%	0.97	0.76
	2.50	1.875	25%	>0.99	0.93
0.8	1.50	1.275	15%	0.62	0.40
	1.50	1.200	20%	0.88	0.64
	1.50	1.125	25%	0.99	0.82
	2.00	1.700	15%	0.70	0.45
	2.00	1.600	20%	0.93	0.65
	2.00	1.500	25%	>0.99	0.87
	2.50	2.125	15%	0.76	0.47
	2.50	2.000	20%	0.95	0.73
	2.50	1.875	25%	>0.99	0.91

Change Section, Text affected, and Rationale


Change Section, Text affected, and Rationale

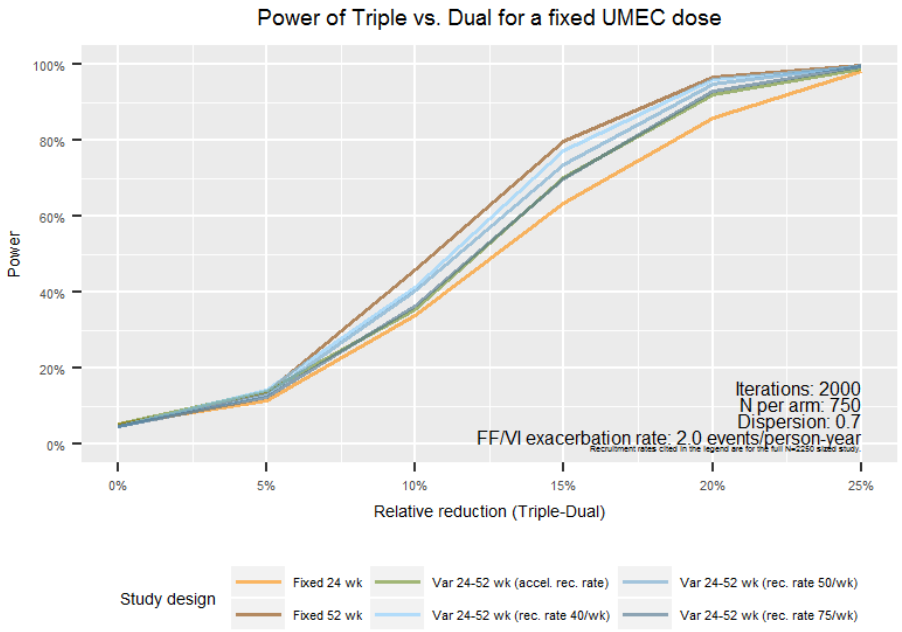


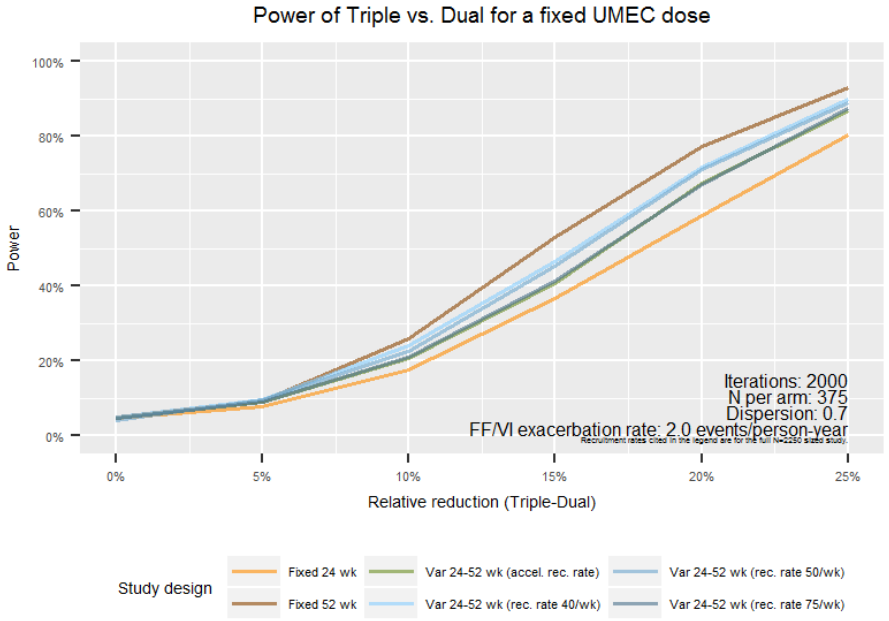
Changed to:

dispersion	FF/VI rate	FF/UMEC/VI rate	Relative Reduction	power	
				n=750/arm	n=375/arm
0.7	1.50	1.275	15%	0.~~66~~***62***	0.~~40~~***37***
	1.50	1.200	20%	0.~~90~~***87***	0.~~63~~***59***
	1.50	1.125	25%	0.98	0.~~84~~***81***
	2.00	1.700	15%	0.~~73~~***70***	0.~~45~~***41***
	2.00	1.600	20%	0.~~94~~***92***	0.~~72~~***67***
	2.00	1.500	25%	~~>~~0.99	0.~~89~~***87***
	2.50	2.125	15%	0.~~77~~***75***	0.~~50~~***49***
	2.50	2.000	20%	0.~~97~~***95***	0.~~76~~***72***
	2.50	1.875	25%	>0.99	0.~~93~~***90***
0.8	1.50	1.275	15%	0.~~62~~***61***	0.~~40~~***36***

