TITLE PAGE

Protocol Title: A Phase III, 12 week, randomized, double-blind, 4 arm parallel group bridging study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI once-daily via a dry powder inhaler with dual combination of FF/VI, administered in Chinese participants with inadequately controlled asthma.

Protocol Number: 214263 Amendment 02

Compound Number or Name: GSK2834425

Brief Title: Efficacy and safety of FF/UMEC/VI in Chinese participants with inadequately controlled asthma

Study Phase: Phase 3

Sponsor Name and Legal Registered Address:

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

Regulatory Agency Identifying Number(s): NA

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

Sponsor Signatory:

David Slade

Senior Clinical Development Director

Approval Date: 18 Jul 2022

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY		
Document	**Date**	**DNG Number**
Amendment 2	18 Jul 2022.	TMF-14804664
Amendment 1	28-Apr-2021.	TMF-12874573
Original Protocol	17-Dec-2020.	2020N447598_00

Amendment 2. 18 Jul 2022

The amendment is substantial.

Overall Rationale for the Amendment 2:

The amendment is mainly made to diminish the data missing risk due to COVID-19 lockdown, and to facilitate the enrolment. Besides, some additional amendments are also made to provide more clear information.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis	In the part of Number of Participants, the estimated screening number is updated from 550 to 890.	When the study is conducting, the observed screening failure rate is higher than the original estimation. Current screening failure rate is around 55-60%, the screening number is updated accordingly.
Section 1.3 Schedule of Activities (SoA)	Footnote 20 is newly added to add the possibility of home ACQ if the Visit 3 or 4 or Early Withdraw (EW) is impacted by COVID-19 lockdown. Footnote 21 is newly added: to allow Visit 4 time window be prolonged if it's impacted by COVID-19 lockdown.	As strict COVID-19 lockdown, some participants couldn't finish on-site visits within current time window. To help collect more data, the possibility of home ACQ is added into footnote 20. And as observed in Global pivotal study that the efficacy of FF/UMEC/VI was stabilized from week 12 to week 24, the time window of Visit 4 is prolonged (on treatment) to ensure efficacy data will be collected at Visit 4.
Section 5.1 Inclusion Criteria	The requirement of daily ICS/LABA for at least 12 weeks prior to Visit 0 is changed to 8 weeks in the part of Current Asthma Maintenance Therapy	Based on GINA, if a patient has persisting uncontrolled symptoms despite 2-3 months of controller treatment, could consider any step up in treatment. To facilitate the enrolment, the duration of daily ICS/LABA before screening is shorten to 8 weeks from 12 weeks.

Section # and Name	Description of Change	Brief Rationale
Section 8. STUDY ASSESSMENTS AND PROCEDURES	It is newly added that allowing Visit 4's time window is prolonged if it's impacted by COVID-19 lockdown.	As strict COVID-19 lockdown, some participants couldn't finish on-site visits within current time window. As observed in Global pivotal study that the efficacy of FF/UMEC/VI was stabilized from week 12 to week 24, the time window of Visit 4 is prolonged (on treatment) to ensure efficacy data will be collected at Visit 4.
Section 8.2.1. Pulmonary Function Test	Under the pre-dose spirometry part, the Visit 1 is corrected to Visit 2.	The visit number was mistakenly written. To avoid incorrect testing time of the pre-dose spirometry, it's corrected.
Section 8.2.2. Asthma control Questionnaire	This section is newly added the possibility of home ACQ if the Visit 3 or 4 or EW is impacted by COVID-19 lockdown.	As strict COVID-19 lockdown, some participants couldn't finish on-site visits within current time window. To help collect more data, the possibility of home ACQ is added.
Section 8.3.4. Clinical Safety Laboratory Assessments	The requirement of collecting pre-dose blood samples is removed. Meantime, it's emphasized that collecting blood sample before the participant's dose of asthma treatment on the day of the visit.	When this trial is being conducted, some sites could only collect blood sample after the reversibility test, and Albuterol/Salbutamol will be used in this test. Considering that albuterol/salbutamol is inhaled, it will not have some significant influence on the haematology assessments and clinical chemistry tests, the blood samples collected after the reversibility test is considered acceptable. To avoid unnecessary confusion about it, the pre-dose is removed. But it's emphasized that collecting blood sample <u>before the participant's dose of asthma treatment on the day of the visit.</u>
Section 8.4.5 Pregnancy	Withdraw from the study if pregnancy is removed.	Efficacy data should be collected regardless treatment discontinuation status, and it's mentioned in Section 7.1 that the participants who withdraw from double-blind study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol

Section # and Name	Description of Change	Brief Rationale
		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. So this part is corrected accordingly.
Section 9.2 Sample Size Determination	The estimated screening number is updated from 550 to 890.	When the study is conducting, the observed screening failure rate is higher than the original estimation. Current screening failure rate is around 55-60%, the screening number is updated accordingly.
Section 10.3.5 Reporting of SAE to GSK	The requirement of SAE reporting in Electronic case report form (eCRF) within 72 hours is removed.	Removal of additional step of eCRF check per GSK new protocol template.
Section 10.3.5 Reporting of SAE to GSK	The contact for SAE reporting is added.	The contact was not listed before.

TABLE OF CONTENTS

PAGE

1. PROTOCOL SUMMARY

1.1. Synopsis

A Phase III, 12 week, randomized, double-blind, 4 arm parallel group bridging study, comparing the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI once-daily via a dry powder inhaler with dual combination of FF/VI, administered in Chinese participants with inadequately controlled asthma.

Brief Title: Efficacy and safety of FF/UMEC/VI in Chinese participants with inadequately controlled asthma

Rationale:

Asthma is a common chronic airway disease imposing a significant burden on families, healthcare systems and the workplace. It is characterized by airway inflammation, increased airway responsiveness, and bronchoconstriction [GINA, 2020]. The goal of asthma treatment is to achieve and maintain asthma control enabling patients to avoid symptoms and flare-ups and lead productive lives with near normal lung function [GINA, 2020].

The prevalence of asthma in China has been increasing in recent years. According to latest data, the prevalence of asthma in China adults is 4.2%, representing about 45.7 million adult patients [Huang, 2019]. Despite availability of treatments and published guidelines, patients may have asthma that is inadequately controlled, and the asthma control is sub-optimal: 29-35% of China patients were still uncontrolled despite of inhaled corticosteroid/long-acting beta$_2$ agonist (ICS/LABA) therapy [HZA113719 China CSR GSK Document number 2013N169446_00 Table 15; HZA113714 China CSR GSK Document number 2013N161713_00 Table 16]. Situations are similar in other regions. In a survey conducted among 8,000 patients with asthma from 11 European countries, 45% of respondents had uncontrolled asthma, and 44% of respondents reported having used oral steroids for asthma in the previous 12 months [Price, 2014]. An analysis of asthma patients in Europe found that 37.6% of asthma patients treated with ICS/LABA therapy remained uncontrolled [Roche, 2020].

International and Chinese asthma guidelines [GINA, 2020; CAPG, 2016] recommend a long-acting muscarinic antagonist (LAMA) as add-on treatment for adults whose asthma is uncontrolled with medium to high dose ICS/ LABA treatment.

GSK has developed a once-daily single-inhaled triple therapy of an ICS/LAMA/LABA combination [fluticasone furoate/ umeclidinium /vilanterol (FF/UMEC/VI)] via a single ELLIPTA dry-powder inhaler device, with the aim of providing a new treatment option for the management of asthma by improving lung function, health-related quality of life (HRQoL) and symptom control over established combination therapies. The results of the global PhIIIa 205715 study established that FF/UMEC/VI provided additional benefit compared with FF/VI in patients ≥18 years old whose asthma was inadequately controlled despite treatment with ICS (>250 µg per day of fluticasone propionate, or equivalent) plus LABA [Study 205715].

- For the primary comparison of FF/UMEC/VI to FF/VI at Week 24 for change from baseline in trough FEV1, statistically significant treatment differences were observed for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 (110 mL, 95% CI: 66, 153; p<0.001) and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 (92 mL, 95% CI: 49, 135; p<0.001). Treatment differences of a similar magnitude were also demonstrated for UMEC 31.25-containing FF/UMEC/VI treatments compared with FF/VI at the same dose of FF, though statistical significance could not be inferred due to the statistical hierarchy.
- For the secondary analysis of annualised rate of moderate/ severe exacerbations, the data from the two FF/UMEC/VI arms for each UMEC dose were pooled and compared with pooled data from the two FF/VI arms. A 13.0% (95% CI: -5.2, 28.1) reduction in the annualised rate of moderate/severe asthma exacerbations was observed across Weeks 1-52 for the FF/UMEC/VI (100 and 200)/62.5/25 group compared with the FF/VI (100 and 200)/25 group; however, the reduction in rate did not reach statistical significance (p=0.151). No meaningful difference was observed in the annualised rate of moderate/severe exacerbations between the UMEC31.25-containing FF/UMEC/VI group and FF/VI group.
- In the patient-reported secondary endpoints included in the statistical hierarchy, large improvements from baseline were seen in all treatment groups. Numeric, dose-ordered treatment differences were observed between FF/UMEC/VI group and FF/VI group with increasing UMEC dose for Asthma Control Questionnaire (ACQ)-7 (UMEC 62.5 µg, treatment difference= -0·09, 95% CI: –0·16 to –0·02), a measure of asthma control, and evaluating respiratory symptoms (E-RS): Asthma, a measure of asthma symptoms (UMEC 62.5 µg, treatment difference= -0.42,95% CI: -0.78, -0.06). As with the analysis of annualised rate of moderate/ severe exacerbations, the data from the two FF/UMEC/VI arms for each UMEC dose were pooled and compared with pooled data from the two FF/VI arms.
- Safety data did not identify any new findings for FF/UMEC/VI in this study considering the known class effects of ICS, LAMA and LABAs in a population of patients with asthma.

However, this study did not include Chinese patients. Given the above results, the efficacy and safety data in this study supports the favourable benefit/risk profile for FF/UMEC/VI in this inadequately controlled asthma population. FF/UMEC/VI 100/62.5/25 µg and 200/62.5/25 µg doses have been submitted for global regulatory review for an indication in asthma in several countries worldwide. On 9 Sep 2020, FF/UMEC/VI 100/62.5/25 µg and 200/62.5/25 µg were approved as the first once-daily single inhaler triple therapies for the treatment of asthma in the US.

GSK plans to extend the body of evidence for FF/ UMEC/ VI with an evaluation in Chinese asthma patients. Through the comparison of FF/UMEC/VI to the dual combination therapy FF/VI, this study aims to provide important information to prescribers regarding the benefit of a once-daily, single-inhaler triple combination therapy in adult Chinese asthma patients who remain inadequately controlled despite treatment with ICS/LABA.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To evaluate the efficacy of FF/UMEC/VI 100/62.5/25 µg on lung function compared with FF/VI 100/25 µg after 12 weeks of treatment	• Change from baseline in trough Forced Expiratory Volume in 1 second (FEV_1) at Week 12
Secondary	
• To evaluate the efficacy of FF/UMEC/VI 200/62.5/25 µg on lung function compared with FF/VI 200/25 µg after 12 weeks of treatment	• Change from baseline in trough FEV_1 at Week 12
Other secondary	
• To evaluate the effects of FF/UMEC/VI compared with FF/VI on asthma control after 12 weeks of treatment	• Change from baseline in ACQ-7 total score at Week 12;
Safety	
• To evaluate the safety of FF/UMEC/VI (100/62.5/25 and 200/62.5/25 µg) compared with FF/VI (100/25 and 200/25 µg) throughout the 12-week treatment period.	• Incidence and type of adverse events • Incidence of exacerbations • Change from baseline in ECG parameters • Incidence of worst vital sign results relative to normal range • Incidence of worst clinical hematological and chemistry results relative to normal range

The primary clinical question of interest is: What is the effect of adding UMEC to FF/VI in a single inhaler when compared with FF/VI on change from baseline in trough FEV_1 after 12 weeks of treatment in Chinese participants with inadequately controlled asthma? This question is to be addressed regardless of study treatment discontinuation unrelated to a pandemic or due to pandemic infection and in the absence of study treatment discontinuation due to the indirect impact of a pandemic (e.g. participant or site related impact such as participant unable to collect/obtain study treatment due to restrictions in place, pharmacist not available to conduct the study and maintain the blind).

