TITLE PAGE

Protocol Title: A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Protocol Number:205832 / Amendment 2

Short Title: **Short Title**: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Compound Number: GW685698+GSK573719

Sponsor Name and Legal Registered Address:

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Medical Monitor Name and Contact Information can be found in the Study Reference Manual.

Regulatory Agency Identifying Number(s): IND No. 104479, EudraCT number 2016-002843-40

Approval Date: 06-JUL-2017

SPONSO[PPD]GNATORY:

PPD

6th July 2017

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 2: 2016N289466_02	*06-Jul-2017*
Amendment 1: 2016N289466_01	*15-Nov-2016*
Original Protocol: 2016N289466_00	*19-Aug-2016*

Amendment 2 06-July-2017

Overall Rationale for the Amendment:
This protocol is being amended to:

- broaden the eligibility criteria of pre-bronchodilator FEV1 from ≤85% to ≤90% reflective of patients with non-obstructed asthma
- Allow re-screening of subjects, with advance approval by the medical monitor.
- Correct minor typographical errors and inconsistencies within the Schedule of Activities (SOA) and the protocol text.

Section # and Name	Description of Change	Brief Rationale
Table of Contents: Section 7.1.3	Update Section 7.1.3 to include albuterol/salbutamol medication for Return process	Update to include albuterol/salbutamol medication and be consistent with the body of the protocol
Section 2: Schedule of Activities (SOA)	Removed the Screen Run-in "Window" day "~~-7d~~"	Removed the Screen Run-in Window day to avoid confusion.
Section 2: Schedule of Activities (SOA)	Added language to clarify when ECG is to be completed: ECG is to be obtained after the vital signs assessment but prior to performing the pre-bronchodilator spirometry assessment (see Section 9.4.3). At all post randomization visits the ECG is to be obtained 15 minutes to 45 minutes after the administration of study treatment.	To correct the inconsistency between the Schedule of Activities (SOA) and body of the protocol
Section 6.1: Inclusion Criteria; inclusion criteria #5	Updating best pre-bronchodilator morning (AM) FEV1 to ≤90%	To allow the inclusion of asthma patients with slightly less restricted lung function. Lung function does not always correlate with asthma severity
Section 6.2.2: Inclusion Criteria for Randomization; inclusion criteria #2	Updating Spirometry: best pre-bronchodilator morning (AM) FEV1 to ≤90%	To allow the inclusion of asthma patients with slightly less restricted lung function. Lung function does not always correlate with asthma severity.
Section 6.4 Pre-Screening/Screening/Run-In/Randomization Failures	Update to Include re-screening language: 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	To allow the re-screening of subjects, with advance medical monitor approval

Section # and Name	Description of Change	Brief Rationale
Section 7.1.3: Study Treatment, albuterol/salbutamol, and FF 100 mcg., Return	Update to include specifically the medication name, albuterol/salbutamol to the return process	Update to include albuterol/salbutamol medication and be consistent with the body of the protocol
Section 9.1.4: Asthma Exacerbation	Added “moderate” to the last sentence in the paragraph	Added “moderate” to be consistent with other sections of the protocol and to clearly state that both moderate and severe exacerbations are to be captured in the eCRF
Section 9.4.3: Electorcardiograms	Added language (“but prior to performing pre-bronchodilator spirometry assessment”) to clarify when the ECG is to be done.	Added (“but prior to performing pre-bronchodilator spirometry assessment”) to clearly explain that the ECG is to be performed after vitals but prior to spirometry. The specific time points for performing ECGs are clarified in the SOA

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Short Title: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Rationale:

In the United States (US), the long-acting muscarinic antagonist (LAMA) tiotropium has been approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of an inhaled corticosteroid (ICS)/LAMA/long-acting beta-2-agonist (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 in adults. Through the evaluation of UMEC 62.5 micrograms (mcg) and 31.25 mcg compared to placebo, this study will provide important information regarding the efficacy, safety and tolerability of UMEC when administered via a separate inhaler to participants on a background of FF without VI.

The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

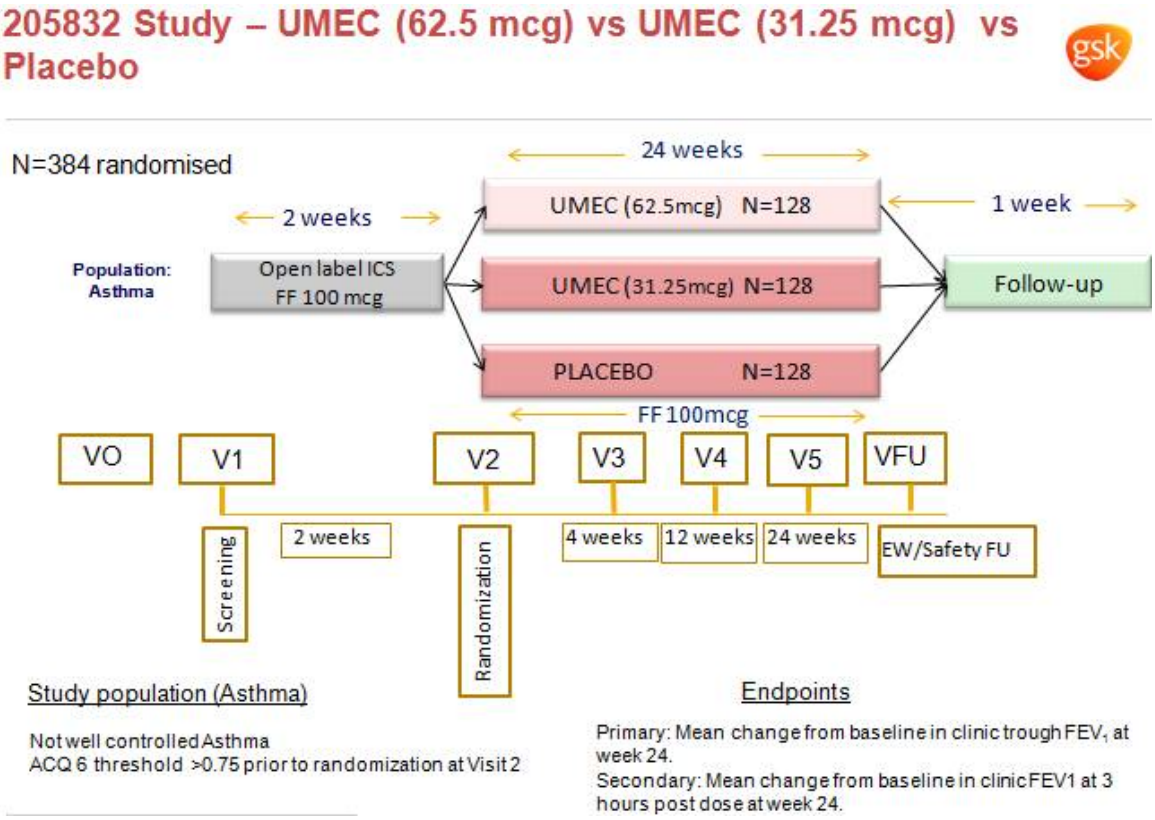
Objectives and Endpoints:

Objective	Endpoint
Primary	
• **Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough Forced Expiratory Volume in 1 second [FEV_{1}]) vs placebo after 24 weeks of treatment.**	• **Mean change from baseline in clinic trough FEV_1 at Week 24**
Secondary	
• Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3hours post dose FEV_1) vs placebo after 24 weeks of treatment.	• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24

Objective	Endpoint
Safety	
To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	Incidence and type of adverse events Electrocardiogram (ECG) measurements Vital signs

Overall Design:

This is a Phase IIb, randomized, double-blind, placebo controlled, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an Asthma Control Questionnaire-6 [ACQ-6] total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS.



Number of Participants:

The total number of randomized participants required is approximately 384, with 128 participants randomized 1:1:1 to each of the 3 double-blind treatment arms.

Treatment Groups and Duration:

Eligible participants will be requested to participate in the study for a maximum of approximately 31 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, participants will complete the following 4 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), including the informed consent process, must be completed within 4 weeks prior to Visit 1 as well as prior to any protocol-required changes to a participant's usual asthma treatment and the initiation of any Visit 1 procedures.

  Participants that receive LABA (or LAMA) as a component of their regular (i.e. pre-study) therapy must stop LABA (or LAMA) treatment from ≥48 hours prior to Visit 1 (Screening) until after they have completed the study; therefore, the investigator must use their clinical judgment to determine if the participant may stop LABA (or LAMA) prior to study entry without incurring undue risk.
- **Screening / run-in:** Participants who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 2 weeks to continue assessing the participant's eligibility for the study. On the morning of Visit 1, participants will refrain from taking the morning dose of their regular (i.e. pre-study) ICS asthma medication. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF 100 mcg via the ELLIPTA dry-powder inhaler (DPI) to take once daily (QD), in the morning, during the 2-week run-in period; the first dose of FF 100 mcg will be self-administered by the participant before leaving the clinic. Participants will refrain from using their own ICS asthma medication during the 2-week run-in and treatment period. Participants will also be provided with rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.
- **Randomization / treatment:** At Visit 2 (the Randomization Visit), participants who meet all of the randomization criteria will be randomized 1:1:1 to receive **one** of the following three double-blind study treatments via the ELLIPTA DPI during the 24-week treatment period:
  - UMEC 62.5 mcg QD
  - UMEC 31.25 mcg QD
  - Placebo QD

  Participants will continue to administer FF 100 mcg once daily (QD), in the morning from a separate ELLIPTA DPI throughout the treatment period. On the morning of Visits 2, 3, 4, and 5, participants will perform their electronic Diary (eDiary) assessments at home but refrain from taking their morning dose of study treatment and FF 100 mcg (as applicable) until instructed to do so by clinic personnel. At Visits 2, 3, 4 and 5, participants will self-administer study treatment immediately followed by FF 100 mcg whilst at the clinic. Participants will take their last dose of study treatment and FF 100 mcg in the clinic on Day 169 (Visit 5). Participants are expected on non-clinic visit days to take their

study treatment and FF 100 mcg at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomized treatment phase, and safety follow-up.

Key Elements of Analysis Plan

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 clinic trough FEV_1 recorded post randomization. Analyses will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, sex, 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 primary comparisons of interest:

- UMEC 62.5 mcg versus Placebo
- UMEC 31.25 mcg versus Placebo

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 reporting and analysis plan (RAP).

The details of the statistical analysis methods for the secondary efficacy endpoint will be provided in the RAP.

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Informed consent (ICF) [a]	X							
Genetic ICF [b]	X							
Inclusion and exclusion criteria		X	X					
Demography [c]	X	X						
Medical history		X						
Asthma history [d]		X						
Exacerbation history		X						
Smoking History and status		X						
Concomitant medication review	X	X	X	X	X	X	X	X
Register visit in Interactive Web Response System (IWRS) (RAMOS NG) [e]	X	X	X	X	X	X	X	
Randomization [f]			X					
Laboratory Assessments								
Urinalysis		X						

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Hematology and clinical chemistry [g]		X						
Hepatitis B and C		X [m]						
Genetic sample			X [n]					
Serum pregnancy test		X [o]				X [o]	X [o]	
Urine pregnancy test			X [o]	X [o]	X [o]			
Safety Assessments								
Physical exam including height and weight [h]		X				X	X	
12-lead Electrocardiogram (ECG) [i]		X		X		X	X	
Vital signs [j]		X	X	X	X	X	X	
Adverse Event (AE) review		X	X	X	X	X	X	X
Serious Adverse Event (SAE) review	X	X	X	X	X	X	X	X
Study Treatment								
Dispense Albuterol/Salbutamol, as required		X	X	X	X			
Collect Albuterol/Salbutamol, as required			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Dispense open label fluticasone furoate (FF) 100 mcg medication		X	X	X	X			
Administer open label FF 100 mcg		X	X	X	X	X		
Collect open label FF 100 mcg			X	X	X	X	X	
Dispense double-blind study treatment			X	X	X			
Administer double-blind study treatment			X[p]	X[p]	X[p]	X[p]		
Collect double-blind study treatment				X	X	X	X	
Assess FF 100 mcg run-in medication compliance			X					
Assess FF 100 mcg and double-blind study treatment compliance				X	X	X	X	
Efficacy Assessments								
Global Assessment of Severity [k]			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Global Assessment of Response to Treatment [k]				X	X	X	X	
Asthma Control Questionnaire (ACQ-6) [k]		X	X [q]					
Asthma Control Questionnaire (ACQ-5) [k]				X	X	X	X	
St. George's Respiratory Questionnaire (SGRQ) [k]			X	X	X	X	X	
Asthma Quality of Life Questionnaire (AQLQ) [k]			X	X	X	X	X	
Evaluating Respiratory Symptoms (E-RS) +Asthma symptoms + Peak Expiratory Flow (PEF) + Home Forced Expiratory Volume in 1 second (FEV)1 [k, l]		X						
eDiary Dispense		X						
eDiary Collect						X	X	
eDiary Review			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window				**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Dispense paper Medical Problems/Medications Taken worksheet	X	X	X	X	X			
Review paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	
Reversibility		X[r]						
Exacerbation assessment			X	X	X	X	X	
Pre-dose spirometry (clinic)		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	
Post-dose spirometry (clinic)			X[t]			X[t]	X[t]	

a) The ICF must be signed before any study procedures, including medication cessation.
b) 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.
c) Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d) The assessment of asthma history will include: the age of the participant 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).
e) The IWRS will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOS NG IWRS manual and SRM for more information).
f) Participants must not be randomized prior to confirming their eligibility to participate in the study.
g) If test otherwise performed within 3 months prior to screening visit, testing at screening is not required.
h) Physical Examination will include height and weight at Visit 1 only.
i) 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 9.4.3). At all post randomization visits the ECG is to be obtained 15 minutes to 45 minutes after the administration of study treatment.
j) The vital signs assessment will include the measurement of blood pressure, heart rate.
k) Assessment(s) to be completed prior to the administration of study treatment.
l) 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.
m) Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. Hep B/C: If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
n) Pharmacogenetic sample may be drawn any time from Visit 2 onwards.
o) Assessments only to be conducted in females of reproductive potential.
p) Study treatment should be administered at approximately the same time of day at each applicable clinic visit.
q) Baseline ACQ-5 will be derived from items 1-5 of the Randomization (Visit 2) ACQ-6.
r) 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 9.1.3. 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 participant may enter the 2-week run-in period.
s) Pre-dose spirometry should 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 and FF 100 mcg. After V2 pre-dose spirometry assessments should be performed within ± 1 hour of the V2 spirometry.
t) 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 within ± 1 hour of the V2 spirometry.

3. INTRODUCTION

3.1. Study Rationale

In the United States (US), the long-acting muscarinic antagonist (LAMA) tiotropium has been approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/long-acting beta-2-agonist (LABA) combination [FF/umeclidinium (UMEC)/vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma in adults. Through the evaluation of UMEC 62.5 mcg and 31.25 mcg compared to placebo this study will provide important information regarding the efficacy and safety of UMEC when administered in a separate inhaler to participants on a background of FF.

The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

3.2. Background

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; Global Initiative for Asthma (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.

Despite the availability of treatments and published guidelines, patients may have asthma that is not well controlled.

This trial will, primarily, evaluate trough FEV_1 to characterize the efficacy of two doses of UMEC (62.5 mcg and 31.25 mcg) in the treatment of asthma when administered as an open combination with FF 100 mcg. UMEC is currently under development as a closed triple therapy in combination with FF and VI in a single inhaler.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events related to FF and UMEC can be found in the Investigator's Brochure(s) (IB). The table below provides a summary of the key risks in association with FF and UMEC. It is noted that both FF and UMEC have also been developed in combination with VI, therefore relevant safety experience is also provided by the FF/VI and UMEC/VI combinations.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GW685698+GSK573719]		
Cardiovascular effects of UMEC	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 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 - Exclusion criteria as specified in Section 6.2 of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per schedule in Section 2 - Vital sign assessments (heart rate and blood pressure) as per schedule in Section 2 - Cardiovascular AEs and SAEs will be captured on the electronic Case Report Form (eCRF) (see Appendix 4) - Protocol defined stopping criteria as per Section 8.1 -MACE analysis -Instream review of blinded data

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Healthy Volunteers (in the Thorough QT study, UMEC 500 mcg daily dose), no effect was observed on heart rate, blood pressure or QT. 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 500 mcg and placebo. UMEC/VI 500/100 mcg increased QTcF on average by 8.2 msec (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. In addition, UMEC/VI has had urinary retention, dysuria, vision blurred, glaucoma and increased intraocular pressure and paradoxical bronchospasm added as ADRs. ICS has a similar class risk of glaucoma and elevated intraocular	- 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. - Review AEs/SAEs

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	pressure (IOP); however, these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.	
Systemic ICS effects -Aderenal 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 participants 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 participants 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 participants 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	- 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
	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 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 participants 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 mcg (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.	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). -Participants 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Pneumonia experience with UMEC 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) 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 participants 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).	resulting in hospitalisation. The occurrence of pneumonia will be recorded in the eCRF. Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a participant 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.	Participants with a history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		stearate are excluded from participation in this study (Section 6.2). -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 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 UMEC 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.	Females who are pregnant or breast-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 100 mcg are recognised pharmacological class effects associated with ICS therapy, which are included in the table above. The experience with FF is provided in the respective IB.

3.3.2. Benefit Assessment

The benefit of UMEC at two dosage strengths 62.5 and 31.25 mcg as compared to Placebo in patients with asthma on background therapy of FF 100 mcg is expected to improve lung function. The inclusion of two strengths of UMEC will allow comparison to placebo for the dose currently marketed in COPD, as well as a lower dose. This will help show the efficacy and safety of UMEC in asthma when administered as an open combination on a background of FF. Another LAMA, tiotropium, is currently approved for the maintenance treatment of asthma.

3.3.3. Overall Benefit: Risk Conclusion

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

The current experience and safety profile with UMEC in previous Phase II asthma studies (alone and in combination with FF) and from clinical trial and marketing experience in the COPD population is supportive of evaluating this compound in asthma patients. The potential risks associated with the known pharmacology of UMEC is offset by the potential significant benefits that are afforded to patients not well controlled on ICS therapy. Furthermore, the approval of another LAMA (tiotropium) for the treatment of asthma demonstrates the suitability for the use of this class of drug in the asthma population.

4. OBJECTIVES AND ENDPOINTS

For a definition of baseline for each of the endpoints listed below, please refer to Section 10.6.

Objectives	Endpoints
Primary • **Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough FEV1) versus placebo after 24 weeks of treatment.**	• **Mean change from baseline in clinic trough FEV1 at Week 24**
Secondary • Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3hours post dose	• Mean change from baseline in clinic FEV1 at 3 hours post dose at Week 24

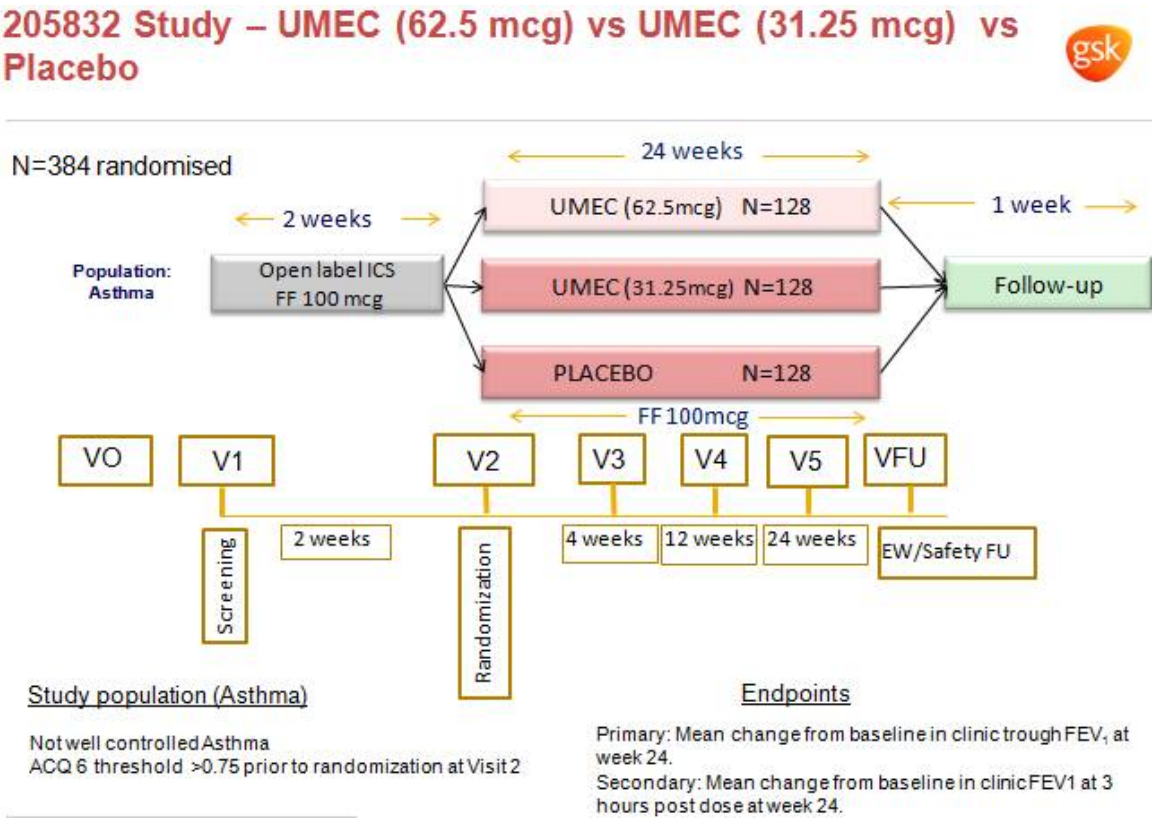
Objectives	Endpoints
FEV1) versus placebo after 24 weeks of treatment.	
Safety • To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Incidence and type of adverse events • ECG measurements • Vital signs
Other • To evaluate other efficacy assessments of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the 24 week treatment period • Mean change from baseline in evening (PM) PEF over the 24 week treatment period • Mean change from baseline in daily home trough FEV1 over the 24 week treatment period • Mean change from baseline in daily rescue medication use over the 24 week treatment period • Mean change from baseline in SGRQ total score 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 SGRQ domain scores at Week 24 • Mean change from baseline in the AQLQ total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement from baseline for the AQLQ total score at Week 24 • Mean change from baseline in E-RS total score over the 24 week treatment period • Mean change from baseline in

Objectives	Endpoints
	ACQ-5 total score at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5 at Week 24 • Annualized rate of moderate/severe asthma exacerbations

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IIb, randomized, double-blind, placebo controlled, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an ACQ-6 total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS.



Eligible participants will be requested to participate in the study for a maximum of approximately 31 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, participants will complete the following 4 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), including the informed consent process, must be completed within 4 weeks prior to Visit 1 as well as prior to any protocol-required changes to a participant's usual asthma treatment and the initiation of any 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 defined in Section 7.9.

  Participants that receive LABA (or LAMA) as a component of their regular (i.e. pre-study) therapy must stop LABA (or LAMA) treatment from ≥48 hours prior to Visit 1 (Screening) until they have completed the study; therefore, the investigator must use their clinical judgment to determine if the participant may stop LABA (or LAMA) prior to study entry without incurring undue risk.

- **Screening / run-in:** Participants who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 2 weeks to continue assessing the participant's eligibility for the study. On the morning of Visit 1, participants will refrain from taking the morning dose of their regular (i.e. pre-study) ICS asthma medication. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF 100 mcg via the ELLIPTA dry-powder inhaler (DPI) to take once daily (QD), in the morning, during the 2-week run-in period; the first dose of FF 100 mcg will be self-administered by the participant before leaving the clinic. Participants will refrain from using their own ICS asthma medication during the 2-week run-in and treatment period. Participants will also be provided with rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.