Change Section, Text affected, and Rationale

	1.50	1.200	20%	0.88***86***	0.64***56***
	1.50	1.125	25%	0.99***97***	0.82***77***
	2.00	1.700	15%	0.70***65***	0.45***41***
	2.00	1.600	20%	0.93***91***	0.65***66***
	2.00	1.500	25%	≥0.99	0.87***85***
	2.50	2.125	15%	0.76***73***	0.47***44***
	2.50	2.000	20%	0.95***94***	0.73***69***
	2.50	1.875	25%	>0.99	0.91***88***



Change	**Section, Text affected, and Rationale**
	 **Rationale:** To capture the change to the power calculation based on the proposed study duration that is truncated to the scheduled visits at Weeks 24, 36 and 52. The original power calculation was based on the variable duration up to Week 52.
32.	Section 9.3.4 Multiple Comparisons and Multiplicity: Multiplicity Adjustment Plan, level 3b AND level 5, mean change from baseline in E-RS total score endpoint: ***Changed from:*** Mean change from baseline in E-RS score over the 24 week treatment period a. (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25) ***Changed to:*** Mean change from baseline in E-RS score over ***Weeks 21 to 24 (inclusive) of*** the ~~24 week~~ treatment period a. (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25) **Rationale:** To align the Multiplicity Adjustment Plan with the Other Secondary endpoints.
33.	Section 9.4 Key Elements of Analysis Plan: second paragraph, third sentence: ***Changed from:***

Change	Section, Text affected, and Rationale
	For the pooled analyses of triple therapy vs. dual on non-lung function efficacy endpoints using combined data from both FF doses, the FF dosage will also be included in the analysis model as a categorical covariate to account for possible heterogeneity and/or data variability resulted in different ICS doses. ***Changed to:*** For the pooled analyses of triple therapy vs. dual on non-lung function efficacy endpoints using combined data from both FF doses, the FF dosage will also be included in the analysis model as a categorical covariate to account for possible heterogeneity and/or data variability resulted ***from*** ~~in~~ different ICS doses. **Rationale:** To correct a typographical error.

12.8.2. Protocol Amendment 02

Protocol changes for Amendment 02 (23-JUN-2017), from amendment 01 (13-DEC-2016)

This amendment applies to all sites.

Amendment 02 Summary and Rationale

List of Specific changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

Change	Section, Text affected, and Rationale
34.	Section 3 Other Objectives: clarify morning or evening. ***Changed from:*** Mean change from baseline in morning evening (PM) PEF over the first 24 weeks of the treatment period ***Changed to:*** Mean change from baseline in ~~morning~~ evening (PM) PEF over the first 24 weeks of the treatment period **Rationale:** To clearly define "evening" (PM) PEF over the first 24 weeks of the treatment period.
35.	Section 3 Other Objectives: amend responder threshold language for ACQ-7,

Change	Section, Text affected, and Rationale
	ACQ-6, ACQ-5, E-RS & AQLQ to clearly define and be consistent with protocol ***Changed from:*** • Percent of patients meeting a responder threshold of ≥0.5 in change • from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change • from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change • from baseline for the ACQ-5 at Week 24 • Percent of patients meeting a responder threshold of 2 points improvement from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period. • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement from baseline for the AQLQ total score at Week 24. ***Changed to:*** • Percent of patients meeting a responder threshold of ≥0.5 ~~in change~~ ***points improvment (decrease)*** from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 ~~in change~~ ***points improvement (decrease)*** from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 ~~in change~~ ***points improvement (decrease)*** from baseline for the ACQ-5 at Week 24 • Percent of patients meeting a responder threshold of ≥ 2 points improvement ***(decrease)*** from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period. • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement ***(increase)*** from baseline for the AQLQ total score at Week 24. **Rationale:** To clearly define the ACQ-7, ACQ-6, ACQ-5, E-RS & AQLQ responder threshold and be consistent with protocol language, as well as "Other Efficacy Endpoints"
36.	Section 5.1 Inclusion Criteria ***Changed from:*** **Current Asthma Maintenance Therapy:**

Change	Section, Text affected, and Rationale
	• Examples of acceptable doses of commonly prescribed ICS medication are provided in the GINA guidelines [GINA 2016]. ***Changed to:*** **Current Asthma Maintenance Therapy:** • Examples of acceptable doses of commonly prescribed ICS medication are provided in the GINA guidelines [GINA 2016, ***BTS/SIGN 2016, Japanese guidelines for adult asthma 2017***]. **Rationale:** To include additional supported guidance in the following documents; BTS/SIGN Guideline (2016) and Japanese guidelines adult asthma (2017).
37.	Section 5.1 Inclusion Criteria ***Changed from:*** **Spirometry:** • A best pre-bronchodilator morning (AM) FEV1 ≥30% and <80% of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer 2012]. ***Changed to:*** **Spirometry:** • A best pre-bronchodilator morning (AM) FEV1 ≥30% and <***85%*** of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer 2012]. **Rationale:** To broaden the eligibility criteria to include patients with less pulmonary impairment who remain uncontrolled on ICS/LABA.
38.	Section 5.3.1 Inclusion Criteria for Enrolment ***Changed from:*** **Percent-predicted FEV_1:** • A best pre-bronchodilator morning (AM) FEV1 ≥30% and <80% of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer 2012].