The primary estimand is described by the following attributes:

- Population: Chinese participants with inadequately controlled asthma.
- Treatment condition: FF/UMEC/VI (100/62.5/25 µg) or FF/VI (100/25 µg) given once daily in the morning (primary treatment comparison is FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg). In addition, rescue albuterol/salbutamol will be provided and is permitted during the study.
- Variable: change from baseline in trough FEV_1 at week 12.
- Summary measure: Mean change from baseline. Comparison: difference in mean change from Baseline
- Intercurrent events:
    - Study treatment discontinuation – if related to an indirect impact of a pandemic it will be handled with a hypothetical strategy (i.e. had the intercurrent event not occurred. In this situation, data collected after study treatment discontinuation will not be included in the statistical analysis and will be treated as missing data). Otherwise it will be handled with a treatment policy strategy and data collected after study treatment discontinuation will be included in the analysis. This will be the primary intercurrent event strategy.

An additional estimand supporting the primary objective is defined similar to the primary estimand except a different intercurrent event strategy will be followed, where study treatment discontinuation due to an indirect impact of the pandemic will be handled with a treatment policy rather than a hypothetical strategy (i.e. all data collected after study treatment discontinuation will be included in the analysis).

The estimand for the secondary objective assessing FEV1 is the same as the primary estimand except the treatment conditions are FF/UMEC/VI (200/62.5/25 µg) or FF/UMEC/VI (200/25 µg) given once daily in the morning.

Overall Design:

This is a 12-week, Phase III, randomized, double-blind, active controlled, 4-arm parallel group bridging study in Chinese asthma participants evaluating FF/UMEC/VI (100/62.5/25 µg) versus FF/VI (100/25 µg) and, FF/UMEC/VI (200/62.5/25 µg) versus FF/ VI (200/25 µg), given once daily in the morning.

Brief Summary:

The purpose of this study is to evaluate the efficacy, safety and tolerability of the fixed dose combination FF/UMEC/VI 100/62.5/25 and 200/62.5/25 µg once-daily compared with dual combination of FF/VI 100/25 and 200/25 µg once-daily, respectively, for improving lung function in Chinese participants with asthma. Study details include:

- Study Duration: 16-18 weeks
- Treatment Duration: 12 weeks
- Number of Visits: 6 visits

The objective of the study is to evaluate the efficacy and safety of FF/UMEC/VI administered once daily via a dry powder inhaler, vs FF/VI for 12 weeks. The primary

estimand is the difference in means between FF/UMEC/VI 100/62.5/25 and FF/VI 100/25 µg in the change from baseline in Trough FEV_1 at Week 12 in Chinese participants with inadequately controlled asthma regardless of study treatment discontinuations unrelated to any pandemic or due to pandemic infections, and in the absence of study treatment discontinuations due to the indirect impact of a pandemic. The secondary estimand assessing FEV1 is as above but for FF/UMEC/VI 200/62.5/25 versus FF/VI 200/25 µg. The study population will be consistent with the 205715 (CAPTAIN study) and consist of adult participants (≥18 years of age) with asthma diagnosis as defined by the Global Initiative for Asthma [GINA, 2020]. In addition, they must have inadequately controlled asthma (ACQ-6 score ≥1.5) despite ICS/LABA maintenance therapy at screening visit (Visit 1) and keep their daily ICS/LABA for at least 12 weeks with no changes to maintenance asthma medications during the 6 weeks immediately prior to Visit 0 (Pre-screening visit). Participants must also have pre-bronchodilator morning (AM) FEV_1 ≥30% and <85% of the predicted normal value at Visit 1 and demonstrated reversibility.

The study consists of a 3-week run-in period, a 12-week treatment period, and a 1-week safety follow-up period. Clinic Visits will occur at Pre-Screening (V0), Screening (V1), Randomisation (Day 1, V2), week 4 (V3), and week 12 (V4). A safety follow-up telephone contact or clinic visit will be conducted approximately 1 week after completing either the randomised treatment period or an Early Withdrawal Visit.

In accordance with the protocol-defined visit schedule, participants will have two on-treatment clinic visits conducted on an outpatient basis scheduled at Visits 3 (Week 4) and 4 (Week 12). One week following the end of the study (or after the early withdrawal visit) a follow-up telephone call or clinic visit will be performed for safety assessments.

A participant will be considered to have completed the study when he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities (SoA).

Number of Participants:

Approximately 890 participants will be screened to achieve 356 randomly assigned to study intervention for a total of 89 participants per intervention group. Randomization will be stratified by pre-study ICS treatment strength (med, high) at screening to ensure treatment balance within each stratum.

Intervention Groups and Duration:

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) must be completed prior to initiating any Visit 1 procedures.
- **Screening / run-in:** Participants who meet all the eligibility criteria at screening (Visit 1), will enter the run-in period for 3 weeks in order to continue to assess the participant's eligibility for the study. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF/VI (100/25 µg via the ELLIPTA dry powder inhaler [DPI]), taken in the morning once daily during the 3-week

run-in period. Rescue medication (albuterol/salbutamol) will be provided to use on an as-needed basis throughout the study. The 3-week run-in period is necessary in order to allow participants to become accustomed to using the ELLIPTA DPI as well as to assess the participant's eligibility for the study and collect baseline electronic diary (eDiary) data.

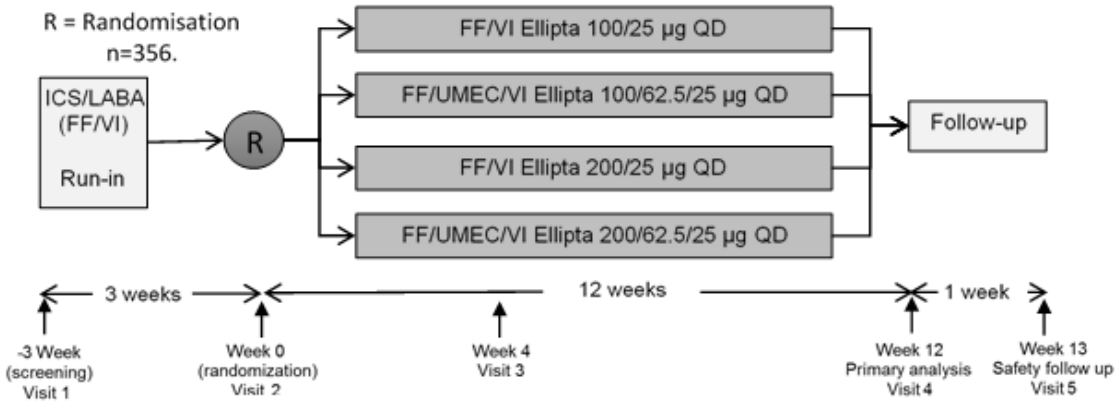
- **Randomization and Treatment:** At the conclusion of the 3-week run-in period (Visit 2), all participants who meet the additional predefined criteria will be randomized 1:1:1:1 (stratified by pre-study ICS dosage [medium, high])to receive either FF/UMEC/VI (100/62.5/25; 200/62.5/25 µg) or FF/VI (100/25; 200/25 µg) via the ELLIPTA DPI for the duration of the 12-week treatment period.
  - FF/VI 100/25 µg once daily (QD)
  - FF/VI 200/25 µg QD
  - FF/UMEC/VI 100/62.5/25 µg QD
  - FF/UMEC/VI 200/62.5/25 µg QD

  Study treatment will be administered via the ELLIPTA DPI in the morning.
- **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 4/end of study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study upon completion of all assessments and procedures for Visit 4/EOS and including a successful follow-up contact/visit.

Data Monitoring/ Other Committee: [Not applicable]

1.2. Schema

Figure 1 Study design



1.3. Schedule of Activities (SoA)

Protocol Activity	Pre-Screen[1]	Screen Run-in	Intervention Period			Early Withdrawal (EW)[3]	Safety Follow-up Contact
Visit	**0**	**1[1]**	**2[2] Randomization**	**3**	**4[21]**	**EW**	**5**
Study Day	**-35 to -22**	**-21**	**1**	**28 days post first dose**	**84 days post first dose**		
Week	**-5 to -4**	**-3**	**0**	**4**	**12**		**1 week after Visit 4/EOS or EW Visit**
Window				**-7/+7d**	**-7/+7d**		**-2/+5d**
Written Informed Consent[4]	x						
Demography	x						
Medical history		x					
Asthma History[5]		x					
Exacerbation History		x					
Concomitant Medication Assessment	x	x	x	x	x	x	x
Inclusion/Exclusion criteria		x	x				
Smoking History and status		x					
Randomization[6]			x				
Register visit in Interactive Response Technology (IRT) (RAMOS NG)[7]	x	x	x	x	x	x	x
Efficacy Assessments							
Dispense paper Medical Problems/Medications Taken worksheet	x	x	x	x	x	x	
Review paper Medical Problems/Medications Taken worksheet		x	x	x	x	x	x
ACQ[8,20]		x	x	x	x	x	
Pre-dose spirometry		x[9]	x[9]	x[9]	x[9]	x[9,10]	

Protocol Activity	**Pre-Screen[1]**	**Screen Run-in**	**Intervention Period**			**Early Withdrawal (EW)[3]**	**Safety Follow-up Contact**
Visit	**0**	**1[1]**	**2[2] Randomization**	**3**	**4[21]**	**EW**	**5**
Study Day	**-35 to -22**	**-21**	**1**	**28 days post first dose**	**84 days post first dose**		
Week	**-5 to -4**	**-3**	**0**	**4**	**12**		**1 week after Visit 4/EOS or EW Visit**
Window				**-7/+7d**	**-7/+7d**		**-2/+5d**
Reversibility test		x[11]					
eDiary/device training and registration		x					
Dispense eDiary		x					
Collect eDiary					x	x	
eDiary review			x	x	x	x	
Safety Assessments							
Physical Examination		x			x	x	
Vital Signs		x[12]	x	x	x	x	
ECG[13]		x		x	x	x	
Adverse Events		x	x	x	x	x	x
Serious Adverse Events	x	x	x	x	x	x	x
Exacerbation assessment			x	x	x	x	x