- **Randomization / treatment:** At Visit 2 (the Randomization Visit), participants who meet all of the randomization criteria will be randomized 1:1:1 to receive **one** of the following three double-blind study treatments via the ELLIPTA DPI during the 24-week treatment period:

  - UMEC 62.5 mcg QD
  - UMEC 31.25 mcg QD
  - Placebo QD

  Participants will continue to administer FF 100 mcg once daily (QD), in the morning from a separate ELLIPTA DPI throughout the treatment period. On the morning of Visits 2, 3, 4, and 5, participants will perform their electronic Diary (eDiary) assessments at home but refrain from taking their morning dose of study treatment and FF 100 mcg (as applicable) until instructed to do so by clinic personnel. At Visits 2, 3, 4 and 5, participants will self-administer study treatment immediately followed by FF 100 mcg whilst at the clinic (see Section 7.2). Participants will take their last dose of study treatment and FF 100 mcg in the clinic on Day 169 (Visit 5). Participants are expected on non-clinic visit days to take their study treatment and FF 100 mcg at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomized treatment phase, and safety follow-up.

To demonstrate the benefit of UMEC the primary comparisons of interest for the primary efficacy endpoint are:

- UMEC 62.5 mcg versus (vs) Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 10.5.3. Participants who permanently discontinue double-blind study treatment are not required to withdraw from the study. Participants 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 8.1)

5.2. Number of Participants

The total number of randomized participants required is approximately 384, with 128 participants randomized 1:1:1 to each of the 3 double-blind treatment arms (see Section 10).

5.3. Participant and Study Completion

A participant will be considered to have completed the study when they have completed all phases of the study including pre-screening, screening, run-in, the randomized treatment phase, and safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities table (see Section 2) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, 3 arm parallel-group design. This is a well-established design to evaluate the efficacy, safety, and tolerability of the UMEC drug. A placebo arm is included. All participants will be placed on open-label FF 100 mcg when they enter the 2 week run-in period and continue it through the 24 week treatment period. The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [FF/UMEC/VI)] in a single device, with the aim of providing a new treatment option for the management of asthma in adults. Through the evaluation of UMEC 62.5 mcg and 31.25 mcg compared to placebo this study will provide important information regarding the efficacy, safety and tolerability of UMEC in asthma when administered via a separate inhaler to participants on a background of FF without VI.

5.5. Dose Justification

The 200699 (IB, GlaxoSmithKline Document 2011N123107_03, / IB Supplement, GlaxoSmithKline Document 2016N284764_00) data showed UMEC 62.5 mcg to be an effective dose; after 4 weeks of treatment in the subset of patients with a primary diagnosis of asthma, an average increase in change from baseline trough FEV1 at Day 29 of 136 mL was observed in those participants treated with FF/UMEC (100/62.5 mcg) compared to those participants 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 both 31.25 and 62.5 mcg doses will be assessed in this study when administered via a separate inhaler to participants treated on a background of FF 100 mcg. No safety signal was identified with any of the UMEC doses (15.6, 62.5, 125 and 250 mcg) evaluated in the 200699 study.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. **Age:** 18 years of age or older at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. **Diagnosis:** Participants with a diagnosis of asthma as defined by the National Institutes of Health [NIH 2007] at least 6 months prior to Visit 0. 3. **Asthma Control:** ACQ-6 total score of >0.75 at Visit 1. 4. **Current Asthma Maintenance Therapy**: Participants are eligible if they have required daily ICS therapy ≥ 100 mcg/day fluticasone propionate (FP, or equivalent) with or without LABA or LAMA for at least 12 weeks prior to Visit 0 and there have been no changes in maintenance asthma medications during the 4 weeks immediately prior to Visit 0. Examples of acceptable doses of commonly prescribed ICS medication will be 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.

5. **Spirometry:** Both of the following:
   a. A best pre-bronchodilator morning (AM) FEV1 ≤90% of the predicted normal value. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer 2012].
   b. A best post-bronchodilator FEV1/ forced vital capacity (FVC) ≥0.7 at Visit 1.
6. **Reversibility of Disease:** Airway reversibility is defined as ≥12% and ≥200 mL increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.

   Note: If the participant 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 FEV1 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 FEV1 of ≥12% and ≥200 mL.*

   Should the participant successfully demonstrate airway reversibility (defined as ≥12% and ≥200 mL increase in FEV1 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 participant may enter the 2-week run-in period (see Section 9.1.3).
7. **Short-Acting β2 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

8. **Gender:**

a. Male participants

b. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

  OR
- A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 5 days after the last dose of study

treatment.
INFORMED CONSENT
9. **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. Participants must be able to read, comprehend, and write at a level sufficient to complete study related materials.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS
1. **Pneumonia:** Chest X-ray documented pneumonia in the 12 weeks prior to Visit 1.
2. **Asthma Exacerbation:** Any severe asthma exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (oral, parenteral or depot) within 12 weeks of Visit 1, or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids within 12 weeks of Visit 1.
3. **Concurrent Respiratory Disease:** Current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, lung cancer, or other respiratory abnormalities other than asthma.
4. **Pregnancy**: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
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**: Participants 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 participant 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 participant otherwise meets entry criteria*

8. **Clinically significant ECG abnormality:** Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening or run-in. The PI will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants 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:
    - 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:** participants 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
10. **Antimuscarinic effects:** Participants 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**: Participants with carcinoma that has not been in complete remission for at least 5 years. Participants 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 participant has been considered cured by treatment.
12. **Questionable validity of consent**: Participants 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.

PRIOR/CONCOMITANT THERAPY

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

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE/RELEVANT HABITS

14. **Tobacco Use:** Current smoker or a smoking history of ≥10 pack years (e.g., 20 cigarettes/day for 10 years). A participant may not have used inhaled tobacco products within the past 12 months (i.e., cigarettes, e-cigarettes/vaping, cigars or pipe tobacco).
15. **Drug/alcohol abuse:** Participants with a known or suspected history of alcohol or

drug abuse within the last 2 years. This includes marijuana, which is considered an abused drug.
Diagnostic assessments
16. **Allergy or Hypersensitivity:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate.
Other Exclusions
17. **Non-compliance:** Participants 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 participant who is unable to read and/or would not be able to complete study related materials.

6.2.1. Randomization Criteria

At the end of the run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

6.2.2. Inclusion Criteria for Randomization

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
1. Asthma Control: ACQ-6 total score of >0.75 at Visit 2. **2. Percent-predicted FEV_1:** Spirometry: A best pre-bronchodilator morning (AM) FEV1 ≤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.

6.2.3. 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 run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the participant's asthma status or the participant's ability to participate in the study. 2. **Asthma exacerbation:** Evidence of a moderate asthma exacerbation leading to a change in therapy or severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
CONCOMITANT MEDICATIONS/TREATMENTS
3. **Asthma medication:** Changes in asthma medication (excluding changes after Visit 0 or 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.

6.3. Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.4. Pre-Screening/Screening/Run-in/Randomization Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the eCRF for participants who are pre-screen failures:

- Demographic information including race, age and gender
- Participant 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-screening failures, screening failures, run-in failures and randomization failures will be defined as follows:

- **Pre-screening failures:** those participants that sign the informed consent document but do not have a Visit 1 (Screening) procedure.

- **Screening failures:** those participants that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period.

  A participant 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 participants that enter the run-in period but do not have any Visit 2 (Randomization) procedures.

- **Randomization failures:** those participants that complete at least one Visit 2 (Randomization) procedure but do not enter the double-blind study treatment period.

  Any participant who completes the run-in period and then meets the randomization criteria and is dispensed the double-blind study treatment at Visit 2 is considered to have entered the treatment period.

RAMOS NG will be contacted to register the participant.

In order to ensure transparent reporting of screen/run-in failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen/run-in/randomization failure information is required including demography, screen/run-in/randomization failure details, eligibility criteria, and any SAEs (see Section 9.2.4 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).

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The term ‘study treatment’ within this trial is used to describe the combination of products received by the participant as per the protocol design. Study treatment may also be used to only reference the randomized study treatment when described together with the FF 100 mcg open-label treatment.

7.1. Treatments Administered

7.1.1. Description of FF 100 mcg and Double-Blind Study Treatment

The ELLIPTA device will be used during the run-in period and the treatment period. The ELLIPTA dry powder inhaler (DPI) is a molded plastic two-sided device with a dose counter that can hold two individual blister strips. The ELLIPTA will deliver, when actuated, the contents of a single blister simultaneously from each of the two strips. The ELLIPTA is individually sealed in a foil laminate overwrap that also contains a silica gel desiccant packet.

A description of the FF (GW685698) 100 mcg inhalation powder administered via the ELLIPTA is provided in Table 1; descriptions of the double-blind study treatments administered via the ELLIPTA are provided in Table 2.

Table 1 Description of FF 100 mcg Inhalation Powder in ELLIPTA

FF 100	First Strip	Second Strip
	GW685698 blended with lactose monohydrate	Lactose monohydrate with magnesium stearate[1]
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose strengths	100 mcg per blister	Not applicable
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 1.0% w/w of total drug product.

Table 2 Description of Study Treatment Inhalation Powder in ELLIPTA

Placebo	First strip	Second strip
	Lactose monohydrate blended with magnesium stearate1	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	White powder	White powder
Route of Administration	Inhaled	
UMEC	**First strip**	**Second strip**
	GSK573719 blended with lactose and magnesium stearate	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose Strengths	31.25 mcg per blister	NA
Physical description	White powder	White powder
Route of Administration	Inhaled	
UMEC	**First strip**	**Second strip**
	GSK573719 blended with lactose and magnesium stearate	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose Strengths	62.5 mcg per blister	NA
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product. 2. Magnesium stearate 1.0% w/w of total drug product

7.1.2. Description of Albuterol/Salbutamol

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.

7.1.3. Study Treatment, albuterol/salbutamol, and FF 100 mcg Return

ELLIPTAs containing FF 100 mcg, and study treatment, in addition to albuterol/salbutamol, will be dispensed to a participant during their visit to the study clinic (as applicable). The participant must return all dispensed ELLIPTAs and albuterol/salbutamol at the subsequent clinic visit. The schedule for dispensing and collecting FF 100 mcg and study treatment ELLIPTAs is provided in the Schedule of Activities table (Section 2).

All used and unused study treatment, FF 100 mcg and albuterol/salbutamol 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 Study Reference Manual (SRM).

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

In addition, any metered dose inhaler (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.

7.2. Dose Modification

There were no dose modifications planned for this protocol.

7.3. Method of Treatment Assignment

Participants 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. Participants will be randomized using an interactive web response system (IWRS) RAMOS NG. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 2-week run-in period and participant to satisfying all eligibility criteria, participants will be randomized 1:1:1 to one of the following three double-blind treatments for the duration of the treatment period:

- UMEC 62.5 mcg QD
- UMEC 31.25 mcg QD
- Placebo QD

The duration of double-blind treatment for each participant is 24 weeks. On the morning of each scheduled clinic study visit, participants will refrain from taking their morning dose of study treatment and FF 100 mcg 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 Randomization Visit (Visit 2). On the other days during the treatment period (i.e. "non-clinic days"), participants 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 IWRS system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IWRS manual and SRM.

7.4. Blinding

This will be a double-blind study and the following will apply.

- The Investigator or treating physician may unblind a participant'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 participant as judged by the Investigator.
- Investigators have direct access to the participant'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 participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and event or condition which led to the unblinding (i.e. the primary reason) will be recorded in source documentation and in the eCRF.

Should a participant's treatment assignment be unblinded then the participant may continue the assigned study treatment and be followed-up as per protocol until the completion of the Safety Follow-up assessments.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant 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 participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy. Participants will not be withdrawn from the study.

7.5. Packaging and Labeling

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

7.6. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.
5. 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.
6. A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.7. Treatment Compliance

When participants are dosed at the site, they will receive FF 100 mcg and 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 participant identification will be confirmed at the time of dosing by a member of the study site staff.

When participants self-administer study treatment(s) at home, compliance with study treatment will be assessed through querying the participant during the site visits and recording the number of doses remaining in the ELLIPTA in the eCRF (see the SRM for details). A record of the number of ELLIPTAs dispensed to each participant must be maintained and reconciled with study treatment and compliance records.

Participant compliance with FF 100 mcg and study treatment will be assessed at scheduled clinic visits by reviewing the eDiary and information from the dose counter on the returned inhaler(s) (see Section 7.1.3). Participants should be ≥80% to ≤120% compliant on taking both FF 100 mcg and study treatment between each pair of

compliant on taking both FF 100 mcg and study treatment between each pair of scheduled and consecutive on-treatment clinic visits, as applicable. Participants who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the participant's source document. If FF 100 mcg and/or study treatment is prematurely discontinued during the course of the study or compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss participant eligibility for continued participation in the study.

7.8. Concomitant Therapy

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.

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 FF 100 mcg and albuterol/salbutamol should not be recorded in the eCRF; however non-study supplied FF 100 mcg and albuterol/salbutamol will be recorded in the eCRF.*

The minimum requirement is that the drug name, reason for use, dose (including unit e.g. mcg) and frequency, route and the dates of administration are to be recorded.

Medications initiated after completion of the assessments at Visit 5/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. Participants who have completed the Early Withdrawal Visit are allowed to use any medications prescribed by the Investigator or primary care physician.

7.8.1. Permitted Medications and Non-Drug Therapies

7.8.1.1. Permitted Asthma Medications

In addition to FF 100 mcg and 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. Participants must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

Temporary changes in medications are permitted for the treatment of moderate asthma exacerbations, 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 SRM for contact information [refer to Section 9.1.4.1 for guidance on moderate asthma exacerbation]):

- An increase in ICS dose.
- Systemic corticosteroids (tablets, suspension or injection) 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.

7.8.1.2. 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: Participants 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 participants 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 participants' lung function or safety assessments (e.g., cardiac measurements). However, no systemic corticosteroids will be permitted.

7.9. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 3 is not permitted during the study.

Table 3 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
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)	2 days 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, 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
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

7.10. Treatment after the End of the Study

Participants 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 participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

Participants who withdraw from 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. If this is not possible, the Investigator must encourage the participant to participate in as much of the study as they are willing (or able) to.

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

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

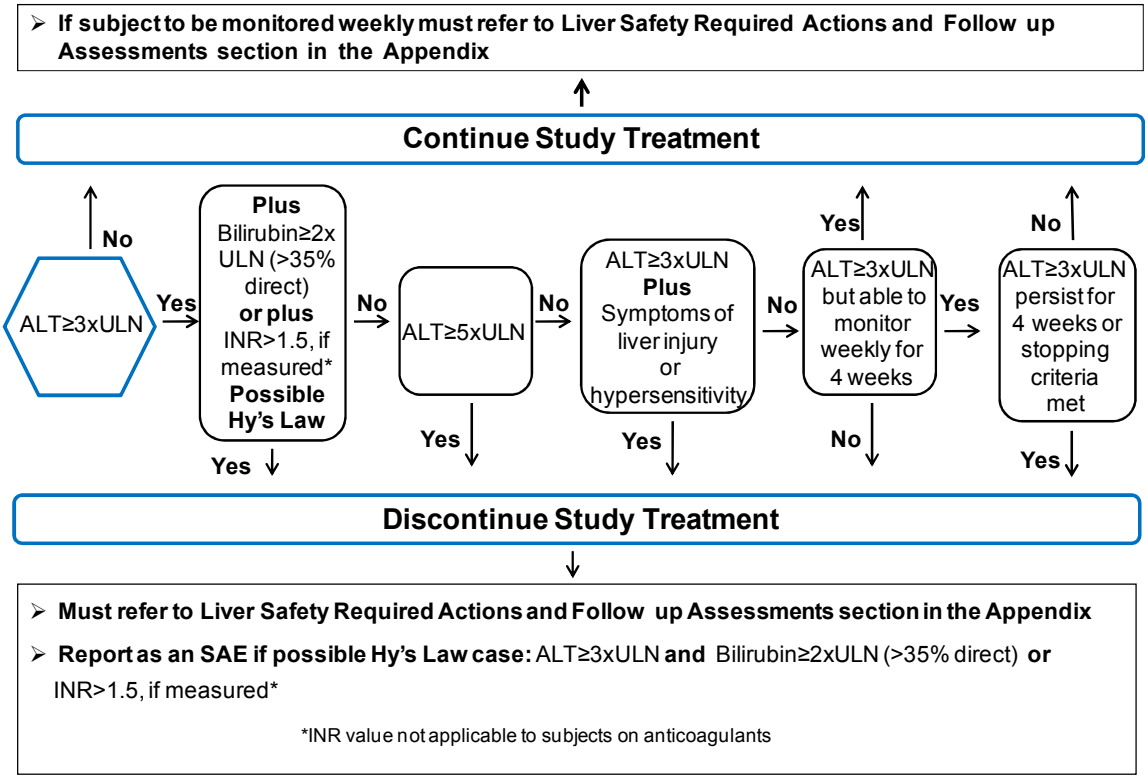
- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria
- QTc: Meets any of the protocol-defined stopping criteria
- Pregnancy: Positive pregnancy test

8.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments can be found in Appendix 7

8.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 9.4.3.

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

- For example, if a participant 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 participant as well.
- Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *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 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, lead to withdrawal from study treatment:

- QTc>500 msec or uncorrected QT>600 msec
- Change from baseline: QTc> 60 msec

- For patients with underlying bundle branch block, follow the discontinuation criteria listed below:
  - Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
  - Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- In the event of early withdrawal from the study, every effort should be made to have the participant 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 Schedule of Activities table (Section 2).

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

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

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 2). There are no protocol waivers or exemptions allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

- Demographic information including race, age and gender
- Participant 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 participant 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
- Questionnaires (ACQ; E-RS)
- Pre-and post-albuterol/salbutamol lung function
- Inclusion/Exclusion criteria assessment
- Physical examination
- 12-lead ECG
- Child bearing status assessment for all potential female participants
- Clinical laboratory tests (including hematology, chemistry, urinalysis and serum pregnancy test)
- AE / 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 FF 100 mcg run-in medication

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in the Schedule of Activities (SoA) (Section 2).

9.1.1. Questionnaires

The questionnaires should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participants 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 participant must be encouraged to complete any missing assessments or items.

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

9.1.1.1. Global Assessment of Severity and Response to Treatment

The participant will be asked to complete the Global Assessment of Severity and Response to Treatment at the visits specified in the Schedule of Activities table (Section 2). The Global Assessment of Severity is a single item questionnaire; participants 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. Instructions for completing the questionnaires can be found in the SRM.

9.1.1.2. Asthma Control Questionnaire (ACQ)

The ACQ measures attributes of asthma control [Juniper 1999], measured with questions designed to be self-completed by the participant. Participants will complete the ACQ at specified study visits. The ACQ-5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of symptoms over the previous week. The ACQ-6 includes an additional item asking about rescue medication use. 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. 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].

9.1.1.3. St. George's Respiratory of Life Questionnaire (SGRQ)

The SGRQ 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 participant [Jones 1992] with a recall over the past 3 months. A change of 4 points is considered a clinically relevant change [Jones 2005].

9.1.1.4. Asthma Quality of Life Questionnaire (AQLQ)

The 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 participant with a recall over the past 2 weeks. A change of ≥0.5 is considered clinically important [Juniper 1994].

9.1.2. Daily Diaries

Participants 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. Participants 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 FEV1
- Morning and Evening PEF
- Morning FF 100 mcg medication use
- Morning double-blind study medication use (during the treatment period only)

Section 9.1.2 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.

Participants 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). Participants 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 participant recall in discussions with the Investigator, for site staff to then enter as appropriate in the eCRF.

9.1.2.1. eDiary Questionnaires, Assessments and Alerts

For information on the eDiary questions, please refer to Appendix 8.

9.1.2.1.1. 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.

9.1.2.1.2. 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.

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

Every morning upon waking (from the morning after Visit 1 onwards), participants will answer a question on the occurrence of night-time awakenings due to asthma symptoms. The participant'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', participants 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, participants 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 (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].

9.1.2.1.4. Morning and Evening Home Spirometry

An electronic home spirometer/eDiary device will be issued to participants 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. Participants will conduct spirometry maneuvers each morning, prior to study treatment and FF 100 mcg dosing, and each evening. Three measurements for each session will be recorded by the participants in the eDiary. Assessments will be performed:

- After completing all other eDiary assessments
- Prior to albuterol/salbutamol use
- Prior to study treatment and FF 100 mcg 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.

9.1.2.1.5. Alerts

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions for the participant to contact the investigator (either by telephone and/or by visiting the study clinic) if any of the alert criteria are met:

- Nocturnal awakening(s) due to asthma requiring albuterol/salbutamol use for 2 consecutive nights.
- An increase from baseline of ≥ 4 puffs /day of albuterol/salbutamol use on 2 consecutive days.
- A ≥30% decrease in AM PEF from baseline on 2 consecutive mornings.
- A ≥30% decrease in PM PEF from baseline on 2 consecutive evenings
- A ≥30% decrease in AM FEV1 from baseline on 2 consecutive mornings.
- A ≥30% decrease in PM FEV1 from baseline on 2 consecutive evenings.

9.1.3. Pulmonary Function Test

The 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 American Thoracic Society / European Respiratory Society (ATS/ERS) standards [Miller 2005]. The highest of 3 technically acceptable measurements will be recorded at each visit:

- **Pre-dose Spirometry:** At Visits 1 through 5/EOS (and the Early Withdrawal Visit, if applicable), participants 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 2 (the baseline assessment).
    - At least 24 hours after the participant's last morning dose of study treatment on the day prior to the visit.

  - Before the participant's morning dose of study treatment on the day of the visit.
- **Post-dose Spirometry:** At Visits 2 and 5/EOS (and the Early Withdrawal Visit, if applicable), spirometry assessments must be performed 3 hours after the participant's morning dose of study treatment; the assessment performed at Visit 5/EOS should be performed at the same time of day (± 1 hour) as the assessment performed at Visit 2 (the baseline assessment). At each visit, participants 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.

9.1.3.1. Reversibility (Albuterol/Salbutamol)

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.

To perform the reversibility assessment, 4 puffs of the provided albuterol/salbutamol 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 albuterol/salbutamol.

Percent reversibility will be calculated as follows:

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

The reversibility requirement for eligibility must be assessed at Visit 1. Participants 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 participant may not enter the 2-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 participant 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 participant may enter the 2-week run-in period.

9.1.4. Asthma Exacerbations

Moderate and severe asthma exacerbation data will be collected from the start of randomized double blinded treatment until Visit 5/EOS Visit or the Early Withdrawal Visit for those participants that withdraw from participation in the study (see Section 8.2). For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

Participants will 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).

9.1.4.1. Moderate Asthma Exacerbation

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 for 3 days or more and/or hospitalization.
- 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.

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 (Refer to Section 7.8.1 above)
The Medical Monitor may be contacted for additional guidance, see the medical monitor/Sponsor Information Page.

9.1.4.2. Severe Asthma Exacerbation

A severe asthma exacerbation is defined as:

The deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection) for at least 3 days.

OR

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

9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 8).

9.2.1. 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 participant consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Screening until the follow-up contact (see Section 9.2.3) at the timepoints specified in the Schedule of Activities (SoA) table (Section 2).
- 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. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant 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

9.2.2. 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 participant 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?”

Participants will be issued with a paper Medical Problems/Medications Taken worksheet to record any medical problems experienced and medications used during the study. This

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. 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). 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

Special interest AE group	Special interest AE subgroup
	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	-
Hypersensitivity	-
Local steroid effects	-

9.2.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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

9.2.7. 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 participant 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).

9.2.8. 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.