Change	Section, Text affected, and Rationale

Changed to:

Percent-predicted FEV_1:

- A best pre-bronchodilator morning (AM) FEV1 ≥30% and <***90%*** of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer 2012].

Rationale: To broaden the eligibility criteria to include patients with less pulmonary impairment who remain uncontrolled on ICS/LABA.

39. Section 7.1 Time and Events Table; Screening visit box for Serum pregnancy test

Changed from:

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period					
				Fixed Treatment Period				Variable Treatment Period	
Visit	0	1[1]	2[2]	3[3] Random-ization	4	5	6	7	8 End of Study (EOS)
Study Day	-49 to -36	-35	-14	1	29	85	169	253	365
Week	-6 to -7	-5	-2	0	4	12	24	36	52
Window					-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d
Laboratory Assessments									
Pharmacogenetic sample[20]				X					
Serum pregnancy test		X					X[21]		X[21]

- Screening visit box for Serum pregnancy test with no footnote

Changed to:

Protocol Activity	Pre-Screen[1]	Screen Run-in	Enrolment Stabilization	Treatment Period					
				Fixed Treatment Period				Variable Treatment Period	
Visit	0	1[1]	2[2]	3[3] Random-ization	4	5	6	7	8 End of Study (EOS)
Study Day	-49 to -36	-35	-14	1	29	85	169	253	365
Week	-6 to -7	-5	-2	0	4	12	24	36	52
Window					-5/+2d	-5/+2d	-5/+2d	-5/+2d	-5/+2d
Laboratory Assessments									
Pharmacogenetic sample[20]				X					
Serum pregnancy test		X[21]					X[21]		X[21]

- Screening visit box for Serum pregnancy test includes footnote #21; Assessments to be conducted in females of reproductive potential

Rationale: clearly define that only assessments of Serum pregnancy to be

Change	Section, Text affected, and Rationale
	conducted in females of reproductive potential
40.	Section 7.3.1.4 Other Efficacy Endpoints: amend responder threshold language for ACQ-7, ACQ-6, ACQ-5, E-RS & AQLQ to clearly define and be consistent with protocol language ***Changed from:*** • Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5 at Week 24 • Percent of patients meeting a responder threshold of ≥ 2 points improvement from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period. • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement from baseline for the AQLQ total score at Week 24. ***Changed to:*** • Percent of patients meeting a responder threshold of ≥0.5 ~~in change~~ ***points improvement (decrease)*** from baseline for the ACQ-7 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 ~~in change~~ ***points improvement (decrease)*** from baseline for the ACQ-6 at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 ~~in change~~ ***points improvement (decrease)*** from baseline for the ACQ-5 at Week 24 • Percent of patients meeting a responder threshold of ≥ 2 points improvement ***(decrease)*** from baseline for the E-RS total score over Weeks 21 to 24 (inclusive) of the treatment period. • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement ***(increase)*** from baseline for the AQLQ total score at Week 24. **Rationale:** To clearly define the ACQ-7, ACQ-6, ACQ-5, E-RS & AQLQ responder threshold and be consistent with the protocol language, as well as consistent with "Other Objectives".
41.	Section 7.3.5.1.6 Alerts ***Changed from:*** Subjects will be instructed to contact the Investigator if any of the above alert

Change	Section, Text affected, and Rationale
	criteria are met (either by telephone and/or by visiting the study clinic). ***Changed to:*** ***The baseline value, for the purpose of alerts, is defined as the average value over the last 7 days prior to randomization***. Subjects will be instructed to contact the Investigator if any of the above alert criteria are met (either by telephone and/or by visiting the study clinic). **Rationale:** To clearly define the baseline value alerts.
42.	Section 9.3.1 Analysis Population: Corrected typographical error. ***Changed from:*** Pharmacokinetic (PK) population: This population will comprise all subject in the ITT Population for whom a PK sample was obtained and analyzed. ***Changed to:*** Pharmacokinetic (PK) population: This population will comprise all subject***s*** in the ITT Population for whom a PK sample was obtained and analyzed. **Rationale:** Corrected typographical error. Added 's' to end of subject.
43.	Section 9.3.4 Multiple Comparisons and Multiplicity ***Changed from:*** A step-down closed testing approach will be applied for the primary and the key secondary efficacy endpoints. Specifically, if the defined treatment comparisons for the primary efficacy endpoint between triple therapy and dual therapy at high dose of UMEC 62.5 mcg are significant at 0.05 level for both fixed FF doses, then the replicate efficacy of UMEC 62.5mcg is demonstrated, and the defined treatment comparison between triple therapy and dual therapy will be test for the key secondary efficacy endpoint on moderate/severe asthma exacerbation based on the combined data of both FF doses. If the test for the key secondary efficacy endpoint is significant at 0.05 level, then the above testing hierarchy for the primary and the key secondary efficacy endpoints will be repeated for the low dose of UMEC 31.25 mcg. The family-wise Type I Error is strongly controlled at 0.05 level for the primary endpoint (trough FEV1) and the key secondary endpoint (moderate/severe asthma exacerbations) for the UMEC 62.5 mcg dose. In addition, for a given UMEC dose, the secondary endpoints (Mean change from baseline in FEV1 at 3 hour post-dose at Week 24, Mean change from baseline in ACQ-7 at Week 24, Mean change from baseline in SGRQ at Week