Protocol Activity	**Pre-Screen**[1]	**Screen Run-in**	**Intervention Period**			**Early Withdrawal (EW)**[3]	**Safety Follow-up Contact**
Visit	**0**	**1**[1]	**2**[2] **Randomization**	**3**	**4**[21]	**EW**	**5**
Study Day	**-35 to -22**	**-21**	**1**	**28 days post first dose**	**84 days post first dose**		
Week	**-5 to -4**	**-3**	**0**	**4**	**12**		**1 week after Visit 4/EOS or EW Visit**
Window				**-7/+7d**	**-7/+7d**		**-2/+5d**
Laboratory Assessments							
Hematology and clinical chemistry		x			x	x	
Urinalysis		x			x	x	
Serum pregnancy test		x[14]			x[14]	x[14]	
Urine pregnancy test[14]			x	x			
Study Treatment							
Dispense ICS/LABA run-in medication		x[15]					
Assess run-in medication compliance			x				
Collect ICS/LABA run-in medication			x				
Administer double-blind study treatment[16]			x	x	x	x[17]	
Dispense double-blind study treatment (Scheduled)			x	x			
Dispense double-blind study treatment (Unscheduled)			x[18]				
Assess double-blind study treatment compliance				x	x	x	

Protocol Activity	**Pre-Screen[1]**	**Screen Run-in**	**Intervention Period**			**Early Withdrawal (EW)[3]**	**Safety Follow-up Contact**
Visit	**0**	**1[1]**	**2[2] Randomization**	**3**	**4[21]**	**EW**	**5**
Study Day	**-35 to -22**	**-21**	**1**	**28 days post first dose**	**84 days post first dose**		
Week	**-5 to -4**	**-3**	**0**	**4**	**12**		**1 week after Visit 4/EOS or EW Visit**
Window				**-7/+7d**	**-7/+7d**		**-2/+5d**
Collect double-blind study treatment (Scheduled)				x	x	x	
Collect double-blind study treatment (Unscheduled)			x[19]				
Dispense albuterol/salbutamol, as required		x	x	x	x		
Collect albuterol/salbutamol, as required			x	x	x	x	

Notes:

1. Visit 1 should be completed [3]1 day but ≤14 days after Visit 0; however, if it is local and routine medical practice to request that a participant withhold their ICS/LABA medication for at least 24 hours prior to a clinic visit then, provided that the participant has complied with the request, Visit 0 and Visit 1 can occur on the same day.
2. Visit 2 must always be conducted [3]21 days but £28 days after Visit 1.
3. EW Visit should be conducted if double-blind study treatment is discontinued AND the participant discontinues from participating in the study.
4. The ICF must be signed before any study procedures, including protocol-specified medication cessation.
5. 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 Study Reference Manual [SRM]).
6. Participants must not be randomized prior to confirming their eligibility to participate in the study.
7. The IRT will be used for randomization, emergency unblinding and study treatment supply management (Please refer to the RAMOSNG IRT manual and SRM for more information).
8. Assessment to be completed prior to the administration of study treatment. ACQ-6 will be evaluated at V1 and 2 for eligibility check, and ACQ-7 (ACQ-6 & 5 will be derived from ACQ-7) will be evaluated at V2, 3, 4 and EW for efficacy assessment.
9. Spirometry to be performed between 6am and 11am after withholding rescue medication for at least 6 hours and prior to taking the morning dose of study treatment. Pre-dose spirometry assessments should be performed at the same time of day at each applicable visit.

10. In the event that double-blind study treatment is not administered at this visit, spirometry assessments should be performed at the same time of day as the pre-dose spirometry assessments at the preceding on-treatment clinic visits.
11. 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 8.2.1.1 for details of the criteria to be met before a repeat of the reversibility assessment is permitted). If airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are met then the participant may commence the 3-week run-in period (starting on the date that airway reversibility was successfully demonstrated at the second attempt).
12. The vital signs assessment will include the measurement of height and weight at this visit only.
13. 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 8.3.3). At all post-randomization visits the ECG is to be obtained 15 minutes to 45 minutes after the administration of study treatment.
14. Assessments only to be conducted in females of reproductive potential.
15. In the event that the reversibility assessment needs to be repeated within 7 days of Visit 1 (see Section 8.2.1.1) then the medication for the 3-week run-in period must not be dispensed until airway reversibility is successfully demonstrated at the second attempt and all other eligibility criteria assessed at Visit 1 are confirmed as met.
16. Study treatment should be administered at the same time of day at each applicable clinic visit.
17. The administration of study treatment at this visit is optional. If study treatment is not administered at this visit then those assessments which are scheduled based on the time of study treatment administration should be performed at approximately the same time of day as performed at the preceding post-randomization visits.
18. Between scheduled visits, unscheduled visits to the study clinic to re-supply the participant with double-blind study treatment is permitted after Visit 2 but before Visit 4/EOS. The IRT will be used for study treatment supply management (Please refer to the RAMOS NG IRT manual and SRM for more information).
19. In the event that the participant attends the study clinic for the unscheduled dispensing of double-blind study treatment, previously dispensed study treatment should be collected for drug accountability purposes.
20. If on-site Visit 3 or Visit 4 or EW could not be conducted within time window due to COVID-19 lockdown, the participant could complete ACQ-6 from home, under the investigator mode (refer to SRM for the details).
21. If Visit 4 couldn't be done on site due to COVID-19 lockdown, the participant will be provided additional study drug and continue study treatment until they could come back to site for Visit 4; the time window of Visit 4 will be extended for 6 more weeks as the longest after 12 weeks' treatment in these participants.

2. INTRODUCTION

FF/UMEC/VI is a fixed-dose triple combination medication containing inhaled corticosteroid fluticasone (FF), inhaled long-acting muscarinic receptor antagonist umeclidinium (UMEC) and inhaled long-acting beta2 agonist vilanterol (VI) that is being developed for once-daily treatment of asthma and chronic obstructive pulmonary disease (COPD).

2.1. Study Rationale

The Global Initiative for Asthma guideline [GINA, 2020] recommends a long-acting muscarinic antagonist (LAMA) as an add-on treatment option for adults (≥18 years) with asthma that are currently taking medium-to-high dose inhaled corticosteroid and long-acting $beta_2$ agonist (ICS/LABA) maintenance therapy and have a history of exacerbations. Exacerbations are an important endpoint in asthma therapy; however, symptom control is also important in determining what patients could benefit from step-up therapy.

GSK has developed a once-daily fixed-dose triple therapy of an ICS/LAMA/LABA combination [fluticasone furoate/ umeclidinium /vilanterol (FF/UMEC/VI)] via a single ELLIPTA dry-powder inhaler device, with the aim of providing a new treatment option for the management of asthma by improving lung function, health-related quality of life (HRQoL) and symptom control over established combination therapies. The results of the global PhIIIa 205715 study has established that FF/UMEC/VI provided additional benefit compared with FF/VI in asthma patients ≥18years old who were inadequately controlled despite treatment with ICS (>250 µg per day of fluticasone propionate, or equivalent) plus LABA [Study 205715].

- For the primary comparison of FF/UMEC/VI to FF/VI at Week 24 for change from baseline in trough FEV1, statistically significant treatment differences were observed for both FF/UMEC/VI 100/62.5/25 compared with FF/VI 100/25 µg (110 mL, 95% CI: 66, 153; p<0.001) and FF/UMEC/VI 200/62.5/25 compared with FF/VI 200/25 µg (92 mL, 95% CI: 49, 135; p<0.001). Treatment differences of a similar magnitude were also demonstrated for UMEC 31.25-containing FF/UMEC/VI treatments compared with FF/VI at the same dose of FF, though statistical significance could not be inferred due to the statistical hierarchy.
- For the secondary analysis of annualised rate of moderate/ severe exacerbations, the data from the two FF/UMEC/VI arms for each UMEC dose were pooled and compared to pooled data from the two FF/VI arms. A 13.0% (95% CI: -5.2, 28.1) reduction in the annualised rate of moderate/severe asthma exacerbations was observed across Weeks 1-52 for the FF/UMEC/VI (100 and 200)/62.5/25 group compared with the FF/VI (100 and 200)/25 group; however, the reduction in rate did not reach statistical significance (p=0.151). No meaningful difference was observed in the annualised rate of moderate/severe exacerbations between the UMEC31.25-containing FF/UMEC/VI group and FF/VI group.

- In the patient reported secondary endpoints included in the statistical hierarchy, large improvements from baseline were seen in all treatment groups. Numeric, dose-ordered treatment differences were observed with increasing UMEC dose for ACQ-7, a measure of asthma control, and E-RS: Asthma, a measure of asthma symptoms.
- Safety data did not identify any new findings for FF/UMEC/VI in this study considering the known class effects of ICS, LAMA and LABAs in a population of patients with asthma. FF/UMEC/VI 100/62.5/25 µg and 200/62.5/25 µg doses have been submitted for global regulatory review for an indication in asthma in several countries worldwide.

The efficacy and safety data above supports the favourable benefit/risk profile for FF/UMEC/VI in this inadequately controlled asthma population under ICS/LABA treatment. Both FF/UMEC/VI 100/62.5/25 µg and 200/62.5/25 µg doses have been submitted for global regulatory review for an indication in asthma in several countries worldwide. On 9 Sep 2020, both FF/UMEC/VI 100/62.5/25 µg and 200/62.5/25 µg were approved as the first once-daily single inhaler triple therapies for the treatment of asthma in the US.

By the end of 02 July 2020, FF/UMEC/VI has been studied in 103 healthy volunteers, 9,781 participants with COPD and 1,734 participants with asthma and the total number of participants exposed to FF/UMEC/VI in all clinical studies was 11,618. Cumulative post-marketing exposure from launch to 31 March 2020 is estimated to be 685,428 patient-years. No new safety concerns were identified that were not already known for FF/VI, UMEC/VI and UMEC.

GSK plans to extend the body of evidence for FF/ UMEC/ VI with an evaluation in Chinese asthma patients. Through the comparison of FF/UMEC/VI to the dual combination therapy FF/VI, this study aims to provide important information to prescribers regarding the benefit of a once-daily, single-inhaler triple combination therapy in adult Chinese asthma patients who remain inadequately controlled despite treatment with ICS/LABA.

2.2. Background

Asthma is a common chronic airway disease imposing a significant burden on families, healthcare systems and the workplace. It is characterized by airway inflammation, increased airway responsiveness, and bronchoconstriction [GINA, 2020]. The prevalence of asthma in China has been increasing in recent years. According to latest data, the prevalence of asthma in China adults is 4.2%, representing about 45.7 million adult patients [Huang, 2019].

The goal of asthma treatment is to achieve and maintain asthma control enabling patients to avoid symptoms and flare-ups and lead productive lives with near normal lung function [GINA, 2020]. Current medications for asthma patients mainly consist of ICS with/without LABA for long term asthma maintenance treatment. ICSs are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2020]. The dose of ICS is selected based on the severity of the patient's asthma. In patients who are symptomatic on ICS alone, add-on therapy with another controller, in

particular a LABA is preferred to increasing the dose of ICS to achieve asthma control [GINA, 2020]. In difficult-to-treat persistent asthma, some patients continue to be symptomatic despite treatment with ICS and LABA combination medications and the current guidelines [GINA, 2020; CAPG, 2016] recommend treatment with high-dose inhaled or oral glucocorticosteroids in combination with LABAs and/or additional controller medications.

Despite availability of treatments and published guidelines, patients may have asthma that is inadequately controlled, and the asthma control is sub-optimal: 29-35% of China patients were still uncontrolled despite of inhaled corticosteroid/long-acting beta$_2$ agonist (ICS/LABA) therapy [[HZA113719 China CSR GSK Document number 2013N169446_00 Table 15; HZA113714 China CSR GSK Document number 2013N161713_00 Table 16].