9.2.9. Pregnancy

Details of all pregnancies in female participants 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.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of 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 eCRF 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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA).

9.4.1. Physical Examinations

Physical exams will be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2).

- 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.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

Vital signs will be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2) prior to conducting spirometry and prior to taking the morning dose of study treatment and FF 100 mcg. 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.

9.4.3. Electrocardiograms

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 assessment but prior to performing the pre-bronchodilator spirometry assessment. Recordings will be made at the time-points defined in the Schedule of Activities (SoA)

table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.

For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.2).

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.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (SoA) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (SoA).

9.5. Pharmacokinetics

Pharmacokinetics is not relevant for this protocol.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 6. 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 6).

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.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to evaluate the efficacy of UMEC 62.5 mcg and UMEC 31.25 mcg compared with placebo in participants with not well controlled asthma over a 24 week treatment period. This is a superiority study to demonstrate the benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg when compared to Placebo in patients on background therapy of FF 100 mcg. The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at Week 24.

The test for the primary efficacy endpoint is such that 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:

- UMEC 62.5mcg vs Placebo
- UMEC 31.25mcg vs Placebo

For each comparison test on the primary endpoint, the null hypothesis is there is no difference between treatment groups. The alternative hypothesis is there is a difference between treatment groups.

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

Details on all pairwise treatment comparisons of interest are provided in Section 10.5.2.

10.2. Sample Size Determination

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 384 randomized participants are required for this study, with 128 participants in each of the three double-blind treatment groups: UMEC 62.5mcg, UMEC 31.25mcg or Placebo. Assuming 10% missing data on spirometry at the end of the 24-week treatment period, due to early withdrawal from study, approximately 115 participants per treatment group will have trough FEV_1 available for the primary 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 350mL based on two previous Tiotropium moderate asthma studies. The study design and population of this study aligns well with these two phase III, 24 week, randomised, double blind, placebo-controlled, parallel-group, active comparator studies of Tiotropium. In patients with moderate asthma on a background therapy of ICS the standard deviations in change from baseline trough FEV1 at Week 24 ranged from 325 to 354mL; from this a SD estimate of 350 mL was chosen. This was estimated from a wide selection of studies, critically to minimise the risk of reduced power for the primary endpoint. The range of observed treatment differences across the Tiotropium treatment groups is 133 – 185mL, which supports the expectation that the treatment effect seen in a moderate asthma population is larger than in the more severe asthma population in study 205715 treated on a background of FF/VI. This is in line with data from GSK study 200699 which showed UMEC 62.5 mcg to be an effective dose. An average increase in change from baseline trough FEV1 at Day 29 of 136 mL was observed in an asthma subset of patients treated with FF/UMEC (100/62.5) compared with FF (100 mcg) alone. The GSK phase III closed triple asthma study 205715, which this study supports, is in a more severe asthma population and conservatively assumes a SD estimate of 400mL.

Based on a true population difference of 130 mL, a sample size of 115 patients per treatment group has an estimated 80% power to observe statistical significance at the two sided 5% level, for each of the two primary comparisons of interest for each UMEC dose. Using the above assumptions the smallest observed effect predicted to result in a

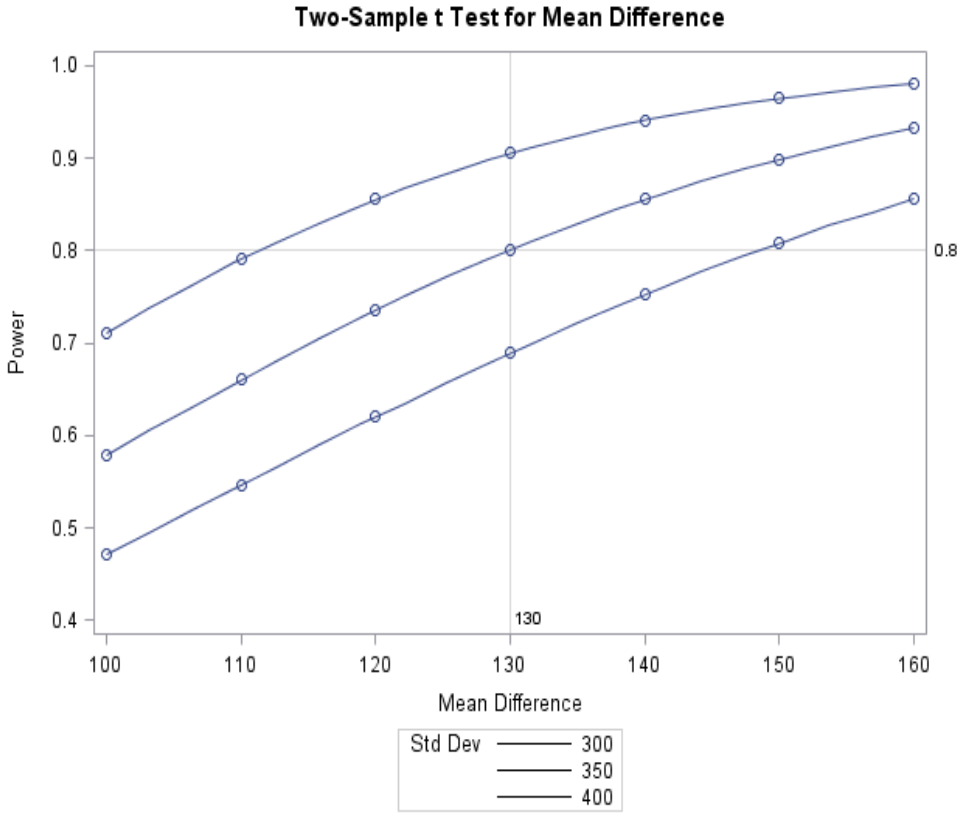
statistically significant difference between treatment groups is 90.5 mL (minimum detectable difference).

No interim analysis is planned for this study.

10.3. 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=115 per arm in the intent to treat (ITT) population for the primary efficacy analysis, varying the true 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	100	115	130	145	160
300	0.71	0.82	0.91	0.95	0.98
350	0.58	0.70	0.80	0.88	0.93
400	0.47	0.58	0.69	0.78	0.86



10.4. Sample site re-estimation or adjustment

No sample size re-estimation is planned.

10.5. Data Analysis

10.5.1. Analysis population

The following participant populations will be identified:

All Participants Enrolled Population: This population will comprise all participants for whom a record exists on the study database, including pre-screened participants that sign the informed consent document but do not complete a Visit 1 (screening) procedure (i.e., pre-screening failures), or participants 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 participant disposition.

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

ITT Population: This population will comprise all randomized participants, excluding those who were randomized in error. A participant who is recorded as a screen failure or

run-in failure, but is randomized and does not receive a dose of study treatment, is considered to be randomized in error. Any other participant who receives a randomization number will be considered to have been randomized. This will constitute the primary population for all efficacy and safety analyses.

10.5.2. Treatment Comparisons

To demonstrate the benefit of UMEC the primary comparisons of interest for the primary efficacy endpoint are:

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 10.5.3.

10.5.3. Multiple Comparisons and Multiplicity

In order to account for multiple tests involving the two UMEC doses 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 test in the hierarchy.

A step-down procedure with the following hierarchy will be used for the primary comparisons in the primary endpoint.

- The contrast between UMEC 62.5 mcg vs Placebo
  (two-sided, alpha = 0.05. Null hypothesis of no treatment difference)
- The contrast between UMEC 31.25 mcg vs Placebo
  (two-sided, alpha = 0.05. Null hypothesis of no treatment difference)

The second hypothesis will be formally tested only if the first hypothesis has been rejected, thus maintaining the overall significance level at 5%.

Specifically, if the defined treatment comparison for the primary efficacy endpoint at the highest dose of UMEC 62.5 mcg is significant at 0.05 level then the efficacy of UMEC 62.5 mcg is demonstrated, and the treatment comparison can be repeated on the UMEC 31.25 mcg dose.

Note that, in the event that the first hypothesis is not rejected a nominal p-value for the second hypothesis may be provided in the displays for descriptive purposes only and will not alter the conclusion of the step-down procedure.

No multiplicity adjustment will be made on these two treatment comparisons on the secondary endpoint.

For all efficacy endpoints (primary, secondary and other), treatment comparisons between UMEC 62.5 vs UMEC 31.25 mcg informally investigating the benefit of increasing UMEC dose will be made without adjusting for multiplicity. Any p-values ≤ 0.05 will be identified as nominally significant.

10.6. Statistical Analysis

Where possible, data from participants 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 RAP.

In general, the baseline value is the last assessment value prior to randomization at Visit 2 for the efficacy endpoints based on assessments at clinic visits. The covariates to be considered in the efficacy analyses include age, sex, and the baseline value, if relevant. Other covariates, if appropriate, may be considered. Specific details will be provided in the RAP.

10.6.1. 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 participant, the baseline value of clinic FEV_1 is the last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomization (either from Visit 2 pre-dose or from Visit 1 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, 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.

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

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 10.5.2 will also be provided for the primary efficacy endpoint.

10.6.2. Secondary Analyses

Full details of the analyses to be performed on the secondary efficacy endpoint will be given in the RAP.

10.6.3. 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.

10.6.4. Interim Analyses

No interim analysis is planned for this study.

10.6.5. Exploratory Analyses

The psychometric properties of the E-RS and Supplemental asthma items will be evaluated to characterize the E-RS as an endpoint for asthma. These exploratory analyses may be provided in a separate RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
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
BMI	Body Mass Index
BPM	Beats Per Minute
BST	Bioanalytical Science and Toxicokinetics
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
eDiary	Electronic Diary
EOS	End of study
E-RS	Evaluating Respiratory Symptoms
ERS	European Respiratory Society
EW	Early Withdrawal
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Axis
HRT	Hormone Replacement Therapy
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWRS	Interactive Web Response System
ITT	Intent to Treat
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LOCS III	Lens Opacities Classification System III
LRTI	Lower Respiratory Tract Infection
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
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PM	Evening
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

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Clinical Laboratory Tests

- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol Schedule of Activities (Section 2) Laboratory requisition forms must be completed and samples must be clearly labelled with the participant 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 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 participant 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.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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 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	• **Follicle stimulating hormone (FSH) and estradiol (as needed in females of non-reproductive potential only)** • **Serum/urine hCG Pregnancy test (as specified in the Schedule of Activities table [Section 2])**

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 8.1.1 and Appendix 7

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- For this study participant 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.

Data Quality Assurance

- 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. Participant initials will not be collected or transmitted to GSK according to GSK policy.
- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• 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 participant'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 participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity • 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 (eg, sprained ankle) which may interfere with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as

severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the assigned SAE contact by telephone.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE Reporting to GSK via Paper CRF

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

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4.

Table 4 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. *Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.*

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of [5, 10, 25] mIU/mL will be performed [and assayed in a certified laboratory OR and assayed in the central laboratory OR using

the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert]

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 participant who becomes pregnant while participating in the study will immediately discontinue study medication.

12.6. Appendix 6: Genetics

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 participant who is enrolled in the study can participate in genetic research. Any participant 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 participant 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 participant 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 participant 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.

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

Informed Consent

Participants 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.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant 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 participant 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 participant 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 participant does not meet the entry criteria for participation in the study, then the Investigator should instruct the participant 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 Participant'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 participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant'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

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

<table>
<tr><th colspan="2">Liver Chemistry Stopping Criteria – Liver Stopping Event</th></tr>
<tr><td>ALT-absolute</td><td>ALT ≥ 5xULN</td></tr>
<tr><td>ALT Increase</td><td>ALT ≥ 3xULN persists for ≥4 weeks</td></tr>
<tr><td>Bilirubin[1, 2]</td><td>ALT ≥ 3xULN and bilirubin ≥ 2xULN (>35% direct bilirubin)</td></tr>
<tr><td>INR[2]</td><td>ALT ≥ 3xULN and INR>1.5, if INR measured</td></tr>
<tr><td>Cannot Monitor</td><td>ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks</td></tr>
<tr><td>Symptomatic[3]</td><td>ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity</td></tr>
<tr><th colspan="2">Required Actions and Follow up Assessments following ANY Liver Stopping Event</th></tr>
<tr><th>Actions</th><th>Follow Up Assessments</th></tr>
<tr><td>• Immediately discontinue study treatment
• Report the event to GSK within 24 hours
• Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2]
• Perform liver event follow up assessments
• Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see MONITORING below)
• Do not restart/rechallenge participant with study treatment unless allowed per protocol and GSK Medical Governance approval is granted (refer to Section 8.1.3)
If restart/rechallenge not allowed per protocol or not granted, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments</td><td>• Viral hepatitis serology[4]
• Blood sample for pharmacokinetic (PK) analysis, obtained 72 hours after last dose[5]
• 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 liver injury, or hypersensitivity, on the AE report form
• Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter</td></tr>
</table>

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week (James 2009) **Not Required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.8. Appendix 8: Daily Diary Questions

12.8.1. Morning Questions

The participant 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

12.8.2. Evening Questions

The participant 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

12.9. Appendix 9: Country-specific requirements

There are currently no country specific requirements.

12.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment 1 15-November-2016

Overall Rationale for the Amendment:

To address typographical errors and inconsistencies between the Schedule of Activities (SOA) and the protocol text. In addition, language has been added to Exclusion criteria #14 to clearly explain examples of inhaled products (e-cigarettes/vaping) as well as provide an example of a drug; in Exclusion #15. (marijuana is considered an abused drug).

Section # and Name	Description of Change	Brief Rationale
Section 2: Schedule of Activities (SOA)	Included Line item "X" in the box for inclusion/exclusion criteria at Visit 2 (randomization)	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.
Section 2: Schedule of Activities (SOA)	Included row for "Exacerbation history" and Line item "X" at "screening"	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.
Section 2: Schedule of Activities (SOA)	Included row for Exacerbation assessment and line item "X" in the boxes from Visit 2 (randomization) to "EOS/EW".	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.

Section # and Name	Description of Change	Brief Rationale
Section 2: Schedule of Activities (SOA) [Study Treatment]	Included row for dispensing Albuterol/Salbutamol and line item "X" at Visit 1 (screening) until Visit 4.	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.
Section 2: Schedule of Activities (SOA) [Study Treatment]	Included row for collection of Albuterol/Salbutamol and line item at Visit 2 until Visit EOS/EW for collection of Albuterol/Salbutamol.	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.
Section 3.3.1 Risk Assessments (Potential Risk of Clinical Significance Systemic ICS effects Adrenal suppression)	Updated the information of HPA study (Mentioned 24 hour urinary cortisol excretion [Previously mentioned as 24 hour **serum** cortisol excretion])	Corrected the information of HPA study
Section 6.2 Exclusion Criteria	Example of tobacco products has been added to Exclusion criteria #14 Tobacco Use (e-cigarettes/vaping)	To clearly explain examples of inhaled tobacco products.
Section 6.2 Exclusion Criteria	Example of a drug has been added to Exclusion criteria 15 Drug/alcohol abuse (marijuana is considered an abused drug).	Updated example of a drug/alcohol abuse.
Section 9, Study Assessments and Procedures	Removed: Healthcare Resource Utilization (HRU) from the additional critical baseline assessments (Screening [Visit 1])	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.

Section # and Name	Description of Change	Brief Rationale
Section 9, Study Assessments and Procedures	Removed: Questionnaires (SGRQ; AQLQ) from the additional critical baseline assessments (Screening [Visit 1])	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.
Section 9, Study Assessments and Procedures	Added: Letters "AE" to the additional critical baseline assessments (Screening [Visit 1])	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.
Section 9.2.1, Time Period and Frequency for collecting AE and SAE Information	Updated the information in the second bullet; (Stated AEs will be collected from the start of Study Screening [Previously mentioned AEs will be collected from the start of Study Treatment])	To correct the inconsistency between the Schedule of Activities (SOA) and the protocol text.

TITLE PAGE

Protocol Title: A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Protocol Number: 205832/ Amendment 1

Short Title: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Compound Number: GW685698+GSK573719

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): IND No. 104479, EudraCT number 2016-002843-40

Approval Date: 15-NOV-2016

SPONSOR'S [illegible]ORY:

PPD

PPD

15th NOV 2016

Steve [illegible]
Vice President,
Head Unit Physician and
Medicines Development Leader
Respiratory Franchise

Date

PPD

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date of Issue**
Amendment 1	*15-Nov-2016*
Original Protocol	*19-Aug-2016*

Overall Rationale for the Amendment:

To address typographical errors and inconsistencies between the Schedule of Activities (SOA) and the protocol text. In addition, language has been added to Exclusion criteria #14 to clearly explain examples of inhaled products (e-cigarettes/vaping) as well as provide an example of a drug ;in Exclusion #15. (marijuana is considered an abused drug).

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TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Short Title: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Rationale:

In the United States (US), the long-acting muscarinic antagonist (LAMA) tiotropium has been approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of an inhaled corticosteroid (ICS)/LAMA/long-acting beta-2-agonist (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 in adults. Through the evaluation of UMEC 62.5 micrograms (mcg) and 31.25 mcg compared to placebo, this study will provide important information regarding the efficacy, safety and tolerability of UMEC when administered via a separate inhaler to participants on a background of FF without VI.

The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

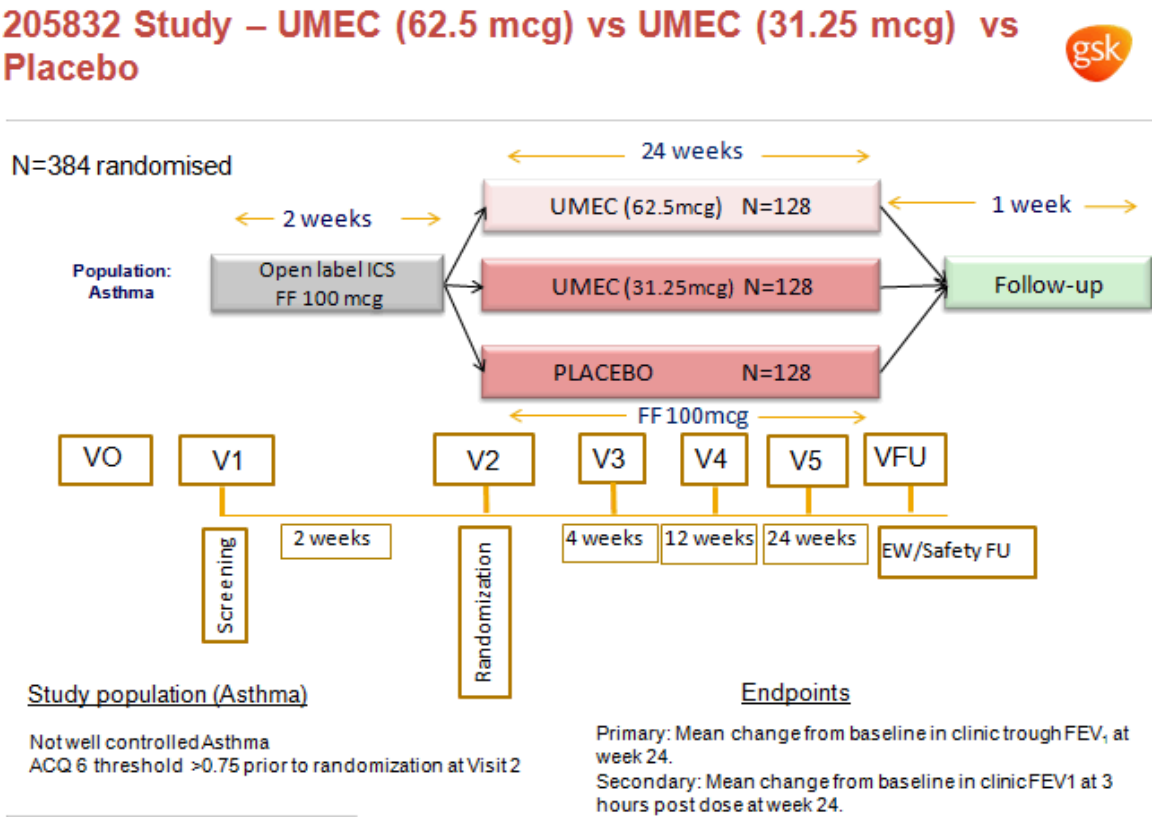
Objectives and Endpoints:

Objective	Endpoint
Primary	
• **Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough Forced Expiratory Volume in 1 second [FEV_1]) vs placebo after 24 weeks of treatment.**	• **Mean change from baseline in clinic trough FEV_1 at Week 24**
Secondary	
• Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3hours post dose FEV_1) vs placebo after 24 weeks of treatment.	• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24

Objective	Endpoint
Safety	
• To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Incidence and type of adverse events • Electrocardiogram (ECG) measurements • Vital signs

Overall Design:

This is a Phase IIb, randomized, double-blind, placebo controlled, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an Asthma Control Questionnaire-6 [ACQ-6] total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS.



Number of Participants:

The total number of randomized participants required is approximately 384, with 128 participants randomized 1:1:1 to each of the 3 double-blind treatment arms.

Treatment Groups and Duration:

Eligible participants will be requested to participate in the study for a maximum of approximately 31 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, participants will complete the following 4 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), including the informed consent process, must be completed within 4 weeks prior to Visit 1 as well as prior to any protocol-required changes to a participant's usual asthma treatment and the initiation of any Visit 1 procedures.

  Participants that receive LABA (or LAMA) as a component of their regular (i.e. pre-study) therapy must stop LABA (or LAMA) treatment from ≥48 hours prior to Visit 1 (Screening) until after they have completed the study; therefore, the investigator must use their clinical judgment to determine if the participant may stop LABA (or LAMA) prior to study entry without incurring undue risk.
- **Screening / run-in:** Participants who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 2 weeks to continue assessing the participant's eligibility for the study. On the morning of Visit 1, participants will refrain from taking the morning dose of their regular (i.e. pre-study) ICS asthma medication. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF 100 mcg via the ELLIPTA dry-powder inhaler (DPI) to take once daily (QD), in the morning, during the 2-week run-in period; the first dose of FF 100 mcg will be self-administered by the participant before leaving the clinic. Participants will refrain from using their own ICS asthma medication during the 2-week run-in and treatment period. Participants will also be provided with rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.
- **Randomization / treatment:** At Visit 2 (the Randomization Visit), participants who meet all of the randomization criteria will be randomized 1:1:1 to receive **one** of the following three double-blind study treatments via the ELLIPTA DPI during the 24-week treatment period:
  - UMEC 62.5 mcg QD
  - UMEC 31.25 mcg QD
  - Placebo QD

  Participants will continue to administer FF 100 mcg once daily (QD), in the morning from a separate ELLIPTA DPI throughout the treatment period. On the morning of Visits 2, 3, 4, and 5, participants will perform their electronic Diary (eDiary) assessments at home but refrain from taking their morning dose of study treatment and FF 100 mcg (as applicable) until instructed to do so by clinic personnel. At Visits 2, 3, 4 and 5, participants will self-administer study treatment immediately followed by FF 100 mcg whilst at the clinic. Participants will take their last dose of study treatment and FF 100 mcg in the clinic on Day 169 (Visit 5). Participants are expected on non-clinic visit days to take their

study treatment and FF 100 mcg at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomized treatment phase, and safety follow-up.

Key Elements of Analysis Plan

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 clinic trough FEV_1 recorded post randomization. Analyses will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, sex, 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 primary comparisons of interest:

- UMEC 62.5 mcg versus Placebo
- UMEC 31.25 mcg versus Placebo

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 reporting and analysis plan (RAP).

The details of the statistical analysis methods for the secondary efficacy endpoint will be provided in the RAP.