Change	Section, Text affected, and Rationale
	24, Mean change from baseline in E-RS score over the 24 week treatment period) are nested under the primary and the key secondary endpoints. If the defined treatment comparisons for the high dose of UMEC 62.5 mcg demonstrate statistical significance at the 5% level on the primary efficacy endpoint and the key secondary endpoint, then inferences relating to the secondary endpoints for the high dose of UMEC 62.5 mcg will be made; the same strategy will be applied for the low dose of UMEC 31.25 mcg. ***Changed to:*** A step-down closed testing approach will be applied for the primary ***efficacy endpoint*** ~~and~~ the key secondary efficacy endpoints, ***and the secondary efficacy endpoints SGRQ, ACQ-7, and E-RS***. Specifically, if the defined treatment comparisons for the primary efficacy endpoint between triple therapy and dual therapy at ***the*** high dose of UMEC 62.5 mcg are ***statistically*** significant at ***the*** 0.05 level for both fixed FF doses ***(100 and 200mcg)***, then the replicate efficacy of UMEC 62.5mcg is demonstrated, and the defined treatment comparison between triple therapy and dual therapy will be test***ed*** for the key secondary efficacy endpoint ~~on~~ ***of*** moderate/severe asthma exacerbation***s*** based on the combined data of both FF doses for ***UMEC 62.5mcg***. If the test for the key secondary efficacy endpoint is ***statistically*** significant at ***the*** 0.05 level, then ***the secondary efficacy endpoints for SGRQ (Mean change from baseline in SGRQ at Week 24) and ACQ-7 (Mean change from baseline in ACQ-7 at Week 24) will be tested sequentially based on the combined data of both FF doses for UMEC 62.5mcg at significance level 0.05***.~~the above testing hierarchy for the primary and the key secondary efficacy endpoints will be repeated for the low dose of UMEC 31.25 mcg.~~ ***If all tests mentioned above for UMEC 62.5 mcg are statistically significant at the 0.05 level, the above testing hierarchy for the primary efficacy endpoint, the key secondary efficacy endpoint, and the secondary efficacy endpoints SGRQ and ACQ-7 will be repeated for the low dose of UMEC 31.25 mcg.*** ***If all tests for the primary, the key secondary, and the secondary efficacy endpoints for SGRQ and ACQ-7 are statistically significant at the 0.05 level for both UMEC 62.5mcg and 31.25mcg, the secondary endpoint for E-RS (Mean change from baseline in E-RS score over the Weeks 21-24 (inclusive) of the treatment period) will be tested at the significance level 0.05 for UMEC 62.5 and UMEC 31.25 in sequence.*** The family-wise Type I Error is strongly controlled at 0.05 level ***for both UMEC 62.5mcg and UMEC 31.25mcg on*** the primary endpoint (trough FEV1) ~~and~~ the key secondary endpoint (moderate/severe asthma exacerbations)***, and the secondary endpoints on SGRQ, ACQ-7, and E-RS*** ~~for the UMEC 62.5 mcg dose~~.

Change	Section, Text affected, and Rationale
	~~In addition, for a given UMEC dose, the secondary endpoints (Mean change from baseline in FEV1 at 3 hour post-dose at Week 24, Mean change from baseline in ACQ-7 at Week 24, Mean change from baseline in SGRQ at Week 24, Mean change from baseline in E-RS score over the 24 week treatment period) are nested under the primary and the key secondary endpoints. If the defined treatment comparisons for the high dose of UMEC 62.5 mcg demonstrate statistical significance at the 5% level on the primary efficacy endpoint and the key secondary endpoint, then inferences relating to the secondary endpoints for the high dose of UMEC 62.5 mcg will be made; the same strategy will be applied for the low dose of UMEC 31.25 mcg.~~ **Rationale:** Miltiplicity adjustment plan has been updated to ensure the strong control on the family-wise Type I Error across multiple endpoints and multiple treatment comparisons.
44.	Section 9.3.4 Multiple Comparisons and Multiplicity, Multiplicity Adjustment Plan: update the order and hierarchy within the multiplicity plan. ***Changed from:*** Level 1: Primary endpoint, UMEC 62.5 mcg: Mean change from baseline in trough FEV1 at Week 24, Two comparisons: FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25. Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 62.5 mcg in order to move to Level 2 test. Level 2: Key secondary endpoint, UMEC 62.5 mcg: annualized rate of moderate/severe asthma exacerbations, One comparison based on pooled data: (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 3 tests. Level 3a: Primary endpoint, UMEC 31.25mcg: Mean change from baseline in trough FEV1 at Week 24, Two comparisons: FF/UMEC/VI 100/31.25/25 vs. FF/VI 100/25 FF/UMEC/VI 200/31.25/25 vs. FF/VI 200/25. Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 31.25mcg and move to Level 4 tests. Level 3b: Secondary endpoints, UMEC 62.5 mcg, four endpoints test sequentially at the level 0.05. • 1) Mean change from baseline in FEV1 at 3 hour post-dose at Week 24. Two comparisons adjust by Hochberg procedure) a) FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 b) FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 • 2) Mean change from baseline in ACQ-7 at Week 24 a) (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25)