International and Chinese guidelines [GINA, 2020; CAPG, 2016] guidelines both recommend a long-acting muscarinic antagonist (LAMA) as add-on treatment for adults whose asthma is uncontrolled with medium to high dose ICS/ LABA treatment.

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

Recently, a Phase III study (IRIDIUM) also demonstrates that ICS–LABA–LAMA once-daily combination therapy of medium-dose and high-dose mometasone furoate, indacaterol acetate, and glycopyrronium bromide (MF–IND–GLY), from a single inhaler, significantly improved lung function versus the respective once-daily MF–IND doses and twice-daily high-dose fluticasone–salmeterol (FLU–SAL), a well-established ICS–LABA combination (Kerstjens, 2020).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of GSK2834425 (FF/UMEC/VI) may be found in the Investigator's Brochure (GSK Document number 2012N131935_10). Marketed ICS/LABA products will be used for run-in (FF/VI) and comparator (FF/VI) treatments. These products will be used in accordance with the product labels and further details on the experience with these products can be found in the Investigator Brochures and/or

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

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention(s) GSK2834425		
Cardiovascular effects	Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists or sympathomimetic agents, including umeclidinium or vilanterol, respectively. Vilanterol, like other beta2-agonists, can produce a clinically significant cardiovascular effect in some patients as measured by increases in pulse rate, systolic or diastolic blood pressure, and also cardiac arrhythmias, such as supraventricular tachycardia and extrasystoles. In addition, beta-agonists have been reported to produce electrocardiographic changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression, although the clinical significance of these findings is unknown. Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. In the completed pivotal study in asthma, 205715, which included 2439 participants which investigated the efficacy and safety of FF/UMEC/VI (100/31.25/25; 200/31.25/25; 100/62.5/25; 200/62.5/25) compared to FF/VI (100/25; 200/25) the percentage of participants with adverse events of special interest (AESIs) in the CV effects special interest group ranged from 4% to 7% across the treatment groups (highest in the FF/UMEC/VI 100/62.5/25 group). CV effects AESI reported in ≥1% of participants in	Mitigation strategy: - The risk of CV effects was mitigated by the exclusion of participants with unstable or life-threatening cardiac disease, collection of medical history at baseline including a detailed history of CV risk factors (Detailed in in Section 5.2 of the Protocol Amendment) - Collection of cardiovascular risk factors and medical history at baseline - ECGs as per schedule in Section 1.3. - Vital sign assessments (heart rate and blood pressure) as per schedule in Section 1.3. - Cardiovascular Adverse Event (AE)s and Serious AEs (SAEs)

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	any treatment group were hypertension (range: 1% to 2%) and blood pressure increased (range: <1% to 1%). Few AESIs in the CV effects special interest group met the criteria of an SAE (range: 0-4 participants (<1% in all groups). There were 2 CV deaths reported, 1 of circulatory collapse in the FF/VI 200/25 group and 1 of hypertrophic cardiomyopathy in FF/UMEC/VI 100/31.25/25. Neither CV death was considered drug-related. There were few participants with >1 on-treatment MACE (broad definition) in each of the treatment groups (range: 2 to 5 participants [<1% to 1%]. For both the FF 100- and FF 200- containing treatment groups, there was a small difference in the number of narrow MACE in the UMEC 62.5-containing FF/UMEC/VI groups vs FF/VI (1 in both FF/VI 100/25 and FF/UMEC/VI 100/31.25/25, and 3 in 100/62.5/25; 0 in both FF/VI 200/25 and FF/UMEC/VI 200/31.25/25, and 2 in 200/62.5/25. No clinically meaningful differences were observed between FF/UMEC/VI and FF/VI for any ECG parameters, vital signs or laboratory parameters. (Seen in IB Section 5.3.6.1.6.)	will be captured on the electronic Case Report Form (eCRF) (see Section 10.3.3) - Protocol defined stopping criteria as per Section 7.1. In general, if a significant finding is identified after enrolment, the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. - Review AEs/SAEs
Anticholinergic effects (including constipation nausea, dry mouth, glaucoma, raised intraocular pressure and blurred vision, urinary retention)	Umeclidinium is a long-acting muscarinic antagonist, which is often referred to as an anticholinergic. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. When binding on the muscarinic receptor in organs or tissues other than the lung, UMEC might induce certain unwanted effects or disease worsening, ie. dry mouth, worsening of urinary retention, etc. In the completed pivotal asthma study, 205715, the percentage of participants with AESIs in the Anticholinergic syndrome (SMQ) special interest group ranged from 1% to 3% across the treatment groups and the events occurring in >1 participant in any treatment group were dizziness	- Patients with known narrow-angle glaucoma, prostatic hyperplasia or bladder outflow obstruction that, in the opinion of the Investigator, contraindicates study participation or use of an inhaled anticholinergic, will be excluded from participating in the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	(range: 1 to 4 participants [<1% in all groups]), pyrexia (range: 0 to 5 participants [<1% in all groups]), and tachycardia (range: 0 to 3 participants [<1% in all groups]). Dry mouth/drying of the airway secretions (broad focus) special interest group was the most frequently reported special interest group across all treatment groups (range: 22% to 24%), driven by nasopharyngitis (range: 13% to 15%). In the Dry mouth/drying of the airway secretions (narrow focus) special interest group, 2 PTs were reported (dry throat and dry mouth), both occurring in few participants (4 participants and 3 participants, respectively).	- Review AEs/SAEs
Systemic ICS effects -Adrenal suppression -Cataracts & glaucoma -	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 that monitored urinary cortisol. During clinical development of FF & FF/VI no events of Adrenal Suppression were reported. No events were reported in the adrenal suppression AESI group in the completed pivotal asthma study, 205715.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.	- Review AEs/SAEs -. Participants with a medical condition of glaucoma 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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In the completed pivotal asthma study, 205715, 3 events of cataract were reported (one event in FF/VI 200/25; 1 event in FF/UMEC/VI 100/62.5/25 and 1 event in FF/UMEC/VI 200/62.5/25). During studies in both participants with asthma and COPD, no associated effect on ocular disorders was observed. Spontaneous data received to date does not alter the understanding of this risk.	
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 the completed pivotal study in asthma, 205715, there was a similar and low incidence of pneumonia AESIs in the participants in the FF/UMEC/VI (range <1% to 2%) and FF/VI (2%) treatment groups. Thirty-six participants had an on-treatment event in the Infective pneumonia. SMQ) special interest group [<1% to 2%]). For 16 participants the Infective pneumonia (SMQ) AESI was serious. There was a small increase in the number of serious Pneumonia AESIs at FF 200 dose groups (n=10 participants) compared with FF 100 dose groups (n=6 participants). There were no pneumonia AESI with a fatal outcome. In the pneumonia eCRF, there was a similar incidence of on-treatment pneumonia in the FF/UMEC/VI (<1%-2%) and FF/VI (2%) treatment groups. There was a small increase in the number of pneumonia events as FF dose increased, 16 participants at FF 100 doses vs 20 participants at FF 200 doses.	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

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In an 18 study integration in the FF/VI asthma program, the incidence of pneumonia (adjusted for exposure) observed with FF/VI 100/25 and FF 100 (8.5/1000 patient years and 9.6/1000 patient years, respectively) was similar to that seen with placebo (9.3/1000 patient years). A higher incidence in the FF/VI 200/25 and FF 200 arms were observed (18.3/1000 patient years and 23.6/1000 patient years, respectively). However, the 95% CIs were wide and overlapped across all treatment groups, including placebo. Few of the pneumonia events led to hospitalisation with either strength, and there were no observed differences in the incidence of serious events between the two treatment strengths. The risk of pneumonia in asthma patients is very low and is consistent with the risk of other ICS.	of any episodes 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 Review AEs/SAEs.
Hypersensitivity	In the completed pivotal asthma study, 205715, AESI for hypersensitivity were balanced across treatment groups for FF/VI and FF/UMEC/VI (4% to 5%) There have been post-marketing reports of hypersensitivity reactions with FF/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 stearate are excluded from participation in this study (Section 5.2).

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		-Review AEs/SAEs
Paradoxical bronchospasm	Rare reports of paradoxical bronchospasm (which may be life threatening) with other inhalational products have been reported. There have been rare post-marketing reports of paradoxical bronchospasm with FF/VI and UMEC/VI.	Patients will undergo regular medical assessments during clinical studies. -Review AEs/SAEs
Pregnancy and lactation	There are no data from the use of FF/UMEC/VI in pregnant women. There has been limited pregnancy exposure to FF and FF/VI in humans. Animal studies have shown reproductive toxicity after administration of corticosteroids and beta2-agonists. There is a limited amount of data from the use of umeclidinium in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. There is limited information on the excretion of FF or VI or their metabolites in human milk. However, other corticosteroids and beta2-agonists are detected in human milk. It is unknown whether umeclidinium is excreted in human milk. The excretion of FF/UMEC/VI in breast milk has not been evaluated. A risk to breastfed new-borns/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 Section 10.4, Appendix 4.

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

2.3.2. Benefit Assessment

dual combinations of FF/VI has been approved as maintenance therapy for both asthma and COPD and UMEC for COPD in China The addition of UMEC to FF/VI in asthma has the potential to improve lung function, reduce moderate/severe exacerbations and improve quality of life in patients whose asthma is inadequately controlled on ICS/LABA alone. The results of the global Ph IIIa 205715 study established that FF/UMEC/VI provided additional benefit compared with FF/VI in asthma patients ≥18years old who were inadequately controlled despite treatment with ICS plus LABA [Study 205715]. Current asthma treatment guidelines recommend the addition of a LAMA (tiotropium) for patients that are uncontrolled on ICS/LABA (GINA, 2020, Steps 4 and 5); the availability of the FF/UMEC/VI combination would therefore be consistent with this approach. The combination in a single-inhaled triple combination would provide the convenience of once daily dosing and reduce the need for multiple inhalers. Furthermore, the availability of two doses of FF (i.e. FF100/UMEC62.5/VI25 and FF200/UMEC62.5/VI25) would allow the prescriber to select an appropriate inhaled corticosteroid dose based on the severity of asthma.

2.3.3. Overall Benefit: Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in the study, the potential risks identified in association with FF/UMEC/VI are justified by the anticipated benefits that may be afforded to participants with asthma. In addition, the efficacy and safety data in the global Ph IIIa 205715 study has shown positive benefit/risk profile for FF/UMEC/VI in this inadequately controlled asthma population.

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

The ICS/LABA used as run-in (FF/VI) is marketed for the treatment of asthma and has favourable benefit-risk profiles.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the effects of FF/UMEC/VI 100/62.5/25 µg on lung function compared with FF/VI 100/25 µg after 12 weeks of treatment	• Change from baseline in trough FEV_1 at Week 12
Secondary	
• To evaluate the effects of FF/UMEC/VI 200/62.5/25 µg on lung function compared with FF/VI 200/25 µg after 12 weeks of treatment	• Change from baseline in trough FEV_1 at Week 12
Other secondary	
• To evaluate the effects of FF/UMEC/VI compared with FF/VI on asthma control after 12 weeks of treatment	• Change from baseline in ACQ-7 total score at Week 12;
Exploratory objectives	
CCI [redacted]	
Safety	
• To evaluate the safety of FF/UMEC/VI (100/62.5/25 and 200/62.5/25 µg) compared with	• Incidence and type of adverse events • Incidence of exacerbations

Objectives	Endpoints
FF/VI (100/25 and 200/25 µg) throughout the 12-week treatment period.	• Change from baseline in ECG parameters • Incidence of worst vital sign results relative to normal range • Incidence of worst clinical hematological and chemistry results relative to normal range

The primary clinical question of interest is: What is the effect of adding UMEC to FF/VI in a single inhaler when compared with FF/VI on change from baseline in trough FEV_1 after 12 weeks of treatment in Chinese participants with inadequately controlled asthma? This question will be addressed regardless of study treatment discontinuation unrelated to a pandemic or due to pandemic infection and in the absence of study treatment discontinuation due to the indirect impact of a pandemic (e.g. participant or site related impact such as participant unable to collect/obtain study treatment due to restrictions in place, pharmacist not available to conduct the study and maintain the blind).