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Informed consent (ICF) [a]	X							
Genetic ICF [b]	X							
Inclusion and exclusion criteria		X	X					
Demography [c]	X	X						
Medical history		X						
Asthma history [d]		X						
Exacerbation history		X						
Smoking History and status		X						
Concomitant medication review	X	X	X	X	X	X	X	X
Register visit in Interactive Web Response System (IWRS) (RAMOS NG) [e]	X	X	X	X	X	X	X	
Randomization [f]			X					
Laboratory Assessments								
Urinalysis		X						

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Hematology and clinical chemistry [g]		X						
Hepatitis B and C		X [m]						
Genetic sample			X [n]					1.
Serum pregnancy test		X [o]				X [o]	X [o]	
Urine pregnancy test			X [o]	X [o]	X [o]			
Safety Assessments								
Physical exam including height and weight [h]		X				X	X	
12-lead Electrocardiogram (ECG) [i]		X		X		X	X	
Vital signs [j]		X	X	X	X	X	X	
Adverse Event (AE) review		X	X	X	X	X	X	X
Serious Adverse Event (SAE) review	X	X	X	X	X	X	X	X
Study Treatment								
Dispense Albuterol/Salbutamol, as required		X	X	X	X			
Collect Albuterol/Salbutamol, as required			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Dispense open label fluticasone furoate (FF) 100 mcg medication		X	X	X	X			
Administer open label FF 100 mcg		X	X	X	X	X		
Collect open label FF 100 mcg			X	X	X	X	X	
Dispense double-blind study treatment			X	X	X			
Administer double-blind study treatment			X[p]	X[p]	X[p]	X[p]		
Collect double-blind study treatment				X	X	X	X	
Assess FF 100 mcg run-in medication compliance			X					
Assess FF 100 mcg and double-blind study treatment compliance				X	X	X	X	
Efficacy Assessments								
Global Assessment of Severity [k]			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Global Assessment of Response to Treatment [k]				X	X	X	X	
Asthma Control Questionnaire (ACQ-6) [k]		X	X [q]					
Asthma Control Questionnaire (ACQ-5) [k]				X	X	X	X	
St. George's Respiratory Questionnaire (SGRQ) [k]			X	X	X	X	X	
Asthma Quality of Life Questionnaire (AQLQ) [k]			X	X	X	X	X	
Evaluating Respiratory Symptoms (E-RS) +Asthma symptoms + Peak Expiratory Flow (PEF) + Home Forced Expiratory Volume in 1 second (FEV)1 [k, l]		X						
eDiary Dispense		X						
eDiary Collect						X	X	
eDiary Review			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Dispense paper Medical Problems/Medications Taken worksheet	X	X	X	X	X			
Review paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	
Reversibility		X[r]						
Exacerbation assessment			X	X	X	X	X	
Pre-dose spirometry (clinic)		X[s]	X[s]	X[s]	X[s]	X[s]	X[s]	
Post-dose spirometry (clinic)			X[t]			X[t]	X[t]	

1. Notes:

a) The ICF must be signed before any study procedures, including medication cessation.
b) 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.
c) Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d) The assessment of asthma history will include: the age of the participant 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).
e) The IWRS will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOS NG IWRS manual and SRM for more information).
f) Participants must not be randomized prior to confirming their eligibility to participate in the study.
g) If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
h) Physical Examination will include height and weight at Visit 1 only.
i) ECG to be obtained 15 minutes to 45 minutes after the administration of study treatment.
j) The vital signs assessment will include the measurement of blood pressure, heart rate.
k) Assessment(s) to be completed prior to the administration of study treatment.
l) 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.
m) Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. Hep B/C: If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
n) Pharmacogenetic sample may be drawn any time from Visit 2 onwards.
o) Assessments only to be conducted in females of reproductive potential.
p) Study treatment should be administered at approximately the same time of day at each applicable clinic visit.
q) Baseline ACQ-5 will be derived from items 1-5 of the Randomization (Visit 2) ACQ-6.
r) 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 9.1.3. 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 participant may enter the 2-week run-in period.
s) Pre-dose spirometry should 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 and FF 100 mcg. After V2 pre-dose spirometry assessments should be performed within ± 1 hour of the V2 spirometry.
t) 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 within ± 1 hour of the V2 spirometry.

1.

3. INTRODUCTION

3.1. Study Rationale

In the United States (US), the long-acting muscarinic antagonist (LAMA) tiotropium has been approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/long-acting beta-2-agonist (LABA) combination [FF/umeclidinium (UMEC)/vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma in adults. Through the evaluation of UMEC 62.5 mcg and 31.25 mcg compared to placebo this study will provide important information regarding the efficacy and safety of UMEC when administered in a separate inhaler to participants on a background of FF.

The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

3.2. Background

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; Global Initiative for Asthma (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.

Despite the availability of treatments and published guidelines, patients may have asthma that is not well controlled.

This trial will, primarily, evaluate trough FEV_1 to characterize the efficacy of two doses of UMEC (62.5 mcg and 31.25 mcg) in the treatment of asthma when administered as an open combination with FF 100 mcg. UMEC is currently under development as a closed triple therapy in combination with FF and VI in a single inhaler.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events related to FF and UMEC can be found in the Investigator's Brochure(s) (IB). The table below provides a summary of the key risks in association with FF and UMEC. It is noted that both FF and UMEC have also been developed in combination with VI, therefore relevant safety experience is also provided by the FF/VI and UMEC/VI combinations.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GW685698+GSK573719]		
Cardiovascular effects of UMEC	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 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 - Exclusion criteria as specified in Section 6.2 of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per schedule in Section 2 - Vital sign assessments (heart rate and blood pressure) as per schedule in Section 2 - Cardiovascular AEs and SAEs will be captured on the electronic Case Report Form (eCRF) (see Appendix 4) - Protocol defined stopping criteria as per Section 8.1 -MACE analysis -Instream review of blinded data

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Healthy Volunteers (in the Thorough QT study, UMEC 500 mcg daily dose), no effect was observed on heart rate, blood pressure or QT. 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 500 mcg and placebo. UMEC/VI 500/100 mcg increased QTcF on average by 8.2 msec (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. In addition, UMEC/VI has had urinary retention, dysuria, vision blurred, glaucoma and increased intraocular pressure and paradoxical bronchospasm added as ADRs. ICS has a similar class risk of glaucoma and elevated intraocular	- 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. - Review AEs/SAEs

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	pressure (IOP); however these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.	
Systemic ICS effects -Aderenal 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 participants 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 participants 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 participants 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	- 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
	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 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 participants 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 mcg (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.	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). -Participants 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Pneumonia experience with UMEC 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) 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 participants 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).	resulting in hospitalisation. The occurrence of pneumonia will be recorded in the eCRF. Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a participant 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.	Participants with a history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		stearate are excluded from participation in this study (Section 6.2). -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 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 UMEC 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.	Females who are pregnant or breast-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 100 mcg are recognised pharmacological class effects associated with ICS therapy, which are included in the table above. The experience with FF is provided in the respective IB.

3.3.2. Benefit Assessment

The benefit of UMEC at two dosage strengths 62.5 and 31.25 mcg as compared to Placebo in patients with asthma on background therapy of FF 100 mcg is expected to improve lung function. The inclusion of two strengths of UMEC will allow comparison to placebo for the dose currently marketed in COPD, as well as a lower dose. This will help show the efficacy and safety of UMEC in asthma when administered as an open combination on a background of FF. Another LAMA, tiotropium, is currently approved for the maintenance treatment of asthma.

3.3.3. Overall Benefit: Risk Conclusion

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

The current experience and safety profile with UMEC in previous Phase II asthma studies (alone and in combination with FF) and from clinical trial and marketing experience in the COPD population is supportive of evaluating this compound in asthma patients. The potential risks associated with the known pharmacology of UMEC is offset by the potential significant benefits that are afforded to patients not well controlled on ICS therapy. Furthermore, the approval of another LAMA (tiotropium) for the treatment of asthma demonstrates the suitability for the use of this class of drug in the asthma population.

4. OBJECTIVES AND ENDPOINTS

For a definition of baseline for each of the endpoints listed below, please refer to Section 10.6.

Objectives	Endpoints
Primary • **Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough FEV1) versus placebo after 24 weeks of treatment.**	• **Mean change from baseline in clinic trough FEV_1 at Week 24**
Secondary • Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3hours post dose	• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24

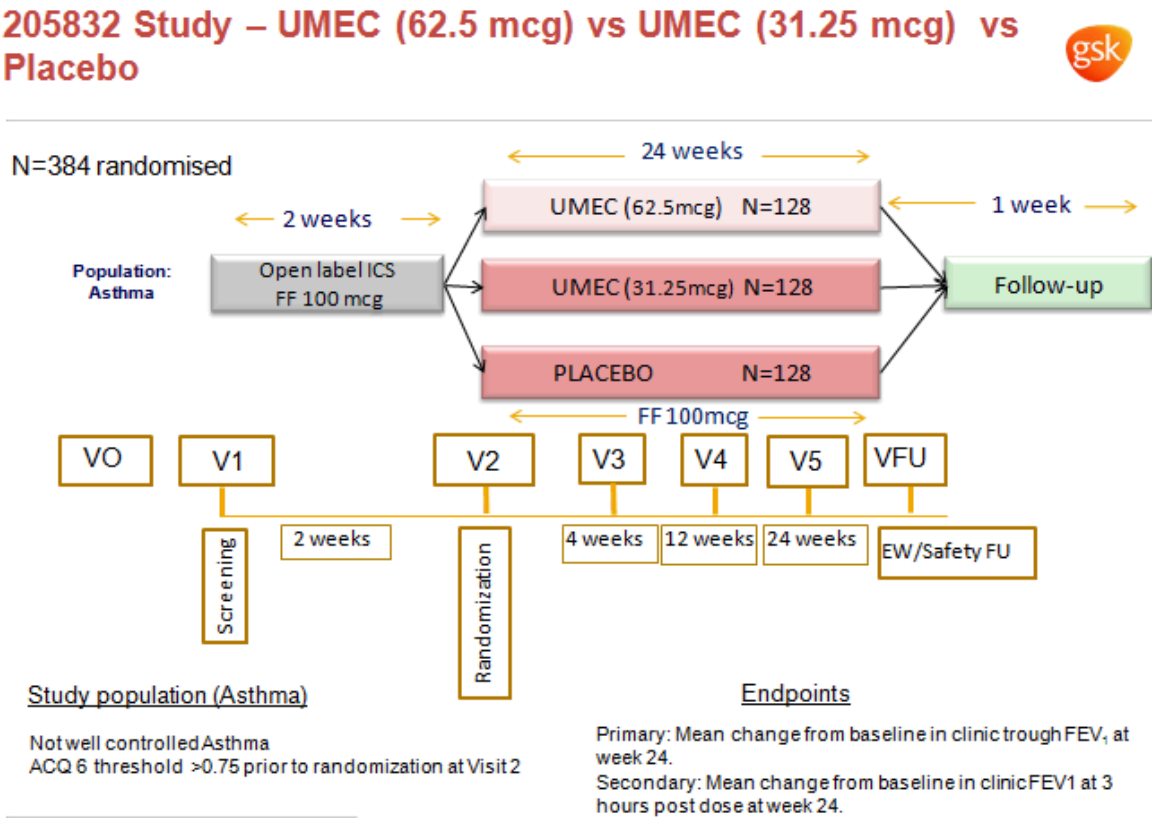
Objectives	Endpoints
FEV1) versus placebo after 24 weeks of treatment.	
Safety • To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Incidence and type of adverse events • ECG measurements • Vital signs
Other • To evaluate other efficacy assessments of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the 24 week treatment period • Mean change from baseline in evening (PM) PEF over the 24 week treatment period • Mean change from baseline in daily home trough FEV1 over the 24 week treatment period • Mean change from baseline in daily rescue medication use over the 24 week treatment period • Mean change from baseline in SGRQ total score 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 SGRQ domain scores at Week 24 • Mean change from baseline in the AQLQ total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement from baseline for the AQLQ total score at Week 24 • Mean change from baseline in E-RS total score over the 24 week treatment period • Mean change from baseline in

Objectives	Endpoints
	ACQ-5 total score at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5 at Week 24 • Annualized rate of moderate/severe asthma exacerbations

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IIb, randomized, double-blind, placebo controlled, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an ACQ-6 total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS.



Eligible participants will be requested to participate in the study for a maximum of approximately 31 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, participants will complete the following 4 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), including the informed consent process, must be completed within 4 weeks prior to Visit 1 as well as prior to any protocol-required changes to a participant's usual asthma treatment and the initiation of any 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 defined in Section 7.9.

  Participants that receive LABA (or LAMA) as a component of their regular (i.e. pre-study) therapy must stop LABA (or LAMA) treatment from ≥48 hours prior to Visit 1 (Screening) until they have completed the study; therefore, the investigator must use their clinical judgment to determine if the participant may stop LABA (or LAMA) prior to study entry without incurring undue risk.

- **Screening / run-in:** Participants who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 2 weeks to continue assessing the participant's eligibility for the study. On the morning of Visit 1, participants will refrain from taking the morning dose of their regular (i.e. pre-study) ICS asthma medication. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF 100 mcg via the ELLIPTA dry-powder inhaler (DPI) to take once daily (QD), in the morning, during the 2-week run-in period; the first dose of FF 100 mcg will be self-administered by the participant before leaving the clinic. Participants will refrain from using their own ICS asthma medication during the 2-week run-in and treatment period. Participants will also be provided with rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.

- **Randomization / treatment:** At Visit 2 (the Randomization Visit), participants who meet all of the randomization criteria will be randomized 1:1:1 to receive **one** of the following three double-blind study treatments via the ELLIPTA DPI during the 24-week treatment period:

  - UMEC 62.5 mcg QD
  - UMEC 31.25 mcg QD
  - Placebo QD

  Participants will continue to administer FF 100 mcg once daily (QD), in the morning from a separate ELLIPTA DPI throughout the treatment period. On the morning of Visits 2, 3, 4, and 5, participants will perform their electronic Diary (eDiary) assessments at home but refrain from taking their morning dose of study treatment and FF 100 mcg (as applicable) until instructed to do so by clinic personnel. At Visits 2, 3, 4 and 5, participants will self-administer study treatment immediately followed by FF 100 mcg whilst at the clinic (see Section 7.2). Participants will take their last dose of study treatment and FF 100 mcg in the clinic on Day 169 (Visit 5). Participants are expected on non-clinic visit days to take their study treatment and FF 100 mcg at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomized treatment phase, and safety follow-up.

To demonstrate the benefit of UMEC the primary comparisons of interest for the primary efficacy endpoint are:

- UMEC 62.5 mcg versus (vs) Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 10.5.3. Participants who permanently discontinue double-blind study treatment are not required to withdraw from the study. Participants 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 8.1)

5.2. Number of Participants

The total number of randomized participants required is approximately 384, with 128 participants randomized 1:1:1 to each of the 3 double-blind treatment arms (see Section 10).

5.3. Participant and Study Completion

A participant will be considered to have completed the study when they have completed all phases of the study including pre-screening, screening, run-in, the randomized treatment phase, and safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities table (see Section 2) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, 3 arm parallel-group design. This is a well-established design to evaluate the efficacy, safety, and tolerability of the UMEC drug. A placebo arm is included. All participants will be placed on open-label FF 100 mcg when they enter the 2 week run-in period and continue it through the 24 week treatment period. The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [FF/UMEC/VI)] in a single device, with the aim of providing a new treatment option for the management of asthma in adults. Through the evaluation of UMEC 62.5 mcg and 31.25 mcg compared to placebo this study will provide important information regarding the efficacy, safety and tolerability of UMEC in asthma when administered via a separate inhaler to participants on a background of FF without VI.

5.5. Dose Justification

The 200699 (IB Supplement, GlaxoSmithKline Document 2011N123107_03) data showed UMEC 62.5 mcg to be an effective dose; after 4 weeks of treatment in the subset of patients with a primary diagnosis of asthma, an average increase in change from baseline trough FEV_1 at Day 29 of 136 mL was observed in those participants treated with FF/UMEC (100/62.5 mcg) compared to those participants 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 both 31.25 and 62.5 mcg doses will be assessed in this study when administered via a separate inhaler to participants treated on a background of FF 100 mcg. No safety signal was identified with any of the UMEC doses (15.6, 62.5, 125 and 250 mcg) evaluated in the 200699 study.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. **Age:** 18 years of age or older at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. **Diagnosis:** Participants with a diagnosis of asthma as defined by the National Institutes of Health [NIH, 2007] at least 6 months prior to Visit 0. 3. **Asthma Control:** ACQ-6 total score of >0.75 at Visit 1. 4. **Current Asthma Maintenance Therapy**: Participants are eligible if they have required daily ICS therapy ≥ 100 mcg/day fluticasone propionate (FP, or equivalent) with or without LABA or LAMA for at least 12 weeks prior to Visit 0 and there have been no changes in maintenance asthma medications during the 4 weeks immediately prior to Visit 0. Examples of acceptable doses of commonly prescribed ICS medication will be 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.

5. **Spirometry:** Both of the following:
   a. A best pre-bronchodilator morning (AM) FEV1 ≤85% of the predicted normal value. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012].
   b. A best post-bronchodilator FEV1/ forced vital capacity (FVC) ≥0.7 at Visit 1.
6. **Reversibility of Disease:** Airway reversibility is defined as ≥12% and ≥200 mL increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.

   Note: If the participant 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 FEV1 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 FEV1 of ≥12% and ≥200 mL.*

   Should the participant successfully demonstrate airway reversibility (defined as ≥12% and ≥200 mL increase in FEV1 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 participant may enter the 2-week run-in period (see Section 9.1.3).
7. **Short-Acting β2 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

8. **Gender:**

a. Male participants

b. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

  OR
- A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 5 days after the last dose of study

treatment.
INFORMED CONSENT
9. **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. Participants must be able to read, comprehend, and write at a level sufficient to complete study related materials.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS
1. **Pneumonia:** Chest X-ray documented pneumonia in the 12 weeks prior to Visit 1.
2. **Asthma Exacerbation:** Any severe asthma exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (oral, parenteral or depot) within 12 weeks of Visit 1, or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids within 12 weeks of Visit 1.
3. **Concurrent Respiratory Disease:** Current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, lung cancer, or other respiratory abnormalities other than asthma.
4. **Pregnancy**: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
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**: Participants 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 participant 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 participant otherwise meets entry criteria*

8. **Clinically significant ECG abnormality:** Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening or run-in. The PI will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants 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:
    - 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:** participants 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
10. **Antimuscarinic effects:** Participants 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**: Participants with carcinoma that has not been in complete remission for at least 5 years. Participants 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 participant has been considered cured by treatment.
12. **Questionable validity of consent**: Participants 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.

PRIOR/CONCOMITANT THERAPY

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

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE/RELEVANT HABITS

14. Tobacco Use: Current smoker or a smoking history of ≥10 pack years (e.g., 20 cigarettes/day for 10 years). A participant may not have used inhaled tobacco products within the past 12 months (i.e., cigarettes, e-cigarettes/vaping, cigars or pipe

tobacco). 15. **Drug/alcohol abuse:** Participants with a known or suspected history of alcohol or drug abuse within the last 2 years. This includes marijuana, which is considered an abused drug.
Diagnostic assessments
16. **Allergy or Hypersensitivity:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate.
Other Exclusions
17. **Non-compliance:** Participants 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 participant who is unable to read and/or would not be able to complete study related materials.

6.2.1. Randomization Criteria

At the end of the run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

6.2.2. Inclusion Criteria for Randomization

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
1. **Asthma Control:** ACQ-6 total score of >0.75 at Visit 2. 2. **Percent-predicted FEV_1:** Spirometry: A best pre-bronchodilator morning (AM) FEV1 ≤85% 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.

6.2.3. 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 run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the participant's asthma status or the participant's ability to participate in the study. 2. **Asthma exacerbation:** Evidence of a moderate asthma exacerbation leading to a change in therapy or severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
CONCOMITANT MEDICATIONS/TREATMENTS
3. **Asthma medication:** Changes in asthma medication (excluding changes after Visit 0 or 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.

6.3. Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.4. Pre-Screening/Screening/Run-in/Randomization Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the eCRF for participants who are pre-screen failures:

- Demographic information including race, age and gender
- Participant 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-screening failures, screening failures, run-in failures and randomization failures will be defined as follows:

- **Pre-screening failures:** those participants that sign the informed consent document but do not have a Visit 1 (Screening) procedure.

- **Screening failures:** those participants that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period.

  A participant 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 participants that enter the run-in period but do not have any Visit 2 (Randomization) procedures.

- **Randomization failures:** those participants that complete at least one Visit 2 (Randomization) procedure but do not enter the double-blind study treatment period.

  Any participant who completes the run-in period and then meets the randomization criteria and is dispensed the double-blind study treatment at Visit 2 is considered to have entered the treatment period.

RAMOS NG will be contacted to register the participant.

In order to ensure transparent reporting of screen/run-in failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen/run-in/randomization failure information is required including demography, screen/run-in/randomization failure details, eligibility criteria, and any SAEs (see Section 9.2.4 and Appendix 4). Further details are provided in the study-specific eCRF completion guidelines document.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The term 'study treatment' within this trial is used to describe the combination of products received by the participant as per the protocol design. Study treatment may also be used to only reference the randomized study treatment when described together with the FF 100 mcg open-label treatment.

7.1. Treatments Administered

7.1.1. Description of FF 100 mcg and Double-Blind Study Treatment

The ELLIPTA device will be used during the run-in period and the treatment period. The ELLIPTA dry powder inhaler (DPI) is a molded plastic two-sided device with a dose counter that can hold two individual blister strips. The ELLIPTA will deliver, when actuated, the contents of a single blister simultaneously from each of the two strips. The ELLIPTA is individually sealed in a foil laminate overwrap that also contains a silica gel desiccant packet.

A description of the FF (GW685698) 100 mcg inhalation powder administered via the ELLIPTA is provided in Table 1; descriptions of the double-blind study treatments administered via the ELLIPTA are provided in Table 2.

Table 1 Description of FF 100 mcg Inhalation Powder in ELLIPTA

FF 100	First Strip	Second Strip
	GW685698 blended with lactose monohydrate	Lactose monohydrate with magnesium stearate[1]
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose strengths	100 mcg per blister	Not applicable
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 1.0% w/w of total drug product.

Table 2 Description of Study Treatment Inhalation Powder in ELLIPTA

Placebo	First strip	Second strip
	Lactose monohydrate blended with magnesium stearate1	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	White powder	White powder
Route of Administration	Inhaled	
UMEC	**First strip**	**Second strip**
	GSK573719 blended with lactose and magnesium stearate	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose Strengths	31.25 mcg per blister	NA
Physical description	White powder	White powder
Route of Administration	Inhaled	
UMEC	**First strip**	**Second strip**
	GSK573719 blended with lactose and magnesium stearate	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose Strengths	62.5 mcg per blister	NA
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product. 2. Magnesium stearate 1.0% w/w of total drug product

7.1.2. Description of Albuterol/Salbutamol

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.

7.1.3. Study Treatment and FF 100 mcg Return

ELLIPTAs containing FF 100 mcg and study treatment will be dispensed to a participant during their visit to the study clinic (as applicable). The participant must return all dispensed ELLIPTAs at the subsequent clinic visit. The schedule for dispensing and collecting FF 100 mcg and study treatment ELLIPTAs is provided in the Schedule of Activities table (Section 2).

All used and unused study treatment, FF 100 mcg and albuterol/salbutamol 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 Study Reference Manual (SRM).

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

In addition, any metered dose inhaler (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.

7.2. Dose Modification

There were no dose modifications planned for this protocol.