Change	Section, Text affected, and Rationale
	• 3) Mean change from baseline in SGRQ at Week 24 a) (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25) • 4) Mean change from baseline in E-RS score over Weeks 21 to 24 (inclusive) of the treatment period a) (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25) Level 4: Key secondary endpoint, UMEC 31.25 mcg: annualized rate of moderate/severe asthma exacerbations, One comparison based on pooled data: (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 5 tests. Level 5: Secondary endpoints, UMEC 31.25 mcg, four endpoints test sequentially at the level 0.05. • 1) Mean change from baseline in FEV1 at 3 hour post-dose at Week 24. Two comparisons adjust by Hochberg procedure) a) FF/UMEC/VI 100/31.25/25 vs. FF/VI 100/25 b) FF/UMEC/VI 200/31.25/25 vs. FF/VI 200/25 • 2) Mean change from baseline in ACQ-7 at Week 24 a) (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25) • 3) Mean change from baseline in SGRQ at Week 24 a) (FF/UMEC/VI 100/62.5/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25) • 4) Mean change from baseline in E-RS score over Weeks 21 to 24 (inclusive) of the treatment period a) (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25) ***Changed to:*** Level 1: Primary endpoint, UMEC 62.5 mcg: Mean change from baseline in trough FEV1 at Week 24, Two comparisons: FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25. Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 62.5 mcg in order to move to Level 2 test. Level 2: Key secondary endpoint, UMEC 62.5 mcg: annualized rate of moderate/severe asthma exacerbations, One comparison based on pooled data: (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 3 tests. Level 3: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in SGRQ at Week 24, One comparison based on pooled data: (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 4 test. Level 4: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in

Change	Section, Text affected, and Rationale
	ACQ-7 at Week 24, One comparison based on pooled data: (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 5 tests. Level 5: Primary endpoint, UMEC 31.25mcg: Mean change from baseline in trough FEV1 at Week 24, Two comparisons: FF/UMEC/VI 100/31.25/25 vs. FF/VI 100/25 FF/UMEC/VI 200/31.25/25 vs. FF/VI 200/25. Both tests need to be significant at 0.05 level in order to demonstrate replicate efficacy for UMEC 31.25mcg and move to Level 6 tests. Level 6: Key secondary endpoint, UMEC 31.25 mcg: annualized rate of moderate/severe asthma exacerbations, One comparison based on pooled data: (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 7 tests. Level 7: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in SGRQ at Week 24, One comparison based on pooled data: (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 8 test. Level 8: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in ACQ-7 at Week 24, One comparison based on pooled data: (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 9 tests. Level 9: Secondary endpoint, UMEC 62.5 mcg: Mean change from baseline in E-RS score over Weeks 21-24 (inclusive) of the treatment period. One comparison based on pooled data: (FF/UMEC/VI 100/62.5/25, 200/62.5/25) vs. (FF/VI 100/25, 200/25). Test needs to be significant at 0.05 level in order to move to Level 10 test. Level 10: Secondary endpoint, UMEC 31.25 mcg: Mean change from baseline in E-RS score over Weeks 21-24 (inclusive) of the treatment period. One comparison based on pooled data: (FF/UMEC/VI 100/31.25/25, 200/31.25/25) vs. (FF/VI 100/25, 200/25) **Rationale:** Miltiplicity adjustment plan has been updated to ensure the strong control on the family-wise Type I Error across multiple endpoints and multiple treatment comparisons.
45.	Section 9.3.4: Multiple Comparisons and Multiplicity, Multiplicity Adjustment Plan ***Changed from:*** For all efficacy endpoints (primary, secondary, and other), treatment comparisons between triple therapy at low dose FF vs. dual therapy with high dose FF, or the benefit of increasing FF dose in a triple therapy, or the benefit of increasing UMEC dose in a triple therapy as outlined in 1) to 3) of Section 9.3.3 , respectively, will also be made without adjusting for multiplicity. Any p-