For this primary clinical question of interest, participant's trough FEV_1 measurements at Week 12 will be used regardless of whether they discontinued study treatment due to pandemic infection (e.g. participant got COVID-19) or for reasons not related to the pandemic. There could be cases of the pandemic at the time of the conduct of this China bridging study and beyond. Given that the disease area of interest is a respiratory disease it is important to estimate the treatment effect regardless of the participant being diagnosed with pandemic infection as this is likely to be the situation that FF/UMEC/VI (if approved and prescribed for asthma) would be taken in. It is unknown currently whether indirect consequences of the pandemic (such as the participant unable to collect/obtain study treatment due to local restrictions/lockdowns) will be an issue at the time of the study, but if participants are unable to collect medication or attend the study site due to concerns around the pandemic (or other operational issues) this is unlikely to be the situation in the future; therefore, we want to estimate the treatment effect in the absence of this.

The primary estimand is described by the following attributes:

- Population: Chinese participants with inadequately controlled.
- Treatment condition: FF/UMEC/VI (100/62.5/25 µg) or FF/VI (100/25 µg) given once daily in the morning (primary treatment comparison is FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25). In addition, rescue albuterol/salbutamol will be provided and is permitted during the study.
- Variable: change from baseline in trough FEV_1 at week 12.
- Summary measure: Mean change from baseline. Comparison: difference in mean change from baseline
- Intercurrent events:
    - Study treatment discontinuation – if related to an indirect impact of a pandemic it will be handled with a hypothetical strategy (i.e. had the intercurrent event not occurred. In this situation, data collected after study

treatment discontinuation will not be included in the statistical analysis and will be treated as missing data). Otherwise it will be handled with a treatment policy strategy and data collected after study treatment discontinuation will be included in the analysis. This will be the primary intercurrent event strategy.

An additional estimand supporting the primary objective is defined similar to the primary estimand except a different intercurrent event strategy will be followed, where study treatment discontinuation due to an indirect impact of the pandemic will be handled with a treatment policy rather than a hypothetical strategy (i.e. all data collected after study treatment discontinuation will be included in the analysis).

The estimand for the secondary objective for FEV1 is the same as the primary estimand except the treatment conditions are FF/UMEC/VI (200/62.5/25 µg) or FF/UMEC/VI (200/25 µg) given once daily in the morning.

4. STUDY DESIGN

4.1. Overall Design

This is a 12-week, Phase III, randomized, double-blind, active controlled, 4-arm parallel group, bridging study in Chinese asthma participants evaluating:

- FF/UMEC/VI (100/62.5/25 µg) versus FF/VI (100/25 µg) and,
- FF/UMEC/VI (200/62.5/25 µg) versus FF/ VI (200/25 µg)

All given once daily in the morning.

Participants who meet all the eligibility criteria at screening (Visit 1), will enter the run-in period for 3 weeks in order to continue to assess the participant's eligibility for the study. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF/VI (100/25 µg via the ELLIPTA dry powder inhaler [DPI]) once a day, taken in the morning, during the 3-week run-in period. Rescue medication (albuterol/salbutamol) will be provided to use on an as-needed basis throughout the study.

At the conclusion of the 3-week run-in period (Visit 2), all participants who meet the additional predefined criteria will be randomised 1:1:1:1 to receive either FF/UMEC/VI (100/62.5/25; 200/62.5/25 µg) or FF/VI (100/25; 200/25 µg) via the ELLIPTA DPI once daily in the morning for the duration of the 12-week treatment period (stratified by pre-study ICS treatment strength [medium, high]).

In accordance with the protocol-defined visit schedule, participants will have two on-treatment clinic visits conducted on an outpatient basis scheduled at Visits 3 (Week 4) and Visits 4 (Week 12). One week following the end of the study (or after the early withdrawal visit) a follow-up telephone call or clinic visit will be performed for safety assessments.

A participant will be considered to have completed the study when he/she has completed all phases of the study including the last scheduled procedure shown in the SoA (Section 1.3).

The end of the study is defined as the date of last scheduled procedure shown in the SoA for the last participant in the trial**.**

Intervention Groups and Duration:

- **Pre-screening:** Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0) must be completed prior to initiating any Visit 1 procedures.
- **Screening / run-in:** Participants who meet all the eligibility criteria at screening (Visit 1), will enter the run-in period for 3 weeks in order to continue to assess the participant's eligibility for the study. Participants satisfying all inclusion/exclusion criteria and who have successfully completed all protocol procedures at screening will be provided with FF/VI (100/25 µg via the ELLIPTA dry powder inhaler [DPI]) once a day, taken in the morning, during the 3-week run-in period. Rescue medication (albuterol/salbutamol) will be provided to use on an as-needed basis throughout the study. The 3-week run-in period is necessary in order to allow participants to become accustomed to using the ELLIPTA DPI as well as to assess the participant's eligibility for the study and collect baseline eDiary data.
- **Randomization and Treatment:** At the conclusion of the 3-week run-in period (Visit 2), all participants who meet the additional predefined criteria will be randomized 1:1:1:1 to receive either FF/UMEC/VI (100/62.5/25; 200/62.5/25 µg) or FF/VI (100/25; 200/25 µg) via the ELLIPTA DPI for the duration of the 12-week treatment period.
  - FF/VI 100/25 µg once daily (QD)
  - FF/VI 200/25 µg QD
  - FF/UMEC/VI 100/62.5/25 µg QD
  - FF/UMEC/VI 200/62.5/25 µg QD

  Study treatment will be administered via the ELLIPTA DPI in the morning.
- **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 4/end of study (EOS) or, if applicable, the Early Withdrawal Visit. A participant will be considered to have completed the study upon completion of all assessments and procedures for Visit 4/EOS and including a successful follow-up contact/visit.

4.2. Scientific Rationale for Study Design

This study will use a multicenter, randomized, double-blind, 4 arm parallel-group design. This is a well-established design to evaluate the efficacy and safety of an investigational drug. A placebo arm is not included as it is not considered appropriate for patients with inadequately controlled asthma despite maintenance therapy.

The primary objective of this study is comparing the efficacy of FF/UMEC/VI administered once daily via a dry powder inhaler, vs FF/VI, in Chinese participants with asthma uncontrolled on ICS/LABA therefore examining the effect of adding UMEC to FF/VI. Trough FEV_1 is a well characterised and accepted endpoint used to assess bronchodilator effects and has shown to be responsive to UMEC with clinically meaningful benefits in the 205715 study.

Assessment of the response after 8-12 weeks is recommended in GINA and China asthma guidelines [GINA, 2020, CAPG, 2016]. This ensures enough time to assess a response to treatment. Relvar (FF/VI) asthma local trials have demonstrated significant improvement in FEV_1 at 12w (China NDA approval in June 2018) with maintenance of effect at Week 24. In addition, the pulmonary function response at 12 weeks is maintained at week 24 in studies of long-acting muscarinic treatments, including UMEC in the global pivotal Phase IIIa study 205715 (CAPTAIN). Thus, we consider that a 12-week study in Chinese asthma patients, in combination with the trough FEV1 data from study 205715 at Week 12, will provide robust data to evaluate the response of asthma patients in China and will minimize the time to bring this medicine to patients.

The study design mirrors the design of study 205715, which demonstrated benefits for a global population of asthma patients uncontrolled on ICS/ LABA. This study will evaluate the effects in Chinese patients and, assuming that effects consistent with the global population are observed, a more precise evaluation of the benefit in this subpopulation will conducted by combing data from the local China study with 205715 using Bayesian dynamic borrowing (see Statistical Considerations in Section 9). The potential to borrow information from the global dataset is based on the premise that the underlying disease, its general management and the response to UMEC is similar in Chinse and non-Chinese patients.

4.3. Justification for Dose

The proposed dose and dosing regimen of FF/UMEC/VI in Chinese patients are 100/62.5/25 and 200/62.5/25 µg once daily, which were included in global pivotal 205715 CAPTAIN study. The dual combinations of FF/VI is available with two doses of FF (100 and 200 µg) combined with VI 25 µg (i.e. 100/25 and 200/25 µg). The global pivotal 205715 CAPTAIN study compared FF/UMEC/VI with the same FF dose of FF/VI (100/62.5/25 or 100/31.25/25 µg vs. 100/25; 200/62.5/25 or 200/31.25/25 vs. 200/25 µg). The objectives of this study are to assess single inhaler triple therapy (FF/UMEC/VI) compared with the same FF dose of FF/ VI in adult Chinese asthma patients (100/62.5/25 vs. 100/25 µg, 200/62.5/25 vs. 200/25 µg).

The 62.5 µg UMEC dose for the FF/UMEC/VI combination has been selected based on data from the pivotal phase III CAPTAIN study. This study demonstrated a clinically

meaningful and statistically significant difference in clinic Trough FEV_1 for UMEC 62.5 containing FF/UMEC/VI treatment groups compared with FF/VI. The numerical difference in trough FEV_1 between the UMEC 31.25- and UMEC 62.5-containing FF/UMEC/VI treatments was small (and it should be noted that the results for groups receiving UMEC 31.25 were not adjusted for multiplicity), but for measures of patient centric outcomes such as asthma control and symptoms a consistently greater effect was observed for UMEC 62.5 containing FF/UMEC/VI treatments compared with UMEC 31.25 containing FF/UMEC/VI treatments. Further, a similar trend was observed for the reduction in annualized rate of moderate/severe exacerbations with FF/UMEC/VI 100/62.5/25 reducing the annualised rate by 21.8% vs 12% for FF/UMEC/VI 100/31.25 /25, both relative to FF/VI 100/25, although the difference was not statistically significant.

Pharmacokinetic (PK) profiles of FF/UMEC/VI as mono- or comb- therapies have been well characterized in Chinese healthy participants. The PK data showed low, dose-dependent systemic exposure and no meaningful PK interactions was observed among the components when combined, which is generally consistent with those in healthy Western participant studies (200587, CTT116415).

In global studies for Trelegy in patients with asthma and COPD indications, systemic exposure of FF, UMEC and VI was low and the PK profiles for the three components showed no clinically relevant difference across ethnicities [205715 PopPK Report GSK Document Number 2018N393131_00; 208059 COPD PK Report GSK Document Number 2017N329683_00].

In COPD studies (208059 COPD PK Report GSK Document 2017N329683_00), that included 15% Chinese patients, consistent systemic exposure of FF, UMEC and VI was observed between Chinese and non-Chinese patients. Some covariates, such as bodyweight, age, smoking etc, were identified as significant covariates on PK in asthma and COPD patients, however, the effects were not considered clinically relevant.