7.3. Method of Treatment Assignment

Participants 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. Participants will be randomized using an interactive web response system (IWRS) RAMOS NG. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 2-week run-in period and participant to satisfying all eligibility criteria, participants will be randomized 1:1:1 to one of the following three double-blind treatments for the duration of the treatment period:

- UMEC 62.5 mcg QD
- UMEC 31.25 mcg QD
- Placebo QD

The duration of double-blind treatment for each participant is 24 weeks. On the morning of each scheduled clinic study visit, participants will refrain from taking their morning dose of study treatment and FF 100 mcg 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 Randomization Visit (Visit 2). On the other days during the treatment period (i.e. "non-clinic days"), participants 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 IWRS system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IWRS manual and SRM.

7.4. Blinding

This will be a double-blind study and the following will apply.

- The Investigator or treating physician may unblind a participant'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 participant as judged by the Investigator.
- Investigators have direct access to the participant'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 participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and event or condition which led to the unblinding (i.e. the primary reason) will be recorded in source documentation and in the eCRF.

Should a participant's treatment assignment be unblinded then the participant may continue the assigned study treatment and be followed-up as per protocol until the completion of the Safety Follow-up assessments.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant 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 participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy. Participants will not be withdrawn from the study.

7.5. Packaging and Labeling

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

7.6. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.7. Treatment Compliance

When participants are dosed at the site, they will receive FF 100 mcg and 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 participant identification will be confirmed at the time of dosing by a member of the study site staff.

When participants self-administer study treatment(s) at home, compliance with study treatment will be assessed through querying the participant during the site visits and recording the number of doses remaining in the ELLIPTA in the eCRF (see the SRM for details). A record of the number of ELLIPTAs dispensed to each participant must be maintained and reconciled with study treatment and compliance records.

Participant compliance with FF 100 mcg and study treatment will be assessed at scheduled clinic visits by reviewing the eDiary and information from the dose counter on the returned inhaler(s) (see Section 7.1.3). Participants should be ≥80% to ≤120% compliant on taking both FF 100 mcg and study treatment between each pair of scheduled and consecutive on-treatment clinic visits, as applicable. Participants who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the participant's source document. If FF 100 mcg and/or study treatment is prematurely discontinued during the course of the study or

compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss participant eligibility for continued participation in the study.

7.8. Concomitant Therapy

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.

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 FF 100 mcg and albuterol/salbutamol should not be recorded in the eCRF; however non-study supplied FF 100 mcg and albuterol/salbutamol will be recorded in the eCRF.*

The minimum requirement is that the drug name, reason for use, dose (including unit e.g. mcg) and frequency, route and the dates of administration are to be recorded.

Medications initiated after completion of the assessments at Visit 5/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. Participants who have completed the Early Withdrawal Visit are allowed to use any medications prescribed by the Investigator or primary care physician.

7.8.1. Permitted Medications and Non-Drug Therapies

7.8.1.1. Permitted Asthma Medications

In addition to FF 100 mcg and 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. Participants must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

Temporary changes in medications are permitted for the treatment of moderate asthma exacerbations, 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 SRM for contact information [refer to Section 9.1.4.1 for guidance on moderate asthma exacerbation]):

- An increase in ICS dose.
- Systemic corticosteroids (tablets, suspension or injection) 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.

7.8.1.2. 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: Participants 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 participants 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 participants' lung function or safety assessments (e.g., cardiac measurements). However, no systemic corticosteroids will be permitted.

7.9. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 3 is not permitted during the study.

Table 3 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
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)	2 days 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, 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
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

7.10. Treatment after the End of the Study

Participants 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 participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

Participants who withdraw from 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. If this is not possible, the Investigator must encourage the participant to participate in as much of the study as they are willing (or able) to.

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

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

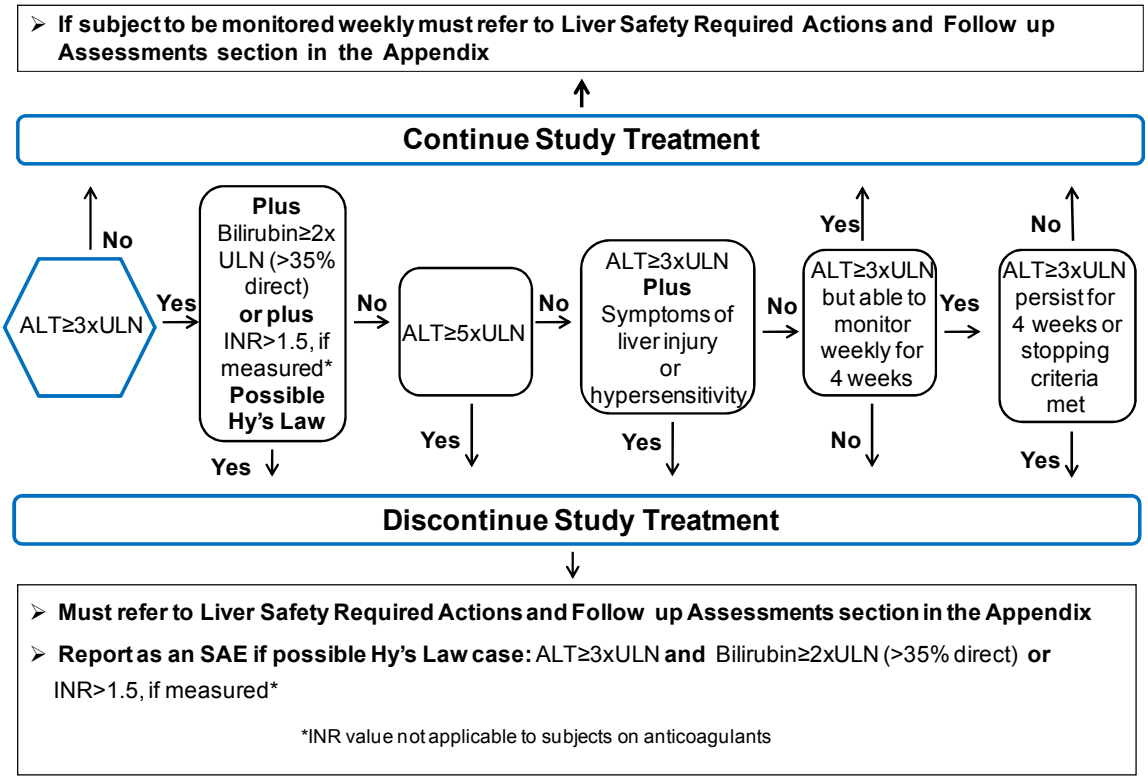
- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria
- QTc: Meets any of the protocol-defined stopping criteria
- Pregnancy: Positive pregnancy test

8.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments can be found in Appendix 7

8.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 9.4.3.

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
  - For example, if a participant 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 participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *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 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, lead to withdrawal from study treatment:
  - QTc>500 msec or uncorrected QT>600 msec

- Change from baseline: QTc> 60 msec

- For patients with underlying bundle branch block, follow the discontinuation criteria listed below:
  - Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
  - Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- In the event of early withdrawal from the study, every effort should be made to have the participant 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 Schedule of Activities table (Section 2).

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3

telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 2). There are no protocol waivers or exemptions allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

- Demographic information including race, age and gender
- Participant 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 participant 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
- Questionnaires (ACQ;; E-RS)
- Pre-and post-albuterol/salbutamol lung function
- Inclusion/Exclusion criteria assessment
- Physical examination
- 12-lead ECG
- Child bearing status assessment for all potential female participants
- Clinical laboratory tests (including hematology, chemistry, urinalysis and serum pregnancy test)
- AE / 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 FF 100 mcg run-in medication

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in the Schedule of Activities (SoA) (Section 2).

9.1.1. Questionnaires

The questionnaires should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participants 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 participant must be encouraged to complete any missing assessments or items.

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

9.1.1.1. Global Assessment of Severity and Response to Treatment

The participant will be asked to complete the Global Assessment of Severity and Response to Treatment at the visits specified in the Schedule of Activities table (Section 2). The Global Assessment of Severity is a single item questionnaire; participants 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. Instructions for completing the questionnaires can be found in the SRM.

9.1.1.2. Asthma Control Questionnaire (ACQ)

The ACQ measures attributes of asthma control [Juniper 1999], measured with questions designed to be self-completed by the participant. Participants will complete the ACQ at specified study visits. The ACQ-5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of symptoms over the previous week. The ACQ-6 includes an additional item asking about rescue medication use. 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. 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].

9.1.1.3. St. George's Respiratory of Life Questionnaire (SGRQ)

The SGRQ 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 participant [Jones 1992] with a recall over the past 3 months. A change of 4 points is considered a clinically relevant change [Jones 2005].

9.1.1.4. Asthma Quality of Life Questionnaire (AQLQ)

The 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 participant with a recall over the past 2 weeks. A change of ≥ 0.5 is considered clinically important [Juniper 1994].

9.1.2. Daily Diaries

Participants 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. Participants 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 PEF
- Morning FF 100 mcg medication use
- Morning double-blind study medication use (during the treatment period only)

Section 9.1.2 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.

Participants 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). Participants 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 participant recall in discussions with the Investigator, for site staff to then enter as appropriate in the eCRF.

9.1.2.1. eDiary Questionnaires, Assessments and Alerts

For information on the eDiary questions, please refer to Appendix 8.

9.1.2.1.1. 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.

9.1.2.1.2. 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.

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

Every morning upon waking (from the morning after Visit 1 onwards), participants will answer a question on the occurrence of night-time awakenings due to asthma symptoms. The participant'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', participants 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, participants 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 (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]).

9.1.2.1.4. Morning and Evening Home Spirometry

An electronic home spirometer/eDiary device will be issued to participants 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. Participants will conduct spirometry maneuvers each morning, prior to study treatment and FF 100 mcg dosing, and each evening. Three measurements for each session will be recorded by the participants in the eDiary. Assessments will be performed:

- After completing all other eDiary assessments
- Prior to albuterol/salbutamol use
- Prior to study treatment and FF 100 mcg 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.

9.1.2.1.5. Alerts

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions for the participant to contact the investigator (either by telephone and/or by visiting the study clinic) if any of the alert criteria are met:

- Nocturnal awakening(s) due to asthma requiring albuterol/salbutamol use for 2 consecutive nights.
- An increase from baseline of ≥ 4 puffs /day of albuterol/salbutamol use on 2 consecutive days.
- A ≥30% decrease in AM PEF from baseline on 2 consecutive mornings.
- A ≥30% decrease in PM PEF from baseline on 2 consecutive evenings
- A ≥30% decrease in AM FEV1 from baseline on 2 consecutive mornings.
- A ≥30% decrease in PM FEV1 from baseline on 2 consecutive evenings.

9.1.3. Pulmonary Function Test

The 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 American Thoracic Society / European Respiratory Society (ATS/ERS) standards [Miller 2005]. The highest of 3 technically acceptable measurements will be recorded at each visit:

- **Pre-dose Spirometry:** At Visits 1 through 5/EOS (and the Early Withdrawal Visit, if applicable), participants 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 2 (the baseline assessment).
  - At least 24 hours after the participant's last morning dose of study treatment on the day prior to the visit.
  - Before the participant's morning dose of study treatment on the day of the visit.
- **Post-dose Spirometry:** At Visits 2 and 5/EOS (and the Early Withdrawal Visit, if applicable), spirometry assessments must be performed 3 hours after the participant's morning dose of study treatment; the assessment performed at Visit 5/EOS should be performed at the same time of day (± 1 hour) as the assessment performed at Visit 2 (the baseline assessment). At each visit, participants 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.

9.1.3.1. Reversibility (Albuterol/Salbutamol)

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.

To perform the reversibility assessment, 4 puffs of the provided albuterol/salbutamol 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 albuterol/salbutamol.

Percent reversibility will be calculated as follows:

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

The reversibility requirement for eligibility must be assessed at Visit 1. Participants 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 participant may not enter the 2-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 participant 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 participant may enter the 2-week run-in period.

9.1.4. Asthma Exacerbations

Moderate and severe asthma exacerbation data will be collected from the start of randomized double blinded treatment until Visit 5/EOS Visit or the Early Withdrawal Visit for those participants that withdraw from participation in the study (see Section 8.2). For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

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

9.1.4.1. Moderate Asthma Exacerbation

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 for 3 days or more and/or hospitalization.
- 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.

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 (Refer to Section 7.8.1 above)
The Medical Monitor may be contacted for additional guidance, see the medical monitor/Sponsor Information Page.

9.1.4.2. Severe Asthma Exacerbation

A severe asthma exacerbation is defined as:

The deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection) for at least 3 days.

OR

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

9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 8).

9.2.1. 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 participant consents to participate in the study up to and including any follow-up contact.

- AEs will be collected from the start of Study Screening until the follow-up contact (see Section 9.2.3) at the timepoints specified in the Schedule of Activities (SoA) table (Section 2).
- 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. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant 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

9.2.2. 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 participant 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?"

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of

participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. 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). 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	Glaucoma (antimuscarinic/corticosteroid)

Special interest AE group	Special interest AE subgroup
effects / Corticosteroids associated eye disorders	Cataracts (corticosteroid)
Pneumonia and LRTI	Pneumonia
	LRTI excluding pneumonia
Adrenal suppression	-
Decreased bone mineral density and associated fractures	-
Effects on glucose	-
Hypersensitivity	-
Local steroid effects	-

9.2.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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

9.2.7. 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 participant 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).

9.2.8. 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.

9.2.9. Pregnancy

Details of all pregnancies in female participants 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.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of 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 eCRF 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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA).

9.4.1. Physical Examinations

Physical exams will be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2).

- 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.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

Vital signs will be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2) prior to conducting spirometry and prior to taking the morning dose of study treatment and FF 100 mcg. 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.

9.4.3. Electrocardiograms

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 Schedule of Activities (SoA) table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.

For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.2).

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.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (SoA) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (SoA).

9.5. Pharmacokinetics

Pharmacokinetics is not relevant for this protocol.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 6. 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 6).

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.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to evaluate the efficacy of UMEC 62.5 mcg and UMEC 31.25 mcg compared with placebo in participants with not well controlled asthma over a 24 week treatment period. This is a superiority study to demonstrate the benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg when compared to Placebo in patients on background therapy of FF 100 mcg. The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at Week 24.

The test for the primary efficacy endpoint is such that 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:

- UMEC 62.5mcg vs Placebo
- UMEC 31.25mcg vs Placebo

For each comparison test on the primary endpoint, the null hypothesis is there is no difference between treatment groups. The alternative hypothesis is there is a difference between treatment groups.

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

Details on all pairwise treatment comparisons of interest are provided in Section 10.5.2.

10.2. Sample Size Determination

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 384 randomized participants are required for this study, with 128 participants in each of the three double-blind treatment groups: UMEC 62.5mcg, UMEC 31.25mcg or Placebo. Assuming 10% missing data on spirometry at the end of the 24-week treatment period, due to early withdrawal from study, approximately 115 participants per treatment group will have trough FEV_1 available for the primary 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 350mL based on two previous Tiotropium moderate asthma studies. The study design and population of this study aligns well with these two phase III, 24 week, randomised, double blind, placebo-controlled, parallel-group, active comparator studies of Tiotropium. In patients with moderate asthma on a background therapy of ICS the standard deviations in change from baseline trough FEV1 at Week 24 ranged from 325 to 354mL; from this a SD estimate of 350 mL was chosen. This was estimated from a wide selection of studies, critically to minimise the risk of reduced power for the primary endpoint. The range of observed treatment differences across the Tiotropium treatment groups is 133 – 185mL, which supports the expectation that the treatment effect seen in a moderate asthma population is larger than in the more severe asthma population in study 205715 treated on a background of FF/VI. This is in line with data from GSK study 200699 which showed UMEC 62.5 mcg to be an effective dose. An average increase in change from baseline trough FEV1 at Day 29 of 136 mL was observed in an asthma subset of patients treated with FF/UMEC (100/62.5) compared with FF (100 mcg) alone. The GSK phase III closed triple asthma study 205715, which this study supports, is in a more severe asthma population and conservatively assumes a SD estimate of 400mL.

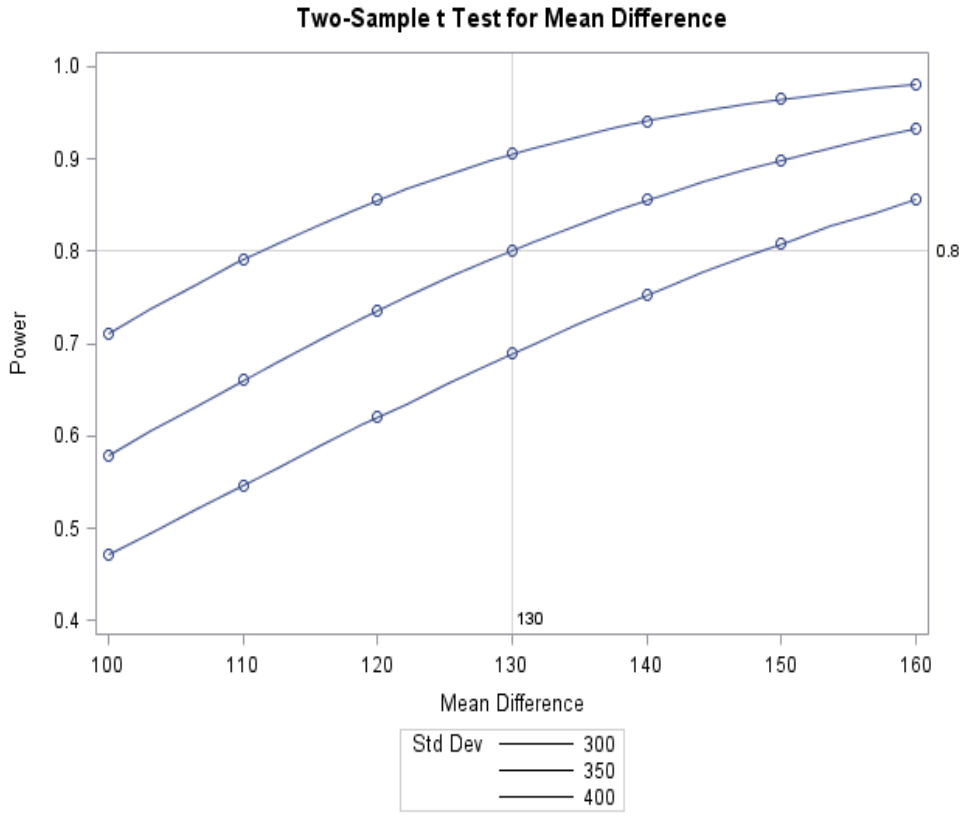
Based on a true population difference of 130 mL, a sample size of 115 patients per treatment group has an estimated 80% power to observe statistical significance at the two sided 5% level, for each of the two primary comparisons of interest for each UMEC dose. Using the above assumptions the smallest observed effect predicted to result in a statistically significant difference between treatment groups is 90.5 mL (minimum detectable difference).

No interim analysis is planned for this study.

10.3. 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=115 per arm in the intent to treat (ITT) population for the primary efficacy analysis, varying the true treatment difference and estimated standard deviation on the change from baseline in trough FEV_1 at the end of the 24-week treatment period.

Standard Deviation	Treatment difference (mL)				
	100	115	130	145	160
300	0.71	0.82	0.91	0.95	0.98
350	0.58	0.70	0.80	0.88	0.93
400	0.47	0.58	0.69	0.78	0.86



10.4. Sample site re-estimation or adjustment

No sample size re-estimation is planned.

10.5. Data Analysis

10.5.1. Analysis population

The following participant populations will be identified:

All Participants Enrolled Population: This population will comprise all participants for whom a record exists on the study database, including pre-screened participants that sign

the informed consent document but do not complete a Visit 1 (screening) procedure (i.e., pre-screening failures), or participants 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 participant disposition.

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

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

10.5.2. Treatment Comparisons

To demonstrate the benefit of UMEC the primary comparisons of interest for the primary efficacy endpoint are:

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 10.5.3.

10.5.3. Multiple Comparisons and Multiplicity

In order to account for multiple tests involving the two UMEC doses 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 test in the hierarchy.

A step-down procedure with the following hierarchy will be used for the primary comparisons in the primary endpoint.

- The contrast between UMEC 62.5 mcg vs Placebo
  (two-sided, alpha = 0.05. Null hypothesis of no treatment difference)
- The contrast between UMEC 31.25 mcg vs Placebo
  (two-sided, alpha = 0.05. Null hypothesis of no treatment difference)

The second hypothesis will be formally tested only if the first hypothesis has been rejected, thus maintaining the overall significance level at 5%.

Specifically, if the defined treatment comparison for the primary efficacy endpoint at the highest dose of UMEC 62.5 mcg is significant at 0.05 level then the efficacy of UMEC 62.5 mcg is demonstrated, and the treatment comparison can be repeated on the UMEC 31.25 mcg dose.

Note that, in the event that the first hypothesis is not rejected a nominal p-value for the second hypothesis may be provided in the displays for descriptive purposes only and will not alter the conclusion of the step-down procedure.

No multiplicity adjustment will be made on these two treatment comparisons on the secondary endpoint.

For all efficacy endpoints (primary, secondary and other), treatment comparisons between UMEC 62.5 vs UMEC 31.25 mcg informally investigating the benefit of increasing UMEC dose will be made without adjusting for multiplicity. Any p-values $\leq$ 0.05 will be identified as nominally significant.

10.6. Statistical Analysis

Where possible, data from participants 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 RAP.

In general, the baseline value is the last assessment value prior to randomization at Visit 2 for the efficacy endpoints based on assessments at clinic visits. The covariates to be considered in the efficacy analyses include age, sex, and the baseline value, if relevant. Other covariates, if appropriate, may be considered. Specific details will be provided in the RAP.

10.6.1. 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 participant, the baseline value of clinic FEV_1 is the last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomization (either from Visit 2 pre-dose or from Visit 1 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, 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.

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

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 10.5.2 will also be provided for the primary efficacy endpoint.

10.6.2. Secondary Analyses

Full details of the analyses to be performed on the secondary efficacy endpoint will be given in the RAP.

10.6.3. 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.

10.6.4. Interim Analyses

No interim analysis is planned for this study.

10.6.5. Exploratory Analyses

The psychometric properties of the E-RS and Supplemental asthma items will be evaluated to characterize the E-RS as an endpoint for asthma. These exploratory analyses may be provided in a separate RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
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
BMI	Body Mass Index
BPM	Beats Per Minute
BST	Bioanalytical Science and Toxicokinetics
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
eDiary	Electronic Diary
EOS	End of study
E-RS	Evaluating Respiratory Symptoms
ERS	European Respiratory Society
EW	Early Withdrawal
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Axis
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWRS	Interactive Web Response System
ITT	Intent to Treat
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LOCS III	Lens Opacities Classification System III
LRTI	Lower Respiratory Tract Infection
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
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PM	Evening
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

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Clinical Laboratory Tests

- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol Schedule of Activities (Section 2) Laboratory requisition forms must be completed and samples must be clearly labelled with the participant 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 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 participant 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.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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; 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	• **Follicle stimulating hormone (FSH) and estradiol (as needed in females of non-reproductive potential only)** • **Serum/urine hCG Pregnancy test (as specified in the Schedule of Activities table [Section 2])**

NOTES :

5. Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 8.1.1 and Appendix 7

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- For this study participant 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.

Data Quality Assurance

- 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. Participant initials will not be collected or transmitted to GSK according to GSK policy.
- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events <u>NOT</u> Meeting the AE Definition
• 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 participant'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 participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 (eg, sprained ankle) which may interfere with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as

severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool

- The primary mechanism for reporting SAE to GSK will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the assigned SAE contact by telephone.
- Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

SAE Reporting to GSK via Paper CRF

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

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

6. Premenarchal
7. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

8. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4.

Table 4 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. *Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.*

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of [5, 10, 25] mIU/mL will be performed [and assayed in a certified laboratory OR and assayed in the central laboratory OR using

the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert]

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 participant who becomes pregnant while participating in the study will immediately discontinue study medication.