Change	Section, Text affected, and Rationale
	values ≤ 0.05 will be identified as nominally significant. ***Changed to:*** For all efficacy endpoints (primary, secondary, and other), treatment comparisons between triple therapy at low dose FF vs. dual therapy with high dose FF, or the benefit of increasing FF dose in a triple therapy, or the benefit of increasing UMEC dose in a triple therapy as outlined in 1) to 3) of Section 9.3.3 respectively, will also be made without adjusting for multiplicity. ~~Any p-values ≤ 0.05 will be identified as nominally significant.~~ **Rationale:** To align the Multiplicity Adjustment Plan with the Reporting and Analysis Plan (RAP).
46.	Section 11.0 References ***Changed from:*** Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135(4):896-902. James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA,et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metab Dispos* 2009;37:1779-1784. Changed to: Hekking PP, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. J Allergy Clin Immunol 2015;135(4):896-902. Ichinose M, Sugiura H, Nagase H, Yamaguchi M, Inoue H, Sagara H, et al. Japanese guidelines for adult asthma 2017. *Allergol Int*. 2017;66(2):163-189 James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA,et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metab Dispos* 2009;37:1779-1784. **Rationale:** Added the reference to Japanese Guidelines for Adult Asthma

12.8.3. Protocol Amendment 03

Protocol changes for Amendment 03 (29-SEP-2017), from amendment 02 (23 JUN-2017)

This amendment applies to all sites.

Amendment 03 Summary and Rationale

List of Specific changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

47.	Section 1: Protocol Synopsis for Study 205715; Treatment Arms and Duration ***Changed from:*** The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. The study treatment cut-off date for all ongoing subjects will then be set at 11 days (i.e. 1 week and 4 days) prior to the study completion date. The study sites will be notified in advance to inform all ongoing subjects of the study treatment cut-off date and the study completion date. Once the study treatment cut-off and study completion dates are determined, ongoing subjects must continue to adhere to their pre-planned study visit schedule; however, the on-treatment clinic assessment visit that is scheduled to occur before but closest to the study treatment cut-off date (without consideration of available visit time-windows) will be defined as the subject's final treatment/EOS visit. The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS. ***Changed to:*** The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. ~~The study treatment cut-off date for all ongoing subjects will then be set at 11 days (i.e. 1 week and 4 days) prior to the study completion date. The study sites will be notified in advance to inform all ongoing subjects of the study treatment cut-off date and the study completion date.~~ ***To determine when the final treatment/EOS visit will occur for each randomized subject in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a date henceforth referred to as the transition date will be communicated to the study sites by GSK. GSK will***

communicate a provisional transition date to all study sites on an ongoing basis during the study, until a fixed actual transition date is communicated at least 20 weeks in advance of the selected date (unless extenuating circumstances dictate otherwise). The date selected by GSK as the actual transition date will always be more than 12 days prior to the study completion date. At the Investigator's discretion, subjects should be informed of the transition date (provisional and actual) on an ongoing basis during the study so that their expected final treatment/EOS visit can be planned using the provisional transition date and then confirmed once the actual transition date is known.

Subjects who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit.

~~Once the study treatment cut-off and study completion dates are determined, ongoing subjects must continue to adhere to their pre-planned study visit schedule; however, the on-treatment clinic assessment visit that is scheduled to occur before but closest to the study treatment cut-off date (without consideration of available visit time-windows) will be defined as the subject's final treatment/EOS visit. The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.~~

After the actual transition date is communicated, subjects must adhere to their study visit schedule and complete a minimum of 24 weeks of study treatment. A subject's final treatment/EOS visit will be defined as follows:

- ***Subjects whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at their Week 24 clinic assessment visit.***
- ***Subjects who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time-windows).***

The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.

Rationale: The protocol is being amended to base the variable treatment period on the planned recruitment rather than the date of the last subject randomized. This aligns planned exposure more closely with actual exposure

	and enables sites and participants to plan according to the variable treatment period. The term 'study treatment cut-off date' will be replaced with 'transition date' to avoid confusion.
48.	Section 4.2: Treatment Arms and Duration; Phase 4, Treatment ***Changed from:*** The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. The study treatment cut-off date for all ongoing subjects will then be set at 11 days (i.e. 1 week and 4 days) prior to the study completion date. The study sites will be notified in advance to inform all ongoing subjects of the study treatment cut-off date and the study completion date. Once the study treatment cut-off and study completion dates are determined, ongoing subjects must continue to adhere to their pre-planned study visit schedule; however, the on-treatment clinic assessment visit that is scheduled to occur before but closest to the study treatment cut-off date (without consideration of available visit time-windows) will be defined as the subject's final treatment/EOS visit. The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS. ***Changed to:*** The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. ~~The study treatment cut-off date for all ongoing subjects will then be set at 11 days (i.e. 1 week and 4 days) prior to the study completion date. The study sites will be notified in advance to inform all ongoing subjects of the study treatment cut-off date and the study completion date.~~ ***To determine when the final treatment/EOS visit will occur for each randomized subject in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a date henceforth referred to as the transition date will be communicated to the study sites by GSK. GSK will communicate a provisional transition date to all study sites on an ongoing basis during the study, until a fixed actual transition date is communicated at least 20 weeks in advance of the selected date (unless extenuating circumstances dictate otherwise). The date selected by GSK as the actual transition date will always be more than 12 days prior to the study completion date. At the Investigator's discretion, subjects should be informed of the transition date (provisional and actual) on an ongoing basis during the study so that their expected final treatment/EOS visit can be planned using the provisional transition date and then confirmed once the actual transition date***