FF/UMEC/VI has a large safety database in patients with asthma in 205715 CAPTAIN study with a total of 2439 patients randomized to the study. Safety data did not identify any new findings for FF/UMEC/VI in the study considering the known class effects of ICS, LAMA and LABAs in a population of patients with asthma. FF/UMEC/VI has a similar safety profile in Japanese asthma patients compared to non-Japanese patients included in the study.

FF/UMEC/VI also has a similar safety profile in Chinese and non-Chinese COPD patients. The safety has been well characterized in large long-term studies across ethnicities and there is a large post marketing safety database globally. As of March 2019, the total cumulative clinical trial exposure was 8,072 patients with 541,890 patient years cumulative marketing experience for FF/UMEC/ VI 100/62.5/25. The safety profile of FF/VI in Chinese and non-Chinese asthma patients is similar.

Based on the information discussed above, the proposed dose and dosing regimen FF/UMEC/VI 100/62.5/25 and 200/62.5/25 µg are considered appropriate to be studied in Chinese participants with asthma.

4.4. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the Schedule of Activities for the last participant in the trial.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last scheduled procedure shown in the Schedule of Activities.

5. STUDY POPULATION

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 18 years or older at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. **Diagnosis:** Participants with documented history asthma diagnosis as defined by the Global Initiative for Asthma [GINA, 2020] at least one year prior to Visit 0.
3. **Symptomatic:** Participants with inadequately controlled asthma (ACQ-6 score $\geqslant$1.5) despite ICS/LABA maintenance therapy at Visit 1.
4. **Current Asthma Maintenance Therapy**: Participants are eligible if they have required daily ICS/LABA for at least 8 weeks prior to Visit 0 with no changes to maintenance asthma medications during the 6 weeks immediately prior to Visit 0 (including no changes to a stable total dose of ICS of >250 µg/day fluticasone proprionate [FP, or equivalent]).

   Examples of acceptable doses of commonly prescribed ICS medication are provided in the GINA guidelines [GINA, 2020]. Dosing regimen (once or twice daily to equal the total daily dose) should be restricted to the current local product labels/treatment guidelines.
5. **Spirometry:**

   A best pre-bronchodilator morning (AM) FEV_1 ≥30% and <85% of the predicted normal value at Visit 1. Predicted values will be based upon the European Respiratory Society (ERS) Global Lung Function Initiative [Quanjer, 2012].
6. **Reversibility of Disease:** airway reversibility defined as ≥12% and ≥200 mL increase in FEV_1 between 20 and 60 minutes following 4 inhalations of albuterol/salbutamol aerosol at Visit 1.

Note: If the 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 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 3-week run-in period (see Section 8.2.1).

7. **Short-Acting β_2 Agonists (SABAs):** All participants 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. Participants must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

Sex

8. Male or female

Contraceptive/Barrier Requirements

Contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:

- Is a woman of non-childbearing potential (WONCBP) as defined in Section 10.4 Contraception and Barrier Guidance;

  OR

- Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, as described in Appendix 4, for the duration of the study – screening to safety follow-up contact. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study intervention.

- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention (see Section 8.3.5: Pregnancy Testing).
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

- Additional requirements for pregnancy testing during and after study intervention are located in Section 8.3.5 Pregnancy Testing
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy

Informed Consent

9. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2. 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 6 weeks prior to Visit 1.
2. **Asthma Exacerbation:** Any asthma exacerbation requiring a change in maintenance asthma therapy in the 6 weeks prior to Visit 1.
    i. *Note: Participants requiring a temporary change in asthma therapy (e.g., oral corticosteroids or increased dose of ICS) to treat an exacerbation in the 6 weeks prior to Visit 1 are not explicitly excluded at Visit 1 provided that, at the Investigator's discretion, the participant's condition is stable after they have resumed their pre-exacerbation maintenance asthma therapy (without modification) and they are considered appropriate for enrolment into this study of up to 12 weeks' duration.*
3. **Chronic Obstructive Pulmonary Disease:** Participants with the diagnosis of chronic obstructive pulmonary disease, as per Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2016) guidelines, including all of the following:
    - History of exposure to risk factors (i.e., especially tobacco smoke, occupational dusts and chemicals, smoke from home cooking and heating fuels). For personal tobacco use, see Exclusion criterion number 14: Tobacco Use;

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

      AND
    - Onset of disease ≥40 years of age
4. **Concurrent respiratory disorders**: Participants with current evidence of pneumonia, active tuberculosis, lung cancer, significant bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung diseases or other active pulmonary diseases or abnormalities other than asthma.

5. **Risk Factors for Pneumonia**: immune suppression (e.g., HIV, Lupus) or other risk factors for pneumonia (e.g., neurological disorders affecting control of the upper airway, such as Parkinson's Disease, Myasthenia Gravis).

   Patients at potentially high risk (e.g., very low BMI, severely malnourished, or very low FEV_1) will only be included at the discretion of the Investigator.
6. **Other diseases/abnormalities**: 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. The Investigator 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:
   - Atrial Fibrillation (AF) with rapid ventricular rate >120 beats per minute (BPM);
   - Sustained or nonsustained ventricular tachycardia (VT);
   - Second degree heart block Mobitz type II and third degree heart block (unless pacemaker or defibrillator had been inserted);
   - QTcF ≥500 msec in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥120 msec
9. **Unstable or life-threatening cardiac disease:** 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 [American Heart Association, 2016]
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

14. **Tobacco Use:** Participants who are:

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

    Note: Refer to the SRM for the formula for calculating pack years.

15. **Drug/alcohol abuse**: Participants with a known or suspected history of alcohol or drug abuse within the last 2 years.

Other Exclusions

16. **Allergy or Hypersensitivity:** A history of allergy or hypersensitivity to any corticosteroid, anticholinergic/muscarinic receptor antagonist, $beta_2$-agonist, lactose/milk protein or magnesium stearate.
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.

5.3. Lifestyle Considerations

Not applicable

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

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

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

- Date of informed consent form (ICF) signature
- Demographic information including race, age and gender
- Participant number
- Investigator signature page

For the purposes of this study pre-screen failures, screening failures and run-in 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 (Randomisation) procedures.
  Any participant who completes the run-in period and then meets the eligibility criteria and is dispensed the treatment period study medication at Visit 2 is considered to have entered the treatment period.

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

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 failure information is required including demography, screen/run-in failure details, eligibility criteria, and any SAEs (see Section 8.4.4 and Section 10.3 Appendix 3). Further details are provided in the study-specific eCRF completion guidelines document.

5.5. Criteria for Randomisation

At the end of the run-in period, a participant will be eligible to enter randomized treatment period of the study if he/she meets the following criteria:

5.5.1. Inclusion Criteria for Randomization

Type of Participant and Diagnosis Including Disease Severity

1. **Inadequately controlled asthma:** Participants with inadequately controlled asthma (ACQ-6 score ≥1.5) at Visit 2.

2. **Percent-predicted FEV_1:** A best pre-bronchodilator morning (AM) FEV_1 ≥30% and <90% of the predicted normal value at Visit 2. Predicted values will be based upon the ERS Global Lung Function Initiative [Quanjer, 2012].

Concurrent Conditions/Medical History

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

Diary

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

5.5.2. Exclusion Criteria for Randomization

Concurrent Conditions/Medical History

1. **Respiratory Infection:** Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the 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. **Severe asthma exacerbation:** Evidence of a severe exacerbation during screening or the run-in period, defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days[1] or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

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

Concomitant Medications/Treatments

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

Diagnostic Assessments And Other Criteria

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

5.6. Criteria for Temporarily Delaying

Temporarily delaying of study intervention administration is not allowed.

6. STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The ELLIPTA device will be used during the run-in period and the treatment period.The ELLIPTA DPI is a moulded plastic two-sided device that can hold two individual blister strips. Descriptions of the study treatments administered via the ELLIPTA are provided in Table 1

Table 1 Description of Study Treatment Inhalation Powder in ELLIPTA

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

Each participant will be instructed on the proper use of the ELLIPTA and will inhale once from the ELLIPTA each morning for the duration of the 3-week run-in period and the subsequent treatment period.

At Visit 2, the run-in period ELLIPTA device will be collected from all participants. All 356 participants will be randomized to one of the 4 double-blind treatment arms 1:1:1:1:

- FF/VI ELLIPTA 100/25 µg QD
- FF/UMEC/VI ELLIPTA 100/62.5/25 µg QD
- FF/VI ELLIPTA 200/25 µg QD
- FF/UMEC/VI ELLIPTA 200/62.5/25 µg QD

Participants will self-administer their first dose of double-blind study treatment in the clinic during Visit 2 and will continue to administer double-blind study treatment at approximately the same time each morning for the duration of the treatment period. Participants will take their last dose of study treatment in the clinic during Visit 4/EOS (or at the Early Withdrawal Visit, if applicable) and a safety follow-up will be conducted approximately one week later.

ARM Name	FF/VI ELLIPTA 100/25 µg QD	FF/UMEC/VI ELLIPTA 100/62.5/25 µg QD	FF/VI ELLIPTA 200/25 µg QD	FF/UMEC/VI ELLIPTA 200/62.5/25 µg QD
Intervention Name	FF/VI ELLIPTA 100/25 µg	FF/UMEC/VI ELLIPTA 100/62.5/25 µg	FF/VI ELLIPTA 200/25 µg	FF/UMEC/VI ELLIPTA 200/62.5/25 µg
Type	Drug	Drug	Drug	Drug
Dose Formulation	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)	ELLIPTA with 30 doses (2 strips with 30 blisters per strip)
Unit Dose Strength(s)	FF100 µg, VI 2 5µg per blister	FF100 µg, UMEC 62.5 µg, VI 25 µg per blister	FF200 µg, VI 25 µg per blister	FF200 µg, UMEC 62.5 µg, VI 25 µg per blister
Dosage Level(s)	one dose daily	one dose daily	one dose daily	one dose daily
Route of Administration	inhaled	inhaled	inhaled	inhaled
Use	active-comparator,	*Experimental*	active-comparator,	*Experimental*
IMP and NIMP	NIMP	IMP	NIMP	IMP
Sourcing	*Provided centrally by the Sponsor*	*Provided centrally by the Sponsor*	*Provided centrally by the Sponsor*	*Provided centrally by the Sponsor*
Packaging and Labeling	Study Intervention will be provided in ELLIPTA. Each ELLIPTA will be labeled as required per country requirement.	Study Intervention will be provided in ELLIPTA. Each ELLIPTA will be labeled as required per country requirement.	Study Intervention will be provided in ELLIPTA. Each ELLIPTA will be labeled as required per country requirement.	Study Intervention will be provided in ELLIPTA. Each ELLIPTA will be labeled as required per country requirement.

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 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.

6.1.1. Study Treatment and albuterol/salbutamol Return

All used and unused study treatment, albuterol/salbutamol will be returned to GSK at the end of the study to be available for disposal. Detailed instructions for the return of the study drug can be found in the 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 IRT system (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 IRT system.

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

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions 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.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
- Further guidance and information for the final disposition of unused study intervention are provided in the Study Reference Manual or other specified location.
- Under normal conditions of handling and administration, study intervention 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.

6.3. Measures to Minimize Bias: Randomization and Blinding

The design is randomized and double-blind. A participant may continue in the study if that participant's intervention assignment is unblinded during the treatment period. Efforts should be made to ensure the data of the participant are collected when possible.

6.3.1. 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 IRT system (RAMOS NG). Once a randomization number is assigned to a participant it cannot be reassigned to any other participant in the study.