12.6. Appendix 6: Genetics

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 participant who is enrolled in the study can participate in genetic research. Any participant 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 participant 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 participant 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 participant 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.

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

Informed Consent

Participants 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.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant 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 participant 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 participant 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 participant does not meet the entry criteria for participation in the study, then the Investigator should instruct the participant 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 Participant'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 participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant'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

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Section 8.1.3) If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 72 hours after last dose[5] • 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 liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week (James 2009) **Not Required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.8. Appendix 8: Daily Diary Questions

12.8.1. Morning Questions

The participant 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

12.8.2. Evening Questions

The participant 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

12.9. Appendix 9: Country-specific requirements

There are currently no country specific requirements.

12.10. Appendix 10: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

TITLE PAGE

Protocol Title: A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Protocol Number: 205832

Short Title: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Compound Number: GW685698+GSK573719

Sponsor Name and Legal Registered Address:

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

Medical Monitor Name and Contact Information can be found in the Study Reference Manual

Regulatory Agency Identifying Number(s): IND No. 104479, EudraCT number 2016-002843-40

Approval Date: 19-AUG-2016

SPONSOR SIGNATORY:

PPD

19th AUG 2016

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

Date

PPD

TABLE OF CONTENTS

PAGE

1. SYNOPSIS

Protocol Title: A Phase IIb, 24 week, randomized, double-blind, 3 arm parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Short Title: A randomized, double-blind, parallel group study, comparing the efficacy, safety and tolerability of two doses of umeclidinium bromide administered once-daily via a dry powder inhaler, versus placebo, in participants with asthma

Rationale:

In the United States (US), the long-acting muscarinic antagonist (LAMA) tiotropium has been approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of an inhaled corticosteroid (ICS)/LAMA/long-acting beta-2-agonist (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 in adults. Through the evaluation of UMEC 62.5 micrograms (mcg) and 31.25 mcg compared to placebo, this study will provide important information regarding the efficacy, safety and tolerability of UMEC when administered via a separate inhaler to participants on a background of FF without VI.

The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

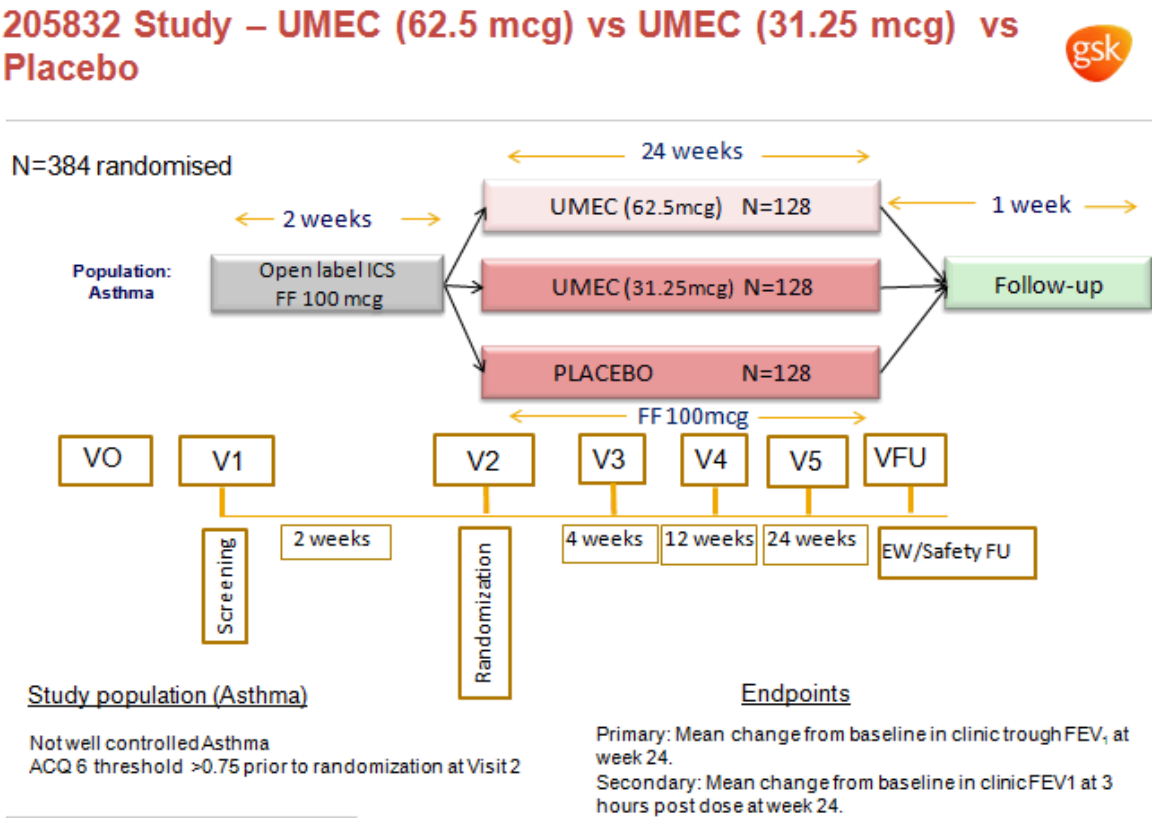
Objectives and Endpoints:

Objective	Endpoint
Primary	
• **Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough Forced Expiratory Volume in 1 second [FEV_{1}]) vs placebo after 24 weeks of treatment.**	• **Mean change from baseline in clinic trough FEV_1 at Week 24**
Secondary	
• Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3hours post dose FEV_1) vs placebo after 24 weeks of treatment.	• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24

Objective	Endpoint
Safety	
• To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Incidence and type of adverse events • Electrocardiogram (ECG) measurements • Vital signs

Overall Design:

This is a Phase IIb, randomized, double-blind, placebo controlled, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an Asthma Control Questionnaire-6 [ACQ-6] total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS.



Number of Participants:

The total number of randomized participants required is approximately 384, with 128 participants randomized 1:1:1 to each of the 3 double-blind treatment arms.

Treatment Groups and Duration:

Eligible participants will be requested to participate in the study for a maximum of approximately 31 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, participants will complete the following 4 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), including the informed consent process, must be completed within 4 weeks prior to Visit 1 as well as prior to any protocol-required changes to a participant's usual asthma treatment and the initiation of any Visit 1 procedures.

  Participants that receive LABA (or LAMA) as a component of their regular (i.e. pre-study) therapy must stop LABA (or LAMA) treatment from ≥48 hours prior to Visit 1 (Screening) until after they have completed the study; therefore, the investigator must use their clinical judgment to determine if the participant may stop LABA (or LAMA) prior to study entry without incurring undue risk.
- **Screening / run-in:** Participants who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 2 weeks to continue assessing the participant's eligibility for the study. On the morning of Visit 1, participants will refrain from taking the morning dose of their regular (i.e. pre-study) ICS asthma medication. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF 100 mcg via the ELLIPTA dry-powder inhaler (DPI) to take once daily (QD), in the morning, during the 2-week run-in period; the first dose of FF 100 mcg will be self-administered by the participant before leaving the clinic. Participants will refrain from using their own ICS asthma medication during the 2-week run-in and treatment period. Participants will also be provided with rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.
- **Randomization / treatment:** At Visit 2 (the Randomization Visit), participants who meet all of the randomization criteria will be randomized 1:1:1 to receive **one** of the following three double-blind study treatments via the ELLIPTA DPI during the 24-week treatment period:
  - UMEC 62.5 mcg QD
  - UMEC 31.25 mcg QD
  - Placebo QD

  Participants will continue to administer FF 100 mcg once daily (QD), in the morning from a separate ELLIPTA DPI throughout the treatment period. On the morning of Visits 2, 3, 4, and 5, participants will perform their electronic Diary (eDiary) assessments at home but refrain from taking their morning dose of study treatment and FF 100 mcg (as applicable) until instructed to do so by clinic personnel. At Visits 2, 3, 4 and 5, participants will self-administer study treatment immediately followed by FF 100 mcg whilst at the clinic. Participants will take their last dose of study treatment and FF 100 mcg in the clinic on Day 169 (Visit 5). Participants are expected on non-clinic visit days to take their

study treatment and FF 100 mcg at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomized treatment phase, and safety follow-up.

Key Elements of Analysis Plan

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 clinic trough FEV_1 recorded post randomization. Analyses will include the fixed, categorical effects of treatment, visit, treatment by visit interaction, sex, 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 primary comparisons of interest:

- UMEC 62.5 mcg versus Placebo
- UMEC 31.25 mcg versus Placebo

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 reporting and analysis plan (RAP).

The details of the statistical analysis methods for the secondary efficacy endpoint will be provided in the RAP.

2. SCHEDULE OF ACTIVITIES (SOA)

Protocol Activity	Pre-Screen	Screen Run-in	Treatment Period				Follow-up	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Informed consent (ICF) [a]	X							
Genetic ICF [b]	X							
Inclusion and exclusion criteria		X						
Demography [c]	X	X						
Medical history		X						
Asthma history [d]		X						
Smoking History and status		X						
Concomitant medication review	X	X	X	X	X	X	X	X
Register visit in Interactive Web Response System (IWRS) (RAMOS NG) [e]	X	X	X	X	X	X	X	
Randomization [f]			X					
Laboratory Assessments								
Urinalysis		X						
Hematology and clinical chemistry [g]		X						
Hepatitis B and C		X [m]						
Genetic sample			X [n]					

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Serum pregnancy test		X [o]				X [o]	X [o]	
Urine pregnancy test			X [o]	X [o]	X [o]			
Safety Assessments								
Physical exam including height and weight [h]		X				X	X	
12-lead Electrocardiogram (ECG) [i]		X		X		X	X	
Vital signs [j]		X	X	X	X	X	X	
Adverse Event (AE) review		X	X	X	X	X	X	X
Serious Adverse Event (SAE) review	X	X	X	X	X	X	X	X
Study Treatment								
Dispense open label fluticasone furoate (FF) 100 mcg medication		X	X	X	X			
Administer open label FF 100 mcg		X	X	X	X	X		
Collect open label FF 100 mcg			X	X	X	X	X	
Dispense double-blind study treatment			X	X	X			

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Administer double-blind study treatment			X [p]	X [p]	X [p]	X [p]		
Collect double-blind study treatment				X	X	X	X	
Assess FF 100 mcg run-in medication compliance			X					
Assess FF 100 mcg and double-blind study treatment compliance				X	X	X	X	
Efficacy Assessments								
Global Assessment of Severity [k]			X	X	X	X	X	
Global Assessment of Response to Treatment [k]				X	X	X	X	
Asthma Control Questionnaire (ACQ-6) [k]		X	X [q]					
Asthma Control Questionnaire (ACQ-5) [k]				X	X	X	X	
St. George's Respiratory Questionnaire (SGRQ) [k]			X	X	X	X	X	

Protocol Activity	**Pre-Screen**	**Screen Run-in**	**Treatment Period**				**Follow-up**	
Visit	**0**	**1**	**2 Randomization**	**3**	**4**	**5/End of Study (EOS)**	**Early Withdrawal (EW)**	**Safety Follow-up Contact**
Study Day	**-42 to -14**	**-14**	**1**	**29**	**85**	**169**		
Week	**-6 to -2**	**-2**	**0**	**4**	**12**	**24**		**1 week after Visit 5/EOS or EW Visit**
Window		**-7d**		**-5/+2d**	**-5/+2d**	**-5/+2d**		**-1/+4d**
Asthma Quality of Life Questionnaire (AQLQ) [k]			X	X	X	X	X	
Evaluating Respiratory Symptoms (E-RS) +Asthma symptoms + Peak Expiratory Flow (PEF) + Home Forced Expiratory Volume in 1 second (FEV)1 [k, l]		X						
eDiary Dispense		X						
eDiary Collect						X	X	
eDiary Review			X	X	X	X	X	
Dispense paper Medical Problems/Medications Taken worksheet	X	X	X	X	X			
Review paper Medical Problems/Medications Taken worksheet		X	X	X	X	X	X	
Reversibility		X [r]						
Pre-dose spirometry (clinic)		X [s]	X [s]	X [s]	X [s]	X [s]	X [s]	
Post-dose spirometry (clinic)			X [t]			X [t]	X [t]	

Notes:

a) The ICF must be signed before any study procedures, including medication cessation.
b) 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.
c) Demography may be captured at either the Pre-screen Visit or Screening Visit (for participants who do not have a Pre-screen Visit).
d) The assessment of asthma history will include: the age of the participant 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).
e) The IWRS will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOS NG IWRS manual and SRM for more information).
f) Participants must not be randomized prior to confirming their eligibility to participate in the study.
g) If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
h) Physical Examination will include height and weight at Visit 1 only.
i) ECG to be obtained 15 minutes to 45 minutes after the administration of study treatment.
j) The vital signs assessment will include the measurement of blood pressure, heart rate,
k) Assessment(s) to be completed prior to the administration of study treatment.
l) 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.
m) Hepatitis C RNA is optional however a confirmatory negative Hepatitis C RNA test must be obtained, to be able to enrol participants with positive Hepatitis C antibody due to prior resolved disease. Hep B/C: If test otherwise performed within 3 months prior to first dose of study treatment, testing at screening is not required.
n) Pharmacogenetic sample may be drawn any time from Visit 2 onwards.
o) Assessments only to be conducted in females of reproductive potential.
p) Study treatment should be administered at approximately the same time of day at each applicable clinic visit.
q) Baseline ACQ-5 will be derived from items 1-5 of the Randomization (Visit 2) ACQ-6.
r) 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 9.1.3. 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 participant may enter the 2-week run-in period.
s) Pre-dose spirometry should 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 and FF 100 mcg. After V2 pre-dose spirometry assessments should be performed within ± 1 hour of the V2 spirometry.
t) 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 within ± 1 hour of the V2 spirometry.

3. INTRODUCTION

3.1. Study Rationale

In the United States (US), the long-acting muscarinic antagonist (LAMA) tiotropium has been approved for the long-term maintenance treatment of asthma in patients 12 years of age and older.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/long-acting beta-2-agonist (LABA) combination [FF/umeclidinium (UMEC)/vilanterol (VI)] in a single device, with the aim of providing a new treatment option for the management of asthma in adults. Through the evaluation of UMEC 62.5 mcg and 31.25 mcg compared to placebo this study will provide important information regarding the efficacy and safety of UMEC when administered in a separate inhaler to participants on a background of FF.

The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

3.2. Background

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; Global Initiative for Asthma (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.

Despite the availability of treatments and published guidelines, patients may have asthma that is not well controlled.

This trial will, primarily, evaluate trough FEV_1 to characterize the efficacy of two doses of UMEC (62.5 mcg and 31.25 mcg) in the treatment of asthma when administered as an open combination with FF 100 mcg. UMEC is currently under development as a closed triple therapy in combination with FF and VI in a single inhaler.

3.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events related to FF and UMEC can be found in the Investigator's Brochure(s) (IB). The table below provides a summary of the key risks in association with FF and UMEC. It is noted that both FF and UMEC have also been developed in combination with VI, therefore relevant safety experience is also provided by the FF/VI and UMEC/VI combinations.

3.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [e.g., GW685698+GSK573719]		
Cardiovascular effects of UMEC	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 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 - Exclusion criteria as specified in Section 6.2 of the protocol - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per schedule in Section 2 - Vital sign assessments (heart rate and blood pressure) as per schedule in Section 2 - Cardiovascular AEs and SAEs will be captured on the electronic Case Report Form (eCRF) (see Appendix 4) - Protocol defined stopping criteria as per Section 8.1 -MACE analysis -Instream review of blinded data

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Healthy Volunteers (in the Thorough QT study, UMEC 500 mcg daily dose), no effect was observed on heart rate, blood pressure or QT. 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 500 mcg and placebo. UMEC/VI 500/100 mcg increased QTcF on average by 8.2 msec (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. In addition, UMEC/VI has had urinary retention, dysuria, vision blurred, glaucoma and increased intraocular pressure and paradoxical bronchospasm added as ADRs. ICS has a similar class risk of glaucoma and elevated intraocular	- 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. - Review AEs/SAEs

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	pressure (IOP); however these effects occur by a different mechanism that is not expected to be synergistic or additive when FF is used in combination with UMEC.	
Systemic ICS effects -Aderenal 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 serum cortisol excretion, and multiple studies with COPD and asthma participants 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 participants 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 participants 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	- 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
	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 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 participants 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 mcg (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.	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). -Participants 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Pneumonia experience with UMEC 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) 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 participants 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).	resulting in hospitalisation. The occurrence of pneumonia will be recorded in the eCRF. Where possible a chest X-ray should be performed to confirm a diagnosis, whenever a participant 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.	Participants with a history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		stearate are excluded from participation in this study (Section 6.2). -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 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 UMEC 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.	Females who are pregnant or breast-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 100 mcg are recognised pharmacological class effects associated with ICS therapy, which are included in the table above. The experience with FF is provided in the respective IB.

3.3.2. Benefit Assessment

The benefit of UMEC at two dosage strengths 62.5 and 31.25 mcg as compared to Placebo in patients with asthma on background therapy of FF 100 mcg is expected to improve lung function. The inclusion of two strengths of UMEC will allow comparison to placebo for the dose currently marketed in COPD, as well as a lower dose. This will help show the efficacy and safety of UMEC in asthma when administered as an open combination on a background of FF. Another LAMA, tiotropium, is currently approved for the maintenance treatment of asthma.

3.3.3. Overall Benefit: Risk Conclusion

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

The current experience and safety profile with UMEC in previous Phase II asthma studies (alone and in combination with FF) and from clinical trial and marketing experience in the COPD population is supportive of evaluating this compound in asthma patients. The potential risks associated with the known pharmacology of UMEC is offset by the potential significant benefits that are afforded to patients not well controlled on ICS therapy. Furthermore, the approval of another LAMA (tiotropium) for the treatment of asthma demonstrates the suitability for the use of this class of drug in the asthma population.

4. OBJECTIVES AND ENDPOINTS

For a definition of baseline for each of the endpoints listed below, please refer to Section 10.6.

Objectives	Endpoints
Primary • **Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (trough FEV1) versus placebo after 24 weeks of treatment.**	• **Mean change from baseline in clinic trough FEV_1 at Week 24**
Secondary • Evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function (3hours post dose	• Mean change from baseline in clinic FEV_1 at 3 hours post dose at Week 24

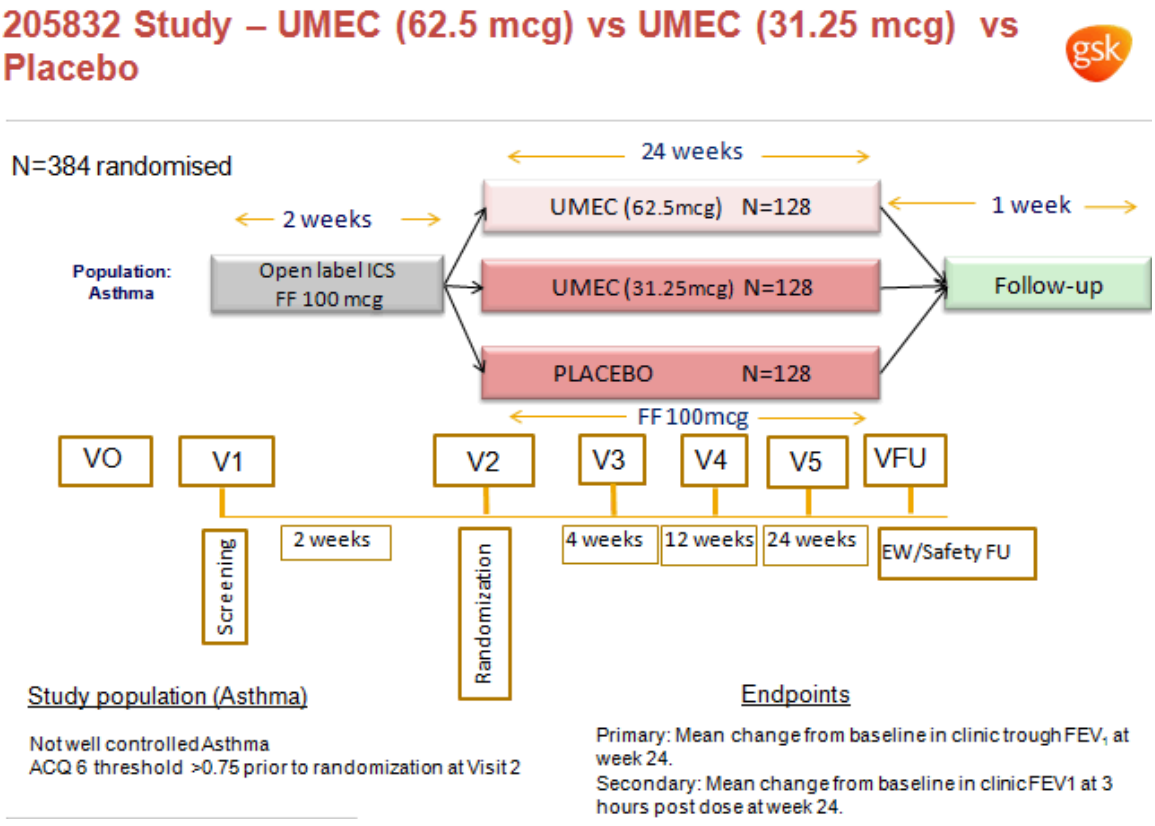
Objectives	Endpoints
FEV1) versus placebo after 24 weeks of treatment.	
Safety • To evaluate the safety and tolerability of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Incidence and type of adverse events • ECG measurements • Vital signs
Other • To evaluate other efficacy assessments of UMEC 62.5 mcg and UMEC 31.25 mcg compared to placebo	• Mean change from baseline in morning (AM) pre-dose Peak Expiratory Flow (PEF) over the 24 week treatment period • Mean change from baseline in evening (PM) PEF over the 24 week treatment period • Mean change from baseline in daily home trough FEV1 over the 24 week treatment period • Mean change from baseline in daily rescue medication use over the 24 week treatment period • Mean change from baseline in SGRQ total score 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 SGRQ domain scores at Week 24 • Mean change from baseline in the AQLQ total score at Week 24 • Percent of patients meeting a responder threshold of ≥ 0.5 points improvement from baseline for the AQLQ total score at Week 24 • Mean change from baseline in E-RS total score over the 24 week treatment period • Mean change from baseline in

Objectives	Endpoints
	ACQ-5 total score at Week 24 • Percent of patients meeting a responder threshold of ≥0.5 in change from baseline for the ACQ-5 at Week 24 • Annualized rate of moderate/severe asthma exacerbations

5. STUDY DESIGN

5.1. Overall Design

This is a Phase IIb, randomized, double-blind, placebo controlled, 3-arm parallel group study, comparing the efficacy, safety and tolerability of UMEC (62.5 mcg and 31.25 mcg) administered once-daily in participants with asthma that is not well controlled (i.e. participants with an ACQ-6 total score >0.75 at Visit 2 [the Randomization Visit]) despite treatment with maintenance ICS.



Eligible participants will be requested to participate in the study for a maximum of approximately 31 weeks (Visit 0 to the Follow-up contact, inclusive) during which time, participants will complete the following 4 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), including the informed consent process, must be completed within 4 weeks prior to Visit 1 as well as prior to any protocol-required changes to a participant's usual asthma treatment and the initiation of any 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 defined in Section 7.9.

  Participants that receive LABA (or LAMA) as a component of their regular (i.e. pre-study) therapy must stop LABA (or LAMA) treatment from ≥48 hours prior to Visit 1 (Screening) until they have completed the study; therefore, the investigator must use their clinical judgment to determine if the participant may stop LABA (or LAMA) prior to study entry without incurring undue risk.