	is known. ***Subjects who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit.*** ~~Once the study treatment cut-off and study completion dates are determined, ongoing subjects must continue to adhere to their pre-planned study visit schedule; however, the on-treatment clinic assessment visit that is scheduled to occur before but closest to the study treatment cut-off date (without consideration of available visit time-windows) will be defined as the subject's final treatment/EOS visit. The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.~~ ***After the actual transition date is communicated, subjects must adhere to their study visit schedule and complete a minimum of 24 weeks of study treatment. A subject's final treatment/EOS visit will be defined as follows:*** – ***Subjects whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at their Week 24 clinic assessment visit.*** – ***Subjects who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time-windows).*** ***The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.*** **Rationale:** The protocol is being amended to base the variable treatment period on the planned recruitment rather than the date of the last subject randomized. This aligns planned exposure more closely with actual exposure and enables sites and participants to plan according to the variable treatment period. The term 'study treatment cut-off date' will be replaced with 'transition date' to avoid confusion.
49.	Section 4.3: Type and Number of Subjects (last sentence) ***Changed from:*** For country-specific requirements on the number of randomized subjects see

	Appendix 7. ***Changed to:*** ~~For country-specific requirements on the number of randomized subjects see Appendix 7.~~ **Rationale:** The minimum requirement for Japanese subjects is no longer dependent on study 205715.
50.	Section 5.7: Subject and Study Completion ***Changed from:*** The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. The study treatment cut-off date for all ongoing subjects will then be set at 11 days (i.e. 1 week and 4 days) prior to the study completion date. The study sites will be notified in advance to inform all ongoing subjects of the study treatment cut-off date and the study completion date. Once the study treatment cut-off and study completion dates are determined, ongoing subjects must continue to adhere to their pre-planned study visit schedule; however, the on-treatment clinic assessment visit that is scheduled to occur before but closest to the study treatment cut-off date (without consideration of available visit time-windows) will be defined as the subject's final treatment/EOS visit. The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS. ***Changed to:*** The date that the whole study will complete (henceforth referred to as the study completion date) will be determined based on the randomization date of the final subject in the study; the study completion date will be set at 181 days (i.e. 25 weeks and 6 days) post the final subject's randomization date. ~~The study treatment cut-off date for all ongoing subjects will then be set at 11 days (i.e. 1 week and 4 days) prior to the study completion date. The study sites will be notified in advance to inform all ongoing subjects of the study treatment cut-off date and the study completion date.~~ ***To determine when the final treatment/EOS visit will occur for each randomized subject in this variable duration study (i.e. at Week 24, Week 36 or Week 52 of the treatment period), a date henceforth referred to as the transition date will be communicated to the study sites by GSK. GSK will communicate a provisional transition date to all study sites on an ongoing basis during the study, until a fixed actual transition date is communicated at least 20 weeks in advance of the selected date (unless extenuating circumstances dictate otherwise). The date selected by GSK as the actual***

transition date will always be more than 12 days prior to the study completion date. At the Investigator's discretion, subjects should be informed of the transition date (provisional and actual) on an ongoing basis during the study so that their expected final treatment/EOS visit can be planned using the provisional transition date and then confirmed once the actual transition date is known.

Subjects who complete 52 weeks of study treatment prior to the actual transition date being communicated will have their final treatment/EOS visit at their Week 52 clinic assessment visit.

~~Once the study treatment cut-off and study completion dates are determined, ongoing subjects must continue to adhere to their pre-planned study visit schedule; however, the on-treatment clinic assessment visit that is scheduled to occur before but closest to the study treatment cut-off date (without consideration of available visit time-windows) will be defined as the subject's final treatment/EOS visit. The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS (See Section 7.1).~~

After the actual transition date is communicated, subjects must adhere to their study visit schedule and complete a minimum of 24 weeks of study treatment. A subject's final treatment/EOS visit will be defined as follows:

- ***Subjects whose Week 24 clinic assessment visit is scheduled to occur on or after the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at their Week 24 clinic assessment visit.***
- ***Subjects who have their Week 24, Week 36 or Week 52 clinic assessment visit scheduled to occur before the actual transition date (without consideration of available visit time-windows) will have their final treatment/EOS visit at the clinic assessment visit that is scheduled to occur before but closest to the actual transition date (without consideration of available visit time-windows).***

The subject's final treatment/EOS visit must include all assessments specified for Visit 8/EOS.

Rationale: The protocol is being amended to base the variable treatment period on the planned recruitment rather than the date of the last subject randomized. This aligns planned exposure more closely with actual exposure and enables sites and participants to plan according to the variable treatment period. The term 'study treatment cut-off date' will be replaced with 'transition date' to avoid confusion.