Following the 3-week run-in period and participant to satisfying all eligibility criteria, participants will be stratified by pre-study ICS treatment dosage strength (medium, high) at screening and randomized 1:1:1:1 to one of the following four double-blind treatments for the duration of the treatment period:

- FF/VI 100/25 µg QD
- FF/UMEC/VI 100/62.5/25 µg QD
- FF/VI 200/25 µg QD
- FF/UMEC/VI 200/62.5/25 µg QD

all given once daily in the morning.

Randomisation of all participants will be stratified by the participant's pre-study ICS dosage (medium or high). 'Medium' dose ICS will be defined as >250 to ⩽500 µg /day FP (or equivalent), and 'high' dose ICS will be defined as >500 µg /day FP (or equivalent). In the analyses, the actual ICS dose taken prior to the study will be used, not the strata under which the participants are randomised.

The duration of double-blind treatment for each participant is 12 weeks. In accordance with the protocol-defined visit schedule, participants will have two on-treatment clinic visits conducted on an outpatient basis scheduled at Visits 3 (Week 4) and 4 (Week 12). 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 IRT system (RAMOS NG) to randomize participants and manage study treatment supplies (including dispensing) is provided in the RAMOS NG IRT manual and SRM.

6.3.2. 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 as soon as possible 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 reason for the unblinding must be fully documented in the eCRF

GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the intervention 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 intervention assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.4. Study Intervention Compliance

- When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the study site staff.
- When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.
- At scheduled clinic visits, participant compliance with study treatment administration since the previous scheduled clinic visit will be assessed by recording the number of doses remaining in the ELLIPTA, as applicable, in the eCRF (see the SRM for details), by reviewing the eDiary (see Section 8.2.2) and by querying the participant, as necessary. Participants should be ≥80% to ≤120% compliant on taking study treatment between each pair of scheduled and consecutive on-treatment clinic visits. 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.
- When participants self-administer study treatment(s) at home (i.e. not at the study site), compliance with study treatment administration should be monitored by the Investigator (or designee) by reviewing the transmitted eDiary data via the vendor-

provided portal (see Section 8.2.2); participants should be immediately contacted for re-education on treatment compliance if non-compliance (as assessed by the Investigator or designee) is observed. This re-education should be documented in the participant's source document.

- A record of the quantity of ELLIPTAs dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.5. Dose Modification

Not Applicable.

6.6. Continued Access to Study Intervention 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 poststudy care of the participant's medical condition, whether or not GSK is providing specific post-study treatment.

6.7. 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 pages. In the event of an overdose of study treatment, the Investigator should use clinical judgment in treating the overdose and contact the GSK medical monitor.

GSK is not recommending specific treatment guidelines for overdose and toxicity management. The Investigator is advised to refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, adverse events, and other significant data pertaining to the study drug being used in this study. Such documents may include, but not be limited to, the IB or equivalent document provided by GSK.

6.8. Concomitant Therapy

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

All non-asthma medications taken during the study (after randomization including posttreatment) and any changes to concomitant medications will be recorded in the eCRF.

Note: Study provided albuterol/salbutamol should not be recorded in the eCRF; however non-study supplied albuterol/salbutamol and other inhaled short-acting beta2-agonist will be recorded in the eCRF.

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

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

6.8.1. Rescue Medicine

The study site will supply inhaled short-acting beta2-agonist rescue medication that will be provided by the sponsor. The following rescue medication may be used:

- Albuterol/Salbutamol MDI

Rescue albuterol/salbutamol will be provided and is permitted during the study. The number of puffs of albuterol/salbutamol self-administered by the participant each day for the relief of asthma symptoms should be recorded morning and evening in the eDiary.

6.8.2. Permitted Medications and Non-Drug Therapies

6.8.2.1. Permitted Asthma Medications

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

- Study-provided albuterol/salbutamol will be dispensed at Visit 1 for use as relief medication throughout the duration of the study. Participants must be judged capable of withholding albuterol/salbutamol for at least 6 hours prior to study visits.

Temporary additions in medications are permitted for the treatment of 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 medical monitor/Sponsor Information Page):

- An increase in ICS dose (including but not limited to the use of FP which may be used by the participant at a total daily dose deemed appropriate by the Investigator/treating physician).

- Systemic corticosteroids (tablets, suspension or injection) for no more than 2 days (or an increase in systemic corticosteroid dose for those participants receiving maintenance systemic corticosteroids for no more than 2 days).
- An Investigator-advised change in SABA use (i.e., routinely scheduled versus as needed use).
- Leukotriene receptor antagonists (LTRAs) and leukotriene modifiers.
- Oral theophylline.
- By definition, a severe asthma exacerbation will be treated with systemic corticosteroid (tablets, suspension or injection) for at least 3 consecutive days (or at least double the existing maintenance dose of systemic corticosteroid, if applicable, for at least 3 consecutive days). See Section 8.4.7.

6.8.2.2. 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 for other conditions will be permitted.

6.8.2.3. Permitted Non-Drug Therapies

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

6.8.3. Prohibited Medications and Non-Drug Therapies

Use of the medications listed in Table 2 is not permitted during the study.

Table 2 Concomitant Medications

Medication	No use during the study and/or within the following time interval before Visit 1
Inhaled short-acting anticholinergics	6 hours
Inhaled short-acting anticholinergics+ Short-acting beta agonist combination	6 hours
Inhaled long-acting anticholinergics other than study treatment	2 days. Temporary use during the study is also prohibited.
Omalizumab [Xolair]	130 days
Other monoclonal antibodies	5 half-lives
Immunosuppressive medications including immunomodulators	12 weeks
Inhaled long-acting beta$_2$-agonists (e.g., salmeterol, formoterol) or combination products containing inhaled long-acting beta$_2$-agonists (e.g., Seretide, Symbicort) Inhaled very long-acting beta2-agonists, (Indacaterol, Olodaterol) Oral long-acting beta$_2$-agonists (e.g., bambuterol)	These must be withheld at least 24h prior to Visit 1; other than the study treatment, they will not be permitted during the study (including for temporary use). 10 days prior to Visit 1 for Indacaterol and Olodaterol component. Temporary use during the study is also prohibited.
Inhaled short-acting beta$_2$-agonist (rescue albuterol/salbutamol will be provided and is permitted during the study)	6 hours (including all study visits)
Theophyllines, slow-release bronchodilators, ketotifen, nedocromil sodium, sodium cromoglycate, roflumilast	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Systemic corticosteroids	6 weeks. Temporary use will be permitted during the study to treat asthma exacerbations.
Anti-leukotrienes	48 hours. Temporary use will be permitted during the study to treat moderate asthma exacerbations
Medical marijuana	6 months. Medical marijuana administered via the inhaled route is strictly prohibited. Other routes of administration of medical marijuana are also prohibited UNLESS written permission is obtained from the Medical Monitor prior to Visit 1.
Any other investigational drug	30 days or within 5 drug half-lives of the investigational drug (whichever is longer)

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If study intervention is permanently discontinued, the participant will remain in the study, if possible, to be evaluated until the last visit per SOA. See the SOA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

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

Participants who withdraw from double-blind study treatment prematurely (for any reason) should, where possible, continue to be followed-up as per protocol until the completion of the Safety Follow-up assessments. 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 acute 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

7.1.1. Liver Chemistry Stopping Criteria

Liver chemistry stopping, and increased monitoring criteria have been designed to assure participant safety and evaluate liver event etiology.

Discontinuation of study intervention for abnormal liver tests is required when:

- a participant meets one of the conditions outlined in the algorithm or
- in the presence of abnormal liver chemistry not meeting protocol-specified stopping rules, if the investigator believes that it is in the best interest of the participant.

7.1.2. QTc Stopping Criteria

- If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment, the investigator or qualified designee will determine if the

participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

Details on performing ECG assessments can be found in Section 8.3.3.

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

7.1.3. Temporary Discontinuation

Not Applicable

7.1.4. Rechallenge

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

7.2. Participant Discontinuation/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, or compliance reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3) . See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- 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.

7.3. 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, 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.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- If Visit 4 couldn't be done on site due to COVID-19 lockdown, the participant will be provided additional study drug and continue study treatment until they could come back to site for Visit 4; the time window of Visit 4 will be extended for 6 more weeks as the longest after 12 weeks' treatment in these participants.
- Protocol waivers or exemptions are not 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 intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., blood count) and obtained before signing of ICF may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the time frame defined in the SoA.
- Safety/Laboratory/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.
- The maximum amount of blood collected from each participant over the duration of the study will not exceed 24 mL.
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1. Screening and Critical Baseline Assessments

8.1.1. Pre-screening

Participants can perform the pre-screening Visit (Visit 0) up to 2 weeks prior (unless specifically authorised by the medical monitor) to or on the same day as the Screening Visit (Visit 1). A participant number will be assigned at the time the ICF is signed. During the Pre-screening Visit, study designated personnel must provide informed consent to study participants.

Once the informed consent document has been signed, pre-screening assessments can be conducted. The following demographic parameters will be captured: year of birth, sex, race and ethnicity. From the pre-screening visit onwards concomitant medications, exacerbations and SAEs (considered as related to study participation) must be reported.

8.1.2. Screening

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

- 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
- Asthma and other concurrent medications
- ACQ-6
- Pre-and post-albuterol/salbutamol lung function
- Inclusion/Exclusion criteria assessment
- 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 run-in medications and albuterol/salbutamol;
- Provide training of inhalation techniques to participants ensure participants can handle the inhalers correctly;

8.1.3. Critical procedures performed at randomization Visit (Baseline Visit 2)

- Review eDiary and retrain participant if required
- Review Inclusion/Exclusion criteria
- Check randomisation criteria
- Dispense double blind treatment and rescue medications
- Check the inhalation techniques of participants and retrain if needed to ensure participants can handle the inhalers correctly;

8.2. Efficacy Assessments

The timing of all efficacy assessments is documented in the SoA (see Section 1.3).

8.2.1. Pulmonary Function Test

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

Pre-dose Spirometry: At Visits 2 through 4/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 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.

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.

8.2.1.1. Reversibility

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

Percent reversibility will be calculated as follows:

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

Albuterol/Salbutamol

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 3-week run-in period; however, the reversibility assessment may be repeated once within 7 days of Visit 1 if either criteria a) or b) are met:

a) [3]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 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 3-week run-in period.

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

8.2.2. Asthma Control Questionnaire (ACQ)

At the clinic visits, 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 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.

The original ACQ (ACQ-7) measures seven attributes of asthma control [Juniper, 1999]. Six attributes are measured with a patient-completed questionnaire, and the questions are designed to be self-completed by the participant. Participants will complete the ACQ at specified study visits. The six patient-reported questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath, wheeze and rescue medication use) enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a zero (no impairment/limitation) to six (total impairment/ limitation) scale. The recall period is the past week. The seventh attribute of the ACQ-7 is lung function (FEV_1%-predicted) which will be included via study visit spirometry.

Two shortened versions of the ACQ exist. The two shortened versions include the ACQ-5 (a five-item measure using only the symptoms items) and the ACQ-6 (six-item measures and rescue bronchodilator use). The measurement properties were very similar for all versions of the ACQ (original 7-item ACQ and shortened versions) [Juniper, 2005; Wyrwich, 2011]. For all versions, a score of $\leq$0.75 indicates well-controlled asthma and a score $\geq$1.5 indicates poorly controlled asthma [Juniper, 2006]. A change of 0.5 in score suggests a clinically important change in score [Juniper, 2005]. The ACQ-7 (and its shorter versions) have been selected for assessment of asthma control due to their validation and acceptance by the Food and Drug Administration (FDA).