- **Screening / run-in:** Participants who meet all the eligibility criteria at Visit 1 (Screening), will enter the run-in period for approximately 2 weeks to continue assessing the participant's eligibility for the study. On the morning of Visit 1, participants will refrain from taking the morning dose of their regular (i.e. pre-study) ICS asthma medication. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF 100 mcg via the ELLIPTA dry-powder inhaler (DPI) to take once daily (QD), in the morning, during the 2-week run-in period; the first dose of FF 100 mcg will be self-administered by the participant before leaving the clinic. Participants will refrain from using their own ICS asthma medication during the 2-week run-in and treatment period. Participants will also be provided with rescue medication (albuterol/salbutamol) to use on an as-needed basis throughout the study.

- **Randomization / treatment:** At Visit 2 (the Randomization Visit), participants who meet all of the randomization criteria will be randomized 1:1:1 to receive **one** of the following three double-blind study treatments via the ELLIPTA DPI during the 24-week treatment period:

  - UMEC 62.5 mcg QD
  - UMEC 31.25 mcg QD
  - Placebo QD

  Participants will continue to administer FF 100 mcg once daily (QD), in the morning from a separate ELLIPTA DPI throughout the treatment period. On the morning of Visits 2, 3, 4, and 5, participants will perform their electronic Diary (eDiary) assessments at home but refrain from taking their morning dose of study treatment and FF 100 mcg (as applicable) until instructed to do so by clinic personnel. At Visits 2, 3, 4 and 5, participants will self-administer study treatment immediately followed by FF 100 mcg whilst at the clinic (see Section 7.2). Participants will take their last dose of study treatment and FF 100 mcg in the clinic on Day 169 (Visit 5). Participants are expected on non-clinic visit days to take their study treatment and FF 100 mcg at home in the morning at approximately the same time each day, as directed by the clinic.

- **Safety follow-up:** A safety follow-up telephone contact or clinic visit will be conducted approximately 7 days after the participant completes all of the protocol-defined procedures for Visit 5/End of Study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study when they have completed all phases of the study including screening, run-in, the randomized treatment phase, and safety follow-up.

To demonstrate the benefit of UMEC the primary comparisons of interest for the primary efficacy endpoint are:

- UMEC 62.5 mcg versus (vs) Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 10.5.3. Participants who permanently discontinue double-blind study treatment are not required to withdraw from the study. Participants 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 8.1)

5.2. Number of Participants

The total number of randomized participants required is approximately 384, with 128 participants randomized 1:1:1 to each of the 3 double-blind treatment arms (see Section 10).

5.3. Participant and Study Completion

A participant will be considered to have completed the study when they have completed all phases of the study including pre-screening, screening, run-in, the randomized treatment phase, and safety follow-up.

The end of the study is defined as the date of the last scheduled procedure shown in the Schedule of Activities table (see Section 2) for the last participant in the trial globally.

5.4. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, 3 arm parallel-group design. This is a well-established design to evaluate the efficacy, safety, and tolerability of the UMEC drug. A placebo arm is included. All participants will be placed on open-label FF 100 mcg when they enter the 2 week run-in period and continue it through the 24 week treatment period. The primary objective of this study is to evaluate the effects of UMEC 62.5 mcg and UMEC 31.25 mcg on lung function compared with placebo after 24 weeks of treatment.

GlaxoSmithKline (GSK) is currently developing a once-daily 'closed' triple therapy of a ICS/LAMA/LABA combination [FF/UMEC/VI)] in a single device, with the aim of providing a new treatment option for the management of asthma in adults. Through the evaluation of UMEC 62.5 mcg and 31.25 mcg compared to placebo this study will provide important information regarding the efficacy, safety and tolerability of UMEC in asthma when administered via a separate inhaler to participants on a background of FF without VI.

5.5. Dose Justification

The 200699 (IB Supplement, GlaxoSmithKline Document 2011N123107_03) data showed UMEC 62.5 mcg to be an effective dose; after 4 weeks of treatment in the subset of patients with a primary diagnosis of asthma, an average increase in change from baseline trough FEV_1 at Day 29 of 136 mL was observed in those participants treated with FF/UMEC (100/62.5 mcg) compared to those participants 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 both 31.25 and 62.5 mcg doses will be assessed in this study when administered via a separate inhaler to participants treated on a background of FF 100 mcg. No safety signal was identified with any of the UMEC doses (15.6, 62.5, 125 and 250 mcg) evaluated in the 200699 study.

6. STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

AGE
1. **Age:** 18 years of age or older at the time of signing the informed consent.
TYPE OF PARTICIPANT AND DISEASE CHARACTERISTICS
2. **Diagnosis:** Participants with a diagnosis of asthma as defined by the National Institutes of Health [NIH, 2007] at least 6 months prior to Visit 0. 3. **Asthma Control:** ACQ-6 total score of >0.75 at Visit 1. 4. **Current Asthma Maintenance Therapy**: Participants are eligible if they have required daily ICS therapy ≥ 100 mg/day fluticasone propionate (FP, or equivalent) with or without LABA or LAMA for at least 12 weeks prior to Visit 0 and there have been no changes in maintenance asthma medications during the 4 weeks immediately prior to Visit 0. Examples of acceptable doses of commonly prescribed ICS medication will be 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.

5. **Spirometry:** Both of the following:
   a. A best pre-bronchodilator morning (AM) FEV1 ≤85% of the predicted normal value. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012].
   b. A best post-bronchodilator FEV1/ forced vital capacity (FVC) ≥0.7 at Visit 1.
6. **Reversibility of Disease:** Airway reversibility is defined as ≥12% and ≥200 mL increase in FEV1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.

   Note: If the participant 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 FEV1 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 FEV1 of ≥12% and ≥200 mL.*

   Should the participant successfully demonstrate airway reversibility (defined as ≥12% and ≥200 mL increase in FEV1 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 participant may enter the 2-week run-in period (see Section 9.1.3).
7. **Short-Acting β2 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

8. **Gender:**

a. Male participants

b. Female participants:

A female participant is eligible to participate if she is not pregnant (see Appendix 5), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 5

  OR
- A WOCBP who agrees to follow the contraceptive guidance in Appendix 5 during the treatment period and for at least 5 days after the last dose of study

treatment.
INFORMED CONSENT
9. **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. Participants must be able to read, comprehend, and write at a level sufficient to complete study related materials.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

MEDICAL CONDITIONS
1. **Pneumonia:** Chest X-ray documented pneumonia in the 12 weeks prior to Visit 1.
2. **Asthma Exacerbation:** Any severe asthma exacerbation, defined as deterioration of asthma requiring the use of systemic corticosteroids (oral, parenteral or depot) within 12 weeks of Visit 1, or an inpatient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids within 12 weeks of Visit 1.
3. **Concurrent Respiratory Disease:** Current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, bronchopulmonary dysplasia, chronic bronchitis, emphysema, chronic obstructive pulmonary disease, lung cancer, or other respiratory abnormalities other than asthma.
4. **Pregnancy**: Women who are pregnant or lactating or are planning on becoming pregnant during the study.
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**: Participants 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 participant 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 participant otherwise meets entry criteria*

8. **Clinically significant ECG abnormality:** Evidence of a clinically significant abnormality in the 12-lead ECG performed during screening or run-in. The PI will determine the clinical significance of each abnormal ECG finding in relation to the participant's medical history and exclude participants 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:
    - 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:** participants 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
10. **Antimuscarinic effects:** Participants 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**: Participants with carcinoma that has not been in complete remission for at least 5 years. Participants 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 participant has been considered cured by treatment.
12. **Questionable validity of consent**: Participants 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.

PRIOR/CONCOMITANT THERAPY

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

PRIOR/CONCURRENT CLINICAL STUDY EXPERIENCE/RELEVANT HABITS

14. Tobacco Use: Current smoker or a smoking history of ≥10 pack years (e.g., 20 cigarettes/day for 10 years). A participant may not have used inhaled tobacco products within the past 12 months (i.e., cigarettes, cigars or pipe tobacco).

15. Drug/alcohol abuse: Participants with a known or suspected history of alcohol or drug abuse within the last 2 years.
Diagnostic assessments
16. Allergy or Hypersensitivity: A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate.
Other Exclusions
17. Non-compliance: Participants 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 participant who is unable to read and/or would not be able to complete study related materials.

6.2.1. Randomization Criteria

At the end of the run-in period (Visit 2), study participants must fulfil the following additional criteria in order to be randomized into the study and enter the treatment period:

6.2.2. Inclusion Criteria for Randomization

TYPE OF PARTICIPANT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
1. Asthma Control: ACQ-6 total score of >0.75 at Visit 2. **2. Percent-predicted FEV_1:** Spirometry: A best pre-bronchodilator morning (AM) FEV1 ≤85% 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.

6.2.3. 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 run-in period that led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the participant's asthma status or the participant's ability to participate in the study. 2. **Asthma exacerbation:** Evidence of a moderate asthma exacerbation leading to a change in therapy or severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.
CONCOMITANT MEDICATIONS/TREATMENTS
3. **Asthma medication:** Changes in asthma medication (excluding changes after Visit 0 or 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.

6.3. Lifestyle Restrictions

No lifestyle restrictions are required for this study.

6.4. Pre-Screening/Screening/Run-in/Randomization Failures

A participant will be assigned a participant number at the time the informed consent is signed at Visit 0.

The study site will be responsible for reporting pre-screen failures. The following information will be collected in the eCRF for participants who are pre-screen failures:

- Demographic information including race, age and gender
- Participant 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-screening failures, screening failures, run-in failures and randomization failures will be defined as follows:

- **Pre-screening failures:** those participants that sign the informed consent document but do not have a Visit 1 (Screening) procedure.

- **Screening failures:** those participants that complete at least one Visit 1 (Screening) procedure but do not enter the run-in period.

  A participant 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 participants that enter the run-in period but do not have any Visit 2 (Randomization) procedures.

- **Randomization failures:** those participants that complete at least one Visit 2 (Randomization) procedure but do not enter the double-blind study treatment period.

  Any participant who completes the run-in period and then meets the randomization criteria and is dispensed the double-blind study treatment at Visit 2 is considered to have entered the treatment period.

RAMOS NG will be contacted to register the participant.

In order to ensure transparent reporting of screen/run-in failure participants, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen/run-in/randomization failure information is required including demography, screen/run-in/randomization failure details, eligibility criteria, and any SAEs (see Section 9.2.4 and Appendix 4). Further details are provided in the study-specific eCRF completion guidelines document.

7. TREATMENTS

Study treatment is defined as any investigational treatment(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol. The term 'study treatment' within this trial is used to describe the combination of products received by the participant as per the protocol design. Study treatment may also be used to only reference the randomized study treatment when described together with the FF 100 mcg open-label treatment.

7.1. Treatments Administered

7.1.1. Description of FF 100 mcg and Double-Blind Study Treatment

The ELLIPTA device will be used during the run-in period and the treatment period. The ELLIPTA dry powder inhaler (DPI) is a molded plastic two-sided device with a dose counter that can hold two individual blister strips. The ELLIPTA will deliver, when actuated, the contents of a single blister simultaneously from each of the two strips. The ELLIPTA is individually sealed in a foil laminate overwrap that also contains a silica gel desiccant packet.

A description of the FF (GW685698) 100 mcg inhalation powder administered via the ELLIPTA is provided in Table 1; descriptions of the double-blind study treatments administered via the ELLIPTA are provided in Table 2.

Table 1 Description of FF 100 mcg Inhalation Powder in ELLIPTA

FF 100	First Strip	Second Strip
	GW685698 blended with lactose monohydrate	Lactose monohydrate with magnesium stearate[1]
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose strengths	100 mcg per blister	Not applicable
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 1.0% w/w of total drug product.

Table 2 Description of Study Treatment Inhalation Powder in ELLIPTA

Placebo	First strip	Second strip
	Lactose monohydrate blended with magnesium stearate1	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters per strip)	
Unit Dose Strengths	Not applicable	Not applicable
Physical description	White powder	White powder
Route of Administration	Inhaled	
UMEC	**First strip**	**Second strip**
	GSK573719 blended with lactose and magnesium stearate	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose Strengths	31.25 mcg per blister	NA
Physical description	White powder	White powder
Route of Administration	Inhaled	
UMEC	**First strip**	**Second strip**
	GSK573719 blended with lactose and magnesium stearate	Lactose monohydrate blended with magnesium stearate2
Dosage Form	ELLIPTA DPI with 30 doses (2 strips with 30 blisters)	
Unit Dose Strengths	62.5 mcg per blister	NA
Physical description	White powder	White powder
Route of Administration	Inhaled	

1. Magnesium stearate 0.6% w/w of total drug product. 2. Magnesium stearate 1.0% w/w of total drug product

7.1.2. Description of Albuterol/Salbutamol

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.

7.1.3. Study Treatment and FF 100 mcg Return

ELLIPTAs containing FF 100 mcg and study treatment will be dispensed to a participant during their visit to the study clinic (as applicable). The participant must return all dispensed ELLIPTAs at the subsequent clinic visit. The schedule for dispensing and collecting FF 100 mcg and study treatment ELLIPTAs is provided in the Schedule of Activities table (Section 2).

All used and unused study treatment, FF 100 mcg and albuterol/salbutamol 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 Study Reference Manual (SRM).

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

In addition, any metered dose inhaler (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.

7.2. Dose Modification

There were no dose modifications planned for this protocol.

7.3. Method of Treatment Assignment

Participants 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. Participants will be randomized using an interactive web response system (IWRS) RAMOS NG. The study will use central-based randomization to allocate treatments. Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 2-week run-in period and participant to satisfying all eligibility criteria, participants will be randomized 1:1:1 to one of the following three double-blind treatments for the duration of the treatment period:

- UMEC 62.5 mcg QD
- UMEC 31.25 mcg QD
- Placebo QD

The duration of double-blind treatment for each participant is 24 weeks. On the morning of each scheduled clinic study visit, participants will refrain from taking their morning dose of study treatment and FF 100 mcg 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 Randomization Visit (Visit 2). On the other days during the treatment period (i.e. "non-clinic days"), participants 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 IWRS system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IWRS manual and SRM.

7.4. Blinding

This will be a double-blind study and the following will apply.

- The Investigator or treating physician may unblind a participant'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 participant as judged by the Investigator.
- Investigators have direct access to the participant'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 participant's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the Investigator must notify GSK within 24 hours after unblinding, but without revealing the treatment assignment of the unblinded participant, unless that information is important for the safety of participants currently in the study.
- The date and event or condition which led to the unblinding (i.e. the primary reason) will be recorded in source documentation and in the eCRF.

Should a participant's treatment assignment be unblinded then the participant may continue the assigned study treatment and be followed-up as per protocol until the completion of the Safety Follow-up assessments.

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any participant 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 participant's treatment assignment, may be sent to Investigators in accordance with local regulations and/or GSK policy. Participants will not be withdrawn from the study.

7.5. Packaging and Labeling

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

7.6. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
2. Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. 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).
4. Further guidance and information for the final disposition of unused study treatment are provided in the SRM.

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure notify the monitor, Medical Monitor and/or GSK study contact.
- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

7.7. Treatment Compliance

When participants are dosed at the site, they will receive FF 100 mcg and 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 participant identification will be confirmed at the time of dosing by a member of the study site staff.

When participants self-administer study treatment(s) at home, compliance with study treatment will be assessed through querying the participant during the site visits and recording the number of doses remaining in the ELLIPTA in the eCRF (see the SRM for details). A record of the number of ELLIPTAs dispensed to each participant must be maintained and reconciled with study treatment and compliance records.

Participant compliance with FF 100 mcg and study treatment will be assessed at scheduled clinic visits by reviewing the eDiary and information from the dose counter on the returned inhaler(s) (see Section 7.1.3). Participants should be ≥80% to ≤120% compliant on taking both FF 100 mcg and study treatment between each pair of scheduled and consecutive on-treatment clinic visits, as applicable. Participants who fall outside this range should be re-educated on treatment compliance by their site. This re-education should be documented in the participant's source document. If FF 100 mcg and/or study treatment is prematurely discontinued during the course of the study or

compliance repeatedly falls outside of acceptable ranges, the study sponsor/site monitor must be contacted to discuss participant eligibility for continued participation in the study.

7.8. Concomitant Therapy

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.

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 FF 100 mcg and albuterol/salbutamol should not be recorded in the eCRF; however non-study supplied FF 100 mcg and albuterol/salbutamol will be recorded in the eCRF.*

The minimum requirement is that the drug name, reason for use, dose (including unit e.g. mcg) and frequency, route and the dates of administration are to be recorded.

Medications initiated after completion of the assessments at Visit 5/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. Participants who have completed the Early Withdrawal Visit are allowed to use any medications prescribed by the Investigator or primary care physician.

7.8.1. Permitted Medications and Non-Drug Therapies

7.8.1.1. Permitted Asthma Medications

In addition to FF 100 mcg and 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. Participants must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

Temporary changes in medications are permitted for the treatment of moderate asthma exacerbations, 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 SRM for contact information [refer to Section 9.1.4.1 for guidance on moderate asthma exacerbation]):

- An increase in ICS dose.
- Systemic corticosteroids (tablets, suspension or injection) 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.

7.8.1.2. 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: Participants 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 participants 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 participants' lung function or safety assessments (e.g., cardiac measurements). However, no systemic corticosteroids will be permitted.

7.9. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 3 is not permitted during the study.

Table 3 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
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)	2 days 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, 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
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

7.10. Treatment after the End of the Study

Participants 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 participant's medical condition, whether or not GSK is providing specific post-study treatment.

8. DISCONTINUATION CRITERIA

8.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. A participant may also be asked to discontinue study treatment at the Investigator's discretion.

Participants who withdraw from 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. If this is not possible, the Investigator must encourage the participant to participate in as much of the study as they are willing (or able) to.

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

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

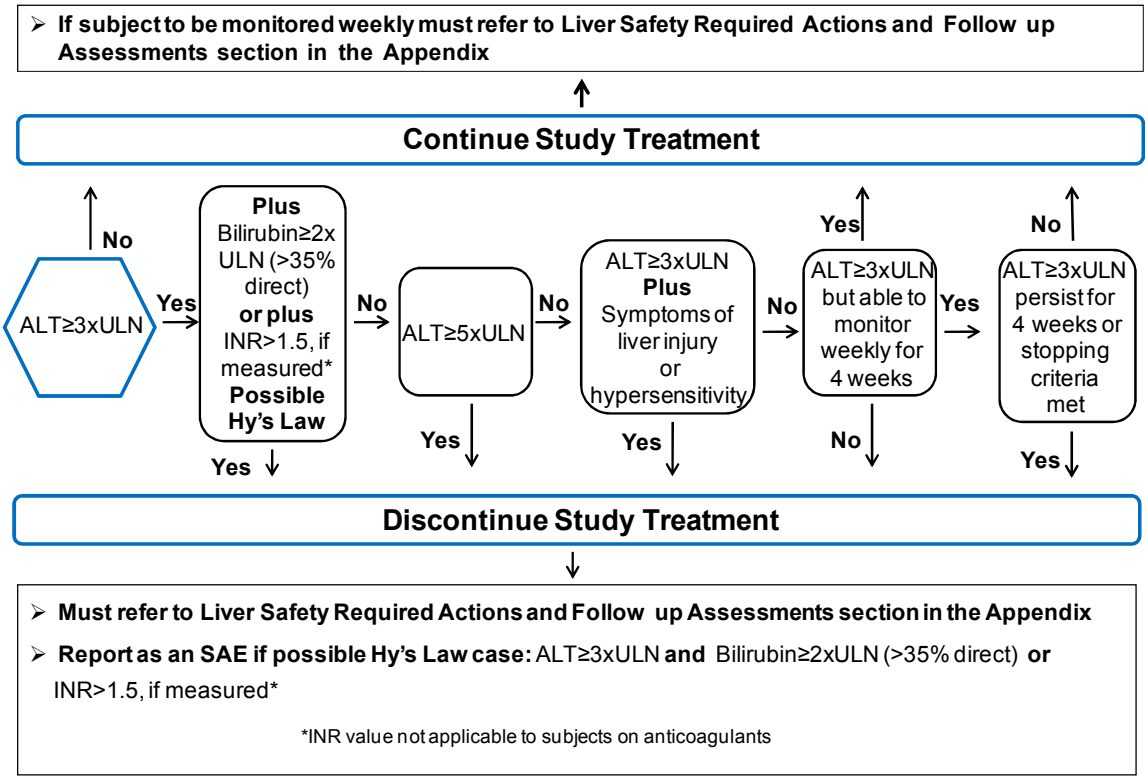
- Liver Chemistry: Meets any of the protocol-defined liver chemistry stopping criteria
- QTc: Meets any of the protocol-defined stopping criteria
- Pregnancy: Positive pregnancy test

8.1.1. Liver Chemistry Stopping Criteria

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

Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Phase II Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments can be found in Appendix 7

8.1.2. QTc Stopping Criteria

Details on performing ECG assessments can be found in Section 9.4.3.

- The *same* QT correction formula *must* be used for *each individual participant* to determine eligibility for and discontinuation from the study. This formula may not be changed or substituted once the participant has been enrolled.
  - For example, if a participant 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 participant as well.
  - Once the QT correction formula has been chosen for a participant's eligibility, the *same formula* must continue to be used for that participant *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 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, lead to withdrawal from study treatment:
  - QTc>500 msec or uncorrected QT>600 msec

- Change from baseline: QTc> 60 msec

- For patients with underlying bundle branch block, follow the discontinuation criteria listed below:
  - Baseline QTc with Bundle Branch Block <450 msec, Discontinuation QTc with Bundle Branch Block >500 msec
  - Baseline QTc with Bundle Branch Block <450-480 msec, Discontinuation QTc with Bundle Branch Block ≥530 msec

8.1.3. Rechallenge

8.1.3.1. Study Treatment Restart or Rechallenge

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

8.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the investigator for safety, behavioral, compliance or administrative reasons.
- If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.
- In the event of early withdrawal from the study, every effort should be made to have the participant 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 Schedule of Activities table (Section 2).

8.3. Lost to Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3

telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

9. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Activities (SoA) (Section 2). There are no protocol waivers or exemptions allowed. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study treatment. Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

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

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

- Demographic information including race, age and gender
- Participant 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 participant 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
- Questionnaires (ACQ; SGRQ; AQLQ; E-RS)
- Healthcare Resource Utilization
- Pre-and post-albuterol/salbutamol lung function
- Inclusion/Exclusion criteria assessment
- Physical examination
- 12-lead ECG
- Child bearing status assessment for all potential female participants
- 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 FF 100 mcg run-in medication

9.1. Efficacy Assessments

The timings of all efficacy assessments are specified in the Schedule of Activities (SoA) (Section 2).

9.1.1. Questionnaires

The questionnaires should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participants 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 participant must be encouraged to complete any missing assessments or items.

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

9.1.1.1. Global Assessment of Severity and Response to Treatment

The participant will be asked to complete the Global Assessment of Severity and Response to Treatment at the visits specified in the Schedule of Activities table (Section

2). The Global Assessment of Severity is a single item questionnaire; participants 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. Instructions for completing the questionnaires can be found in the SRM.

9.1.1.2. Asthma Control Questionnaire (ACQ)

The ACQ measures attributes of asthma control [Juniper 1999], measured with questions designed to be self-completed by the participant. Participants will complete the ACQ at specified study visits. The ACQ-5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of symptoms over the previous week. The ACQ-6 includes an additional item asking about rescue medication use. 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. 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].

9.1.1.3. St. George's Respiratory of Life Questionnaire (SGRQ)

The SGRQ 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 participant [Jones1992] with a recall over the past 3 months. A change of 4 points is considered a clinically relevant change [Jones2005].