51.	Section 7.1: Time and Events Table; Footnote #22 (last sentence) ***Changed from:*** (see Appendix 7 for country-specific requirements) ***Changed to:*** ~~(see Appendix 7 for country-specific requirements)~~ **Rationale:** The minimum requirement for Japanese subjects is no longer dependent on study 205715.
52.	Section 7.6.1.1: Pharmacokinetic Substudy (2nd Paragraph, last sentence) ***Changed from:*** See Appendix 7 or country-specific requirements related to the PK sub-study ***Changed to:*** ~~See Appendix 7 for country-specific requirements related to the PK sub-study.~~ **Rationale:** The minimum requirement for Japanese subjects is no longer dependent on study 205715.
53.	Section 12.7.1: Country Specific Requirement for the Randomization of Subjects ***Changed from:*** **Japan Only:** The total number of randomized subjects required in Japan is approximately 300 of the 2250 randomized subjects required for the study, with approximately 50 Japanese subjects randomized to each of the 6 double-blind treatment arms. At Visit 3, approximately 20% of consenting Japanese subjects who are randomised to participate in the main study will be entered into the PK sub-study (see Section 7.6) Subjects will be stratified by pre-study ICS treatment dosage strength (mid, high) at screening and will be assigned to study treatment in accordance with a country-specific randomization schedule (to ensure treatment balance within each stratum (mid- or high-dose pre-study ICS treatment dosage strength). The randomization code will be generated by GSK using a validated computerized system. Subjects will be randomized using an IRT system (RAMOS NG). Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study. ***Changed to:*** ~~**Japan Only:** The total number of randomized subjects required in Japan is~~

~~approximately 300 of the 2250 randomized subjects required for the study, with approximately 50 Japanese subjects randomized to each of the 6 double-blind treatment arms. At Visit 3, approximately 20% of consenting Japanese subjects who are randomised to participate in the main study will be entered into the PK sub-study (see Section 7.6)~~

Japan Only: Subjects will be stratified by pre-study ICS treatment dosage strength (mid, high) at screening and will be assigned to study treatment in accordance with a country-specific randomization schedule (to ensure treatment balance within each stratum (mid- or high-dose pre-study ICS treatment dosage strength). The randomization code will be generated by GSK using a validated computerized system. Subjects will be randomized using an IRT system (RAMOS NG). Once a randomization number is assigned to a subject it cannot be reassigned to any other subject in the study.

Rationale: The minimum requirement for Japanese subjects is no longer dependent on study 205715.

12.8.4. Protocol Amendment 04

Protocol changes for Amendment 04 (05-DEC-2017), from amendment 03 (29-SEP-2017)

This amendment applies to all sites.

Amendment 04 Summary and Rationale

List of Specific changes:

Text which has been added to the protocol is highlighted in ***bold, italic*** typeface. Text which has been deleted from the protocol is indicated by ~~strike-through~~ format.

54.	Section 6.1: Investigational Product and Other Study Treatment, paragraphs 10 and 11 ***Changed from:*** At the Investigator's discretion, provision will be made from Visit 1[1] onwards for subjects to temporarily receive fluticasone propionate (FP 100 mcg [or equivalent]) via DISKUS DPI to treat the symptoms of a moderate asthma exacerbation (see Section 6.9.1.1 and Section 7.3.6.1). Treatment start and stop dates will be recorded in the eCRF. *[1]Note: Should the subject use the provided FP prior to randomization at Visit 3, the enrolment or randomization concomitant medication exclusion criteria would be met (see Section 5.3.2 and Section 5.4.2).* FP will be sourced from local commercial stock; if not available locally, GSK

	will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements. A record of the number of FP-containing DISKUS DPIs dispensed to each subject must be maintained and reconciled with study treatment records. ***Changed to:*** At the Investigator's discretion, provision will be made from Visit 1[1] onwards for subjects to temporarily receive ***inhaled*** fluticasone propionate (FP***)*** ~~100 mcg [or equivalent]) via DISKUS DPI~~ to treat the symptoms of a moderate asthma exacerbation (see Section 6.9.1.1 and Section 7.3.6.1). Treatment start and stop dates will be recorded in the eCRF. [1]*Note: Should the subject use the provided FP prior to randomization at Visit 3, the enrolment or randomization concomitant medication exclusion criteria would be met (see Section 5.3.2 and Section 5.4.2).* FP will be sourced from local commercial stock; if not available locally, GSK will source centrally. The contents of the label will be in accordance with all applicable regulatory requirements. A record of the number of FP-containing ~~DISKUS DPIs~~ ***inhalers*** dispensed to each subject must be maintained and reconciled with study treatment records. **Rationale:** FP is being provided (at the Investigator's discretion) for the treatment of symptoms of a moderate asthma exacerbation; it is not necessary for the administration of FP to be via the DISKUS DPI.
55.	Section 7.2: Screening and Critical Baseline Assessments; final bullet-point ***Changed from:*** • Dispense FP ***Changed to:*** • Dispense FP ***(as applicable, per Investigator discretion)*** **Rationale:** To clarify that dispensing FP to subjects at Visit 1 is at the Investigator's discretion.