9.1.1.4. Asthma Quality of Life Questionnaire (AQLQ)

The 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 participant with a recall over the past 2 weeks. A change of ≥ 0.5 is considered clinically important [Juniper 1994].

9.1.2. Daily Diaries

Participants 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. Participants 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 PEF
- Morning FF 100 mcg medication use
- Morning double-blind study medication use (during the treatment period only)

Section 9.1.2 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.

Participants 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). Participants 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 participant recall in discussions with the Investigator, for site staff to then enter as appropriate in the eCRF.

9.1.2.1. eDiary Questionnaires, Assessments and Alerts

For information on the eDiary questions, please refer to Appendix 8.

9.1.2.1.1. 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.

9.1.2.1.2. 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.

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

Every morning upon waking (from the morning after Visit 1 onwards), participants will answer a question on the occurrence of night-time awakenings due to asthma symptoms. The participant'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', participants 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, participants 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 (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]).

9.1.2.1.4. Morning and Evening Home Spirometry

An electronic home spirometer/eDiary device will be issued to participants 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. Participants will conduct spirometry maneuvers each morning, prior to study treatment and FF 100 mcg dosing, and each evening. Three measurements for each session will be recorded by the participants in the eDiary. Assessments will be performed:

- After completing all other eDiary assessments
- Prior to albuterol/salbutamol use
- Prior to study treatment and FF 100 mcg 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.

9.1.2.1.5. Alerts

For safety the following alerts, indicative of worsening asthma, will be programmed into the eDiary with instructions for the participant to contact the investigator (either by telephone and/or by visiting the study clinic) if any of the alert criteria are met:

- Nocturnal awakening(s) due to asthma requiring albuterol/salbutamol use for 2 consecutive nights.
- An increase from baseline of ≥ 4 puffs /day of albuterol/salbutamol use on 2 consecutive days.
- A ≥30% decrease in AM PEF from baseline on 2 consecutive mornings.
- A ≥30% decrease in PM PEF from baseline on 2 consecutive evenings
- A ≥30% decrease in AM FEV1 from baseline on 2 consecutive mornings.
- A ≥30% decrease in PM FEV1 from baseline on 2 consecutive evenings.

9.1.3. Pulmonary Function Test

The 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 American Thoracic Society / European Respiratory Society (ATS/ERS) standards [Miller, 2005]. The highest of 3 technically acceptable measurements will be recorded at each visit:

- **Pre-dose Spirometry:** At Visits 1 through 5/EOS (and the Early Withdrawal Visit, if applicable), participants 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 2 (the baseline assessment).
  - At least 24 hours after the participant's last morning dose of study treatment on the day prior to the visit.
  - Before the participant's morning dose of study treatment on the day of the visit.
- **Post-dose Spirometry:** At Visits 2 and 5/EOS (and the Early Withdrawal Visit, if applicable), spirometry assessments must be performed 3 hours after the participant's morning dose of study treatment; the assessment performed at Visit 5/EOS should be performed at the same time of day (± 1 hour) as the assessment performed at Visit 2 (the baseline assessment). At each visit, participants 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.

9.1.3.1. Reversibility (Albuterol/Salbutamol)

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.

To perform the reversibility assessment, 4 puffs of the provided albuterol/salbutamol 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 albuterol/salbutamol.

Percent reversibility will be calculated as follows:

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

The reversibility requirement for eligibility must be assessed at Visit 1. Participants 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 participant may not enter the 2-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 participant 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 participant may enter the 2-week run-in period.

9.1.4. Asthma Exacerbations

Moderate and severe asthma exacerbation data will be collected from the start of randomized double blinded treatment until Visit 5/EOS Visit or the Early Withdrawal Visit for those participants that withdraw from participation in the study (see Section 8.2). For consistency, exacerbations separated by less than 7 days will be treated as a continuation of the same exacerbation.

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

9.1.4.1. Moderate Asthma Exacerbation

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 for 3 days or more and/or hospitalization.
- 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.

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 (Refer to Section 7.8.1 above)
The Medical Monitor may be contacted for additional guidance, see the medical monitor/Sponsor Information Page.

9.1.4.2. Severe Asthma Exacerbation

A severe asthma exacerbation is defined as:

The deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension or injection) for at least 3 days.

OR

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

9.2. Adverse Events

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

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment or withdraw from the study (see Section 8).

9.2.1. 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 participant 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 9.2.3) at the timepoints specified in the Schedule of Activities (SoA) table (Section 2).
- 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. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.
- Investigators are not obligated to actively seek AEs or SAEs in former study participants. However, if the Investigator learns of any SAE, including a death, at any time after a participant 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

9.2.2. 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 participant 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?”

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

9.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 9.2.5), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 8.3). Further information on follow-up procedures is given in Appendix 4

9.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of

participants and the safety of a study treatment under clinical investigation are met.

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information eg, summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

9.2.5. 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). 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	Glaucoma (antimuscarinic/corticosteroid)

Special interest AE group	Special interest AE subgroup
effects / Corticosteroids associated eye disorders	Cataracts (corticosteroid)
Pneumonia and LRTI	Pneumonia
	LRTI excluding pneumonia
Adrenal suppression	-
Decreased bone mineral density and associated fractures	-
Effects on glucose	-
Hypersensitivity	-
Local steroid effects	-

9.2.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Appendix 4 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the eCRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

The CV eCRFs are presented as queries in response to reporting of certain CV MedDRA terms. The CV information should be recorded in the specific cardiovascular section of the eCRF within one week of receipt of a CV Event data query prompting its completion.

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

9.2.7. 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 participant 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).

9.2.8. 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.

9.2.9. Pregnancy

Details of all pregnancies in female participants 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.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

9.3. Treatment of 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 eCRF 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.

9.4. Safety Assessments

Planned time points for all safety assessments are provided in the Schedule of Activities (SoA).

9.4.1. Physical Examinations

Physical exams will be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2).

- 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.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

9.4.2. Vital Signs

Vital signs will be performed at the time points specified in the Schedule of Activities (SoA) table (Section 2) prior to conducting spirometry and prior to taking the morning dose of study treatment and FF 100 mcg. 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.

9.4.3. Electrocardiograms

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 Schedule of Activities (SoA) table (Section 2). All ECG measurements will be made with the participant in a supine position having rested in this position for approximately 5 minutes before each reading.

For participants who meet the QTc, protocol defined stopping criteria, triplicate ECGs (over a brief period of time) should be performed (Section 8.1.2).

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.

9.4.4. Clinical Safety Laboratory Assessments

- Refer to Appendix 2 for the list of clinical laboratory tests to be performed and to the Schedule of Activities (SoA) for the timing and frequency.
- The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 days after the last dose of study treatment should be repeated until the values return to normal or baseline or are no longer considered significantly abnormal by the investigator or medical monitor.
- If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the Schedule of Activities (SoA).

9.5. Pharmacokinetics

Pharmacokinetics is not relevant for this protocol.

9.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

9.7. Genetics

Information regarding genetic/ pharmacogenetic (PGx) research is included in Appendix 6. 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 6).

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.

9.8. Biomarkers

Biomarkers are not evaluated in this study.

9.9. Health Economics OR Medical Resource Utilization and Health Economics

Health Economics/Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

10. STATISTICAL CONSIDERATIONS

10.1. Hypotheses

The primary objective of this study is to evaluate the efficacy of UMEC 62.5 mcg and UMEC 31.25 mcg compared with placebo in participants with not well controlled asthma over a 24 week treatment period. This is a superiority study to demonstrate the benefit of UMEC at two dosage strengths 62.5 mcg and 31.25 mcg when compared to Placebo in patients on background therapy of FF 100 mcg. The primary efficacy endpoint is the mean change from baseline in trough FEV_1 at Week 24.

The test for the primary efficacy endpoint is such that 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:

- UMEC 62.5mcg vs Placebo
- UMEC 31.25mcg vs Placebo

For each comparison test on the primary endpoint, the null hypothesis is there is no difference between treatment groups. The alternative hypothesis is there is a difference between treatment groups.

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

Details on all pairwise treatment comparisons of interest are provided in Section 10.5.2.

10.2. Sample Size Determination

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 384 randomized participants are required for this study, with 128 participants in each of the three double-blind treatment groups: UMEC 62.5mcg, UMEC 31.25mcg or Placebo. Assuming 10% missing data on spirometry at the end of the 24-week treatment period, due to early withdrawal from study, approximately 115 participants per treatment group will have trough FEV_1 available for the primary 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 350mL based on two previous Tiotropium moderate asthma studies. The study design and population of this study aligns well with these two phase III, 24 week, randomised, double blind, placebo-controlled, parallel-group, active comparator studies of Tiotropium. In patients with moderate asthma on a background therapy of ICS the standard deviations in change from baseline trough FEV1 at Week 24 ranged from 325 to 354mL; from this a SD estimate of 350 mL was chosen. This was estimated from a wide selection of studies, critically to minimise the risk of reduced power for the primary endpoint. The range of observed treatment differences across the Tiotropium treatment groups is 133 – 185mL, which supports the expectation that the treatment effect seen in a moderate asthma population is larger than in the more severe asthma population in study 205715 treated on a background of FF/VI. This is in line with data from GSK study 200699 which showed UMEC 62.5 mcg to be an effective dose. An average increase in change from baseline trough FEV1 at Day 29 of 136 mL was observed in an asthma subset of patients treated with FF/UMEC (100/62.5) compared with FF (100 mcg) alone. The GSK phase III closed triple asthma study 205715, which this study supports, is in a more severe asthma population and conservatively assumes a SD estimate of 400mL.

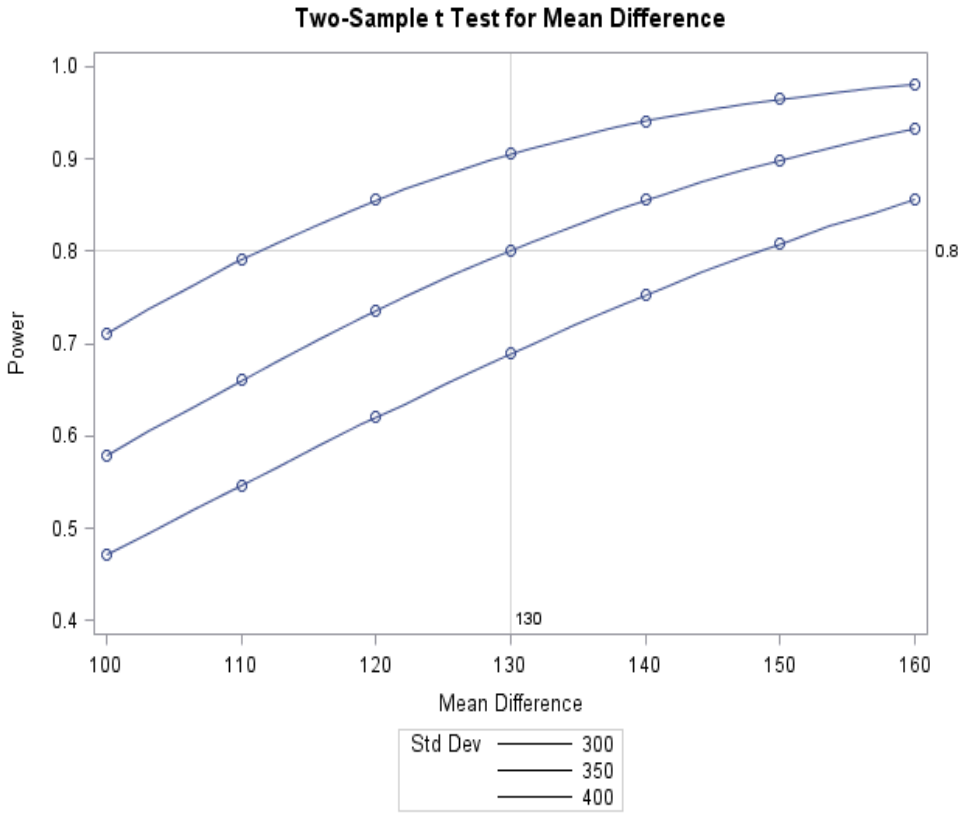
Based on a true population difference of 130 mL, a sample size of 115 patients per treatment group has an estimated 80% power to observe statistical significance at the two sided 5% level, for each of the two primary comparisons of interest for each UMEC dose. Using the above assumptions the smallest observed effect predicted to result in a statistically significant difference between treatment groups is 90.5 mL (minimum detectable difference).

No interim analysis is planned for this study.

10.3. 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=115 per arm in the intent to treat (ITT) population for the primary efficacy analysis, varying the true treatment difference and estimated standard deviation on the change from baseline in trough FEV_1 at the end of the 24-week treatment period.

Standard Deviation	Treatment difference (mL)				
	100	115	130	145	160
300	0.71	0.82	0.91	0.95	0.98
350	0.58	0.70	0.80	0.88	0.93
400	0.47	0.58	0.69	0.78	0.86



10.4. Sample site re-estimation or adjustment

No sample size re-estimation is planned.

10.5. Data Analysis

10.5.1. Analysis population

The following participant populations will be identified:

All Participants Enrolled Population: This population will comprise all participants for whom a record exists on the study database, including pre-screened participants that sign

the informed consent document but do not complete a Visit 1 (screening) procedure (i.e., pre-screening failures), or participants 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 participant disposition.

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

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

10.5.2. Treatment Comparisons

To demonstrate the benefit of UMEC the primary comparisons of interest for the primary efficacy endpoint are:

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

Other pairwise treatment comparisons of interest that aim to informally estimate any potential benefit of increasing the UMEC dose are given below for all efficacy endpoints.

- UMEC 62.5 mcg vs UMEC 31.25 mcg

For the multiple comparisons and multiplicity adjustment, please see Section 10.5.3.

10.5.3. Multiple Comparisons and Multiplicity

In order to account for multiple tests involving the two UMEC doses 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 test in the hierarchy.

A step-down procedure with the following hierarchy will be used for the primary comparisons in the primary endpoint.

- The contrast between UMEC 62.5 mcg vs Placebo
  (two-sided, alpha = 0.05. Null hypothesis of no treatment difference)
- The contrast between UMEC 31.25 mcg vs Placebo
  (two-sided, alpha = 0.05. Null hypothesis of no treatment difference)

The second hypothesis will be formally tested only if the first hypothesis has been rejected, thus maintaining the overall significance level at 5%.

Specifically, if the defined treatment comparison for the primary efficacy endpoint at the highest dose of UMEC 62.5 mcg is significant at 0.05 level then the efficacy of UMEC 62.5 mcg is demonstrated, and the treatment comparison can be repeated on the UMEC 31.25 mcg dose.

Note that, in the event that the first hypothesis is not rejected a nominal p-value for the second hypothesis may be provided in the displays for descriptive purposes only and will not alter the conclusion of the step-down procedure.

No multiplicity adjustment will be made on these two treatment comparisons on the secondary endpoint.

For all efficacy endpoints (primary, secondary and other), treatment comparisons between UMEC 62.5 vs UMEC 31.25 mcg informally investigating the benefit of increasing UMEC dose will be made without adjusting for multiplicity. Any p-values $\leq$ 0.05 will be identified as nominally significant.

10.6. Statistical Analysis

Where possible, data from participants 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 RAP.

In general, the baseline value is the last assessment value prior to randomization at Visit 2 for the efficacy endpoints based on assessments at clinic visits. The covariates to be considered in the efficacy analyses include age, sex, and the baseline value, if relevant. Other covariates, if appropriate, may be considered. Specific details will be provided in the RAP.

10.6.1. 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 participant, the baseline value of clinic FEV_1 is the last acceptable/borderline acceptable (pre-dose) FEV1 value obtained prior to randomization (either from Visit 2 pre-dose or from Visit 1 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, 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.

- UMEC 62.5 mcg vs Placebo
- UMEC 31.25 mcg vs Placebo

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 10.5.2 will also be provided for the primary efficacy endpoint.

10.6.2. Secondary Analyses

Full details of the analyses to be performed on the secondary efficacy endpoint will be given in the RAP.

10.6.3. 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.

10.6.4. Interim Analyses

No interim analysis is planned for this study.

10.6.5. Exploratory Analyses

The psychometric properties of the E-RS and Supplemental asthma items will be evaluated to characterize the E-RS as an endpoint for asthma. These exploratory analyses may be provided in a separate RAP.

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12. APPENDICES

12.1. Appendix 1: Abbreviations and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
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
BMI	Body Mass Index
BPM	Beats Per Minute
BST	Bioanalytical Science and Toxicokinetics
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
(e)CRF	(Electronic) Case Report Form
eDiary	Electronic Diary
EOS	End of study
E-RS	Evaluating Respiratory Symptoms
ERS	European Respiratory Society
EW	Early Withdrawal
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone Furoate
FP	Fluticasone Propionate
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good clinical practice
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
hCG	Human Chorionic Gonadotropin
HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Axis
HRT	Hormone Replacement Therapy
IB	Investigator’s Brochure

ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
IWRS	Interactive Web Response System
ITT	Intent to Treat
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LOCS III	Lens Opacities Classification System III
LRTI	Lower Respiratory Tract Infection
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
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PM	Evening
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

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
None

12.2. Appendix 2: Clinical Laboratory Tests

- All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol Schedule of Activities (Section 2) Laboratory requisition forms must be completed and samples must be clearly labelled with the participant 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 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 participant 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.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 6 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

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; 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	• **Follicle stimulating hormone (FSH) and estradiol (as needed in females of non-reproductive potential only)** • **Serum/urine hCG Pregnancy test (as specified in the Schedule of Activities table [Section 2])**

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 8.1.1 and Appendix 7

12.3. Appendix 3: Study Governance Considerations

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IEC/IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
    - Notifying the IRB/IEC of SAE or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions regarding the study.

- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.

Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

- For this study participant 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.

Data Quality Assurance

- 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. Participant initials will not be collected or transmitted to GSK according to GSK policy.
- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Study and Site Closure

GSK or its designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of GSK. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study treatment development

12.4. Appendix 4: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • 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 study treatment.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to progression of underlying disease). • 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 before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug 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 it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" constitutes an AE or SAE.

Events NOT Meeting the AE Definition
• 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 participant'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 participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which 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.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant 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 inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. 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 persistent disability/incapacity

- 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 (eg, sprained ankle) which may interfere with 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 SAE 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 participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include 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.

Recording AE and SAE

AE and SAE Recording
• When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE information in the CRF. • It is **not** acceptable for the investigator to send photocopies of the participant'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 case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK. • The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories: • Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as

severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/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 underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in 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 in which 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 before the initial transmission of the SAE data to** GSK**.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant 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 t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool 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 participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the assigned SAE contact by telephone. • Contacts for SAE reporting can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

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

12.5. Appendix 5: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below)

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

Note: Documentation can come from the site personnel's: review of participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female

- A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 4.

Table 4 Highly Effective Contraceptive Methods

Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation • oral • intravaginal • transdermal
Progestogen-only hormonal contraception associated with inhibition of ovulation[b] • injectable
Highly Effective Methods That Are User Independent
• Implantable progestogen-only hormonal contraception associated with inhibition of ovulation[b] • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • bilateral tubal occlusion
Vasectomized partner *(A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.)*
Sexual abstinence (*Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drug. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)*

NOTES:

a. *Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants in clinical studies.*

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine or serum pregnancy test
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of [5, 10, 25] mIU/mL will be performed [and assayed in a certified laboratory OR and assayed in the central laboratory OR using

the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert]

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, 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 participant who becomes pregnant while participating in the study will immediately discontinue study medication.

12.6. Appendix 6: Genetics

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 participant who is enrolled in the study can participate in genetic research. Any participant 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 participant 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 participant 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 participant 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.

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

Informed Consent

Participants 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.

Participant Withdrawal from Study

If a participant who has consented to participate in genetic research withdraws from the clinical study for any reason other than being lost to follow-up, the participant 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 participant 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 participant 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 participant does not meet the entry criteria for participation in the study, then the Investigator should instruct the participant 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 Participant'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 participant, family members, insurers, or employers of individual genotyping results that are not known to be relevant to the participant'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

Chen H, Yu KD, Xu GZ. Association between Variant Y402H in Age-Related Macular Degeneration (AMD) Susceptibility Gene CFH and Treatment Response of AMD: A Meta-Analysis. PloS ONE 2012; 7: e42464

Gorin MB. Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics. Mol. Asp. Med. 2012; 33: 467-486.

12.7. Appendix 7: Liver Safety: Required Actions and Follow-up Assessments

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

Phase II liver chemistry stopping criteria and required follow up assessments

Liver Chemistry Stopping Criteria – Liver Stopping Event	
ALT-absolute	ALT ≥ 5xULN
ALT Increase	ALT ≥ 3xULN persists for ≥4 weeks
Bilirubin[1, 2]	ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin)
INR[2]	ALT ≥ 3xULN **and** INR>1.5, if INR measured
Cannot Monitor	ALT ≥ 3xULN and cannot be monitored weekly for 4 weeks
Symptomatic[3]	ALT ≥ 3xULN associated with symptoms (new or worsening) believed to be related to liver injury or hypersensitivity

Required Actions and Follow up Assessments following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• **Immediately** discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the participant until liver chemistries resolve, stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol and GSK Medical Governance approval **is** granted (refer to Section 8.1.3) If restart/rechallenge **not allowed per protocol or not granted**, permanently discontinue study treatment and may continue participant in the study for any protocol specified follow up assessments	• Viral hepatitis serology[4] • Blood sample for pharmacokinetic (PK) analysis, obtained 72 hours after last dose[5] • 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 liver injury, or hypersensitivity, on the AE report form • Record use of concomitant medications on the concomitant medications report form including acetaminophen, herbal remedies, other over the counter

MONITORING: **<u>For bilirubin or INR criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24 hrs** • Monitor participants twice weekly until liver chemistries resolve, stabilize or return to within baseline • A specialist or hepatology consultation is recommended **<u>For All other criteria:</u>** • Repeat liver chemistries (include ALT, AST, alkaline phosphatase, bilirubin) and perform liver event follow up assessments within **24-72 hrs** • Monitor participants weekly until liver chemistries resolve, stabilize or return to within baseline	medications. • Record alcohol use on the liver event alcohol intake case report form **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week (James 2009) **Not Required in China** • Liver imaging (ultrasound, magnetic resonance, or computerised tomography) and /or liver biopsy to evaluate liver disease; complete Liver Imaging and/or Liver Biopsy CRF forms.

1. Serum bilirubin fractionation should be performed if testing is available. If serum bilirubin fractionation is not immediately available, discontinue study treatment for that participant if ALT ≥ 3xULN **and** bilirubin ≥ 2xULN.. Additionally, if serum bilirubin fractionation testing is unavailable, **record presence of detectable urinary bilirubin on dipstick**, indicating direct bilirubin elevations and suggesting liver injury.
2. All events of ALT ≥ 3xULN **and** bilirubin ≥ 2xULN (>35% direct bilirubin) or ALT ≥ 3xULN **and** INR>1.5, if INR measured which may indicate severe liver injury (possible 'Hy's Law'), **must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis)**; INR measurement is not required and the threshold value stated will not apply to participants receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. PK sample may not be required for participants known to be receiving placebo or non-GSK comparator treatments.) Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the participant's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

Phase II liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥3xULN and <5xULN **and** bilirubin <2xULN**, without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 4 weeks	• Notify the GSK medical monitor **within 24 hours** of learning of the abnormality to discuss participant safety. • Participant can continue study treatment • Participant must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time participant meets the liver chemistry stopping criteria, proceed as described above • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

References

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

12.8. Appendix 8: Daily Diary Questions

12.8.1. Morning Questions

The participant 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

12.8.2. Evening Questions

The participant 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

12.9. Appendix 9: Country-specific requirements

There are currently no country specific requirements.