In this study, participants will complete the ACQ-6 at the screening and randomization visits to determine eligibility for the study. ACQ-7 will be evaluated at V2, 3, 4 and EW for efficacy assessment. The ACQ-6 and ACQ-5 will be derived from ACQ-7.

If on-site V3 or V4 or EW could not be conducted within time window due to COVID-19 lockdown, the participant could complete ACQ-6 from home, under the investigator mode (refer to SRM for the details).

8.2.3. Daily Diaries

Participants will be issued with an 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:

- The number of inhalations of rescue albuterol/salbutamol used during the day and night.
- Morning FF/VI medication use (during the run-in period only)
- Morning double-blind study medication use (during the treatment period only)

The data from the eDiary device will be automatically transmitted to a centralised server on a daily basis. The Investigator and designee(s) will be provided with access to the transmitted eDiary data via a vendor-provided portal and should review the data on an ongoing basis to check participant compliance with eDiary use and study treatment administration.

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.

8.2.3.1. Daily Diary Questionnaires, Assessments

Rescue Albuterol/Salbutamol Use

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

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

8.2.4. Alerts

For participants' safety, the following alerts for a change from baseline in rescue medication use that may indicate the worsening of asthma, will be programmed into the eDiary:

- 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.

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

8.3. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.3.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.3.2. Vital Signs

Vital signs will be performed at the time points specified in the SoA (Section 1.3) prior to conducting spirometry and prior to taking the morning dose of study treatment. Blood pressure (systolic and diastolic) and pulse rate will be measured in the sitting position after approximately 5 minutes rest. A single set of values will be collected and recorded in the source documentation and eCRF.

8.3.3. Electrocardiograms

All sites will use standardised ECG equipment provided by a centralized external vendor. At the Screening Visit (Visit 1), a single 12-lead ECG and rhythm strip will be recorded after the measurement of vital signs but before performing the pre-bronchodilator spirometry assessment. At the post-randomization visits, a single 12-lead ECG and rhythm strip will be recorded 15 to 45 minutes after the administration of study treatment. Recordings will be made at the time-points defined in the SoA (Section 1.3). 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 7.1.2).

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.

8.3.4. Clinical Safety Laboratory Assessments

All protocol required laboratory assessments (haematology, clinical chemistry and urinalysis) must be conducted in accordance with the Laboratory Manual, and Protocol SoA (Section 1.3). 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 ranges for all safety parameters will be provided to the site by the laboratory responsible for the assessments.

All blood samples will be sent to a central laboratory for analysis (details provided in the Laboratory Manual). The blood sample will be collected before the participant's dose of asthma treatment on the day of the visit. 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.

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed in Table 3.

Table 3 Protocol Required Safety Laboratory Assessments

Laboratory Assessments	Parameters
Haematology	Platelet Count; RBC Indices:; WBC count with Differential: Red Blood Cell (RBC) Count; Mean Corpuscula Volume (MCV); Neutrophils Hemoglobin; MCH; Lymphocytes Hematocrit; ; Monocytes ; ; Eosinophils ; ; Basophils
Clinical Chemistry [1]	Blood Urea Nitrogen (BUN); Potassium; AST (SGOT); Total and direct bilirubin Creatinine; Sodium; ALT (SGPT); Total Protein Glucose; Calcium; Alkaline phosphatise; Albumin
Routine Urinalysis	• Specific gravity • pH, glucose, protein, blood and ketones by dipstick • Microscopic examination (if blood or protein is abnormal)
Other Screening Tests	• FSH and estradiol (as needed in females of non-reproductive potential only) • Serum/urine hCG Pregnancy test (as specified in the SoA [Section 1.3])
NOTES: • Details of Liver Chemistry Stopping Criteria and Required Actions and Follow-Up Assessments after liver stopping or monitoring event are given in Section 7.1.1 and Appendix 5.	

All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 clinically significant/any 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.

8.3.5. Pregnancy Testing

- Refer to Section 5.1 Inclusion Criteria for pregnancy testing entry criteria.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at scheduled study visits during study intervention period.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in Section 5.1 Inclusion Criteria
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.4. Adverse Events (AEs), Serious Adverse Events (SAEs) and Other Safety Reporting

The definitions of adverse events (AE) or serious adverse events (SAEs) can be found in Section 10.3.

The definitions of unsolicited and solicited adverse events can be found in Section 10.3.

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified 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 intervention or the study, or that caused the participant to discontinue the study intervention or study (see Section 7).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Section 10.3.

8.4.1. Time Period and Frequency for Collecting AE and SAE Information

- All SAEs will be collected from the signature of consent form until the follow-up visit at the time points specified in the SoA (Section 1.3). However, any SAEs assessed as related to study participation (e.g., study intervention, 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.
- All AEs will be collected from the start of intervention until the follow-up visit at the time points specified in the SoA (Section 1.3).
- Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded as Medical History/Current Medical Conditions not as AEs.

- All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. 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 information on AEs or SAEs after the conclusion of the study participation. 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 to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.4.2. Method of Detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AE and/or SAE. 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 medical problems experienced and medications used during the study (please refer to the SRM for further details). This paper worksheet will be used to assist participant recall in discussions with the Investigator (or designee), for site staff to then enter as appropriate in the eCRF.

8.4.3. 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 8.4.8), will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3.

8.4.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention 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 intervention 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.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure (GSK Document

number 2012N131935_10) /IDFU/package insert or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

- 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.

8.4.5. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study intervention and until the safety follow-up contact/visit.
- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to GSK within 24 hours of learning of the female participant pregnancy. While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.4.4. 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 discontinue study intervention. If possible, they could continue to be followed-up as per protocol until the completion of the Safety Follow-up assessments.

8.4.6. Cardiovascular and Death Events

For any cardiovascular events detailed in Section 10.3.3 and all deaths, whether or not they are considered SAEs, specific Cardiovascular (CV) and Death sections of the CRF will be required to be completed. These sections include questions regarding cardiovascular (including sudden cardiac death) and non-cardiovascular death.

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

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

8.4.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs

For the purposes of this study, severe asthma exacerbations will be collected and recorded on the asthma exacerbation eCRF page from the start of randomized double blinded treatment until Visit 4/EOS Visit or the Early Withdrawal Visit for those participants that withdraw from participation in the study (see Section 7). Severe asthma exacerbations should not be recorded as an adverse event unless:

- They meet the definition of an Adverse Event (see Appendix 3) and occur:
  - After the start of study treatment until the start of double blinded study treatment or;
  - After completion of the Visit 4/EOS Visit (or Early Withdrawal Visit) assessments until the follow-up contact

  OR

- They meet the definition of a Serious Adverse Event. (see Appendix 3)

  Note: The SAE page of the eCRF should be completed in addition to the asthma exacerbation eCRF page if the exacerbation occurs after the start of double blinded treatment but before completion of the Visit 4/EOS Visit or Early Withdrawal Visit assessments.

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

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

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

Severe Asthma Exacerbation

A severe asthma exacerbation is defined as:

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

**For participants receiving maintenance systemic corticosteroids, at least double the maintenance systemic corticosteroid dose for at least 3 days is required.*

OR

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

8.4.8. Adverse Events of Special Interest

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

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

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

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

8.4.9. Medical Device

Medical devices are being provided by GSK for use in this study. GSK medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study.

The definition of a Medical Device Deficiency can be found in Section 10.6.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 10.3 of the Protocol Amendment.

Medical Device – this is any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application intended by the manufacturer to be used for human beings for the purpose of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease;
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap;
- investigation, replacement or modification of the anatomy or of a physiological process;
- control of conception

and which does not achieve its principle action in or on the human body by pharmacological, immunological or metabolic means, but may be assisted in its function by such means.

Note: if these means fulfill the main purpose of the product, it is a Medicinal Product. The term medical device includes *in vitro* diagnostic (IVD) devices.

The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study.

Incident – Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health.

Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that

- An incident associated with a device happened and
- The incident was such that, if it occurred again, it might lead to death or serious deterioration in health

A serious deterioration in state of health can include:

- A life-threatening illness (a)
- Permanent impairment of body function or permanent damage to a body structure (b)
- A condition necessitating medical or surgical intervention to prevent (a) or (b)
- Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within the manufacturer's instructions for use
- Fetal distress, fetal death or any congenital abnormality or birth defects

Incidents include, for example:

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

Incidents do not include for example:

- medical occurrences associated with metered-dose inhalers that do not fulfill the definition of a medical device (such events will be reported as medicinal product AEs)
- non-serious medical occurrences which have no further safety implications for the participant or the device

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

Remedial Action – Any action other than routine maintenance or servicing of a device where such action is necessary to prevent recurrence of a reportable incident.

8.4.10. 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 [mm3] 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).

8.4.11. 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.

8.5. Pharmacokinetics

Based on systemic PK properties of FF/UMCE/VI as inhaled drugs, as well as abundant PK data for mono- or comb- therapies available from Chinese healthy and patients in historical studies, the current data are considered adequate for characterizing systemic PK profiles of FF/UMEC/VI in Chinese asthma patients. Therefore, no PK sample collection will be scheduled in the study.

8.6. Genetics and/or Pharmacogenomics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Immunogenicity are not evaluated in this study.

8.9. Health Economics

Health Economics parameters are not evaluated in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypotheses

This is a bridging study designed to evaluate the add-on benefit of UMEC in a single inhaler when compared to FF/VI in Chinese patients. The primary objective is to evaluate the effects of FF/UMEC/VI 100/62.5/25 µg on lung function, as measured by change from baseline in trough FEV1 regardless of study treatment discontinuation unrelated to a pandemic or due to any pandemic infection and in the absence of study treatment discontinuation due to the indirect impact of a pandemic, compared with FF/VI 100/25 µg in Chinese participants with asthma over a 12-week treatment period. The effects of FF/UMEC/VI 200/62.5/25 µg on change from baseline in trough FEV1 at week 12 compared with FF/VI 200/25 µg will also be assessed (secondary objective). The Chinese patient data collected in this study will be supplemented with data on the treatment difference for the same lung function endpoint from the global PhIIIa study 205715, using a Bayesian Dynamic Borrowing approach to analysis of the study (Schmidli, 2014).

A frequentist hypothesis test will not be performed. Instead, the posterior distributions of the difference for both FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg and FF/UMEC/VI 200/62.5/25 µg vs. FF/VI 200/25 µg in trough FEV1 at Week 12 will be derived, based on the Bayesian analysis including the global PhIIIa study 205715 information and the data collected on Chinese patients in this study. The hypothesis of interest for each treatment comparison is that this difference is larger than zero, and the study will be considered to have shown evidence that supports this hypothesis if the posterior probability that the difference is larger than zero is at least 95% (a “positive result”). Please see Section 10.7.1 (Appendix 7) for further information on the choice of posterior probability.

A hierarchical testing approach will be used to test each treatment comparison. If the test for the primary treatment comparison of FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg meets the definition of a positive result then the study will be deemed a success and then the secondary treatment comparison of FF/UMEC/VI 200/62.5/25 µg vs. FF/VI 200/25 µg will then be tested.

9.2. Sample Size Determination

Approximately 890 participants will be screened to achieve 356 randomly assigned to study intervention (89 patients per arm). This sample size denotes the number of participants with trough FEV_1 data at Week 12, regardless of whether they are still on randomized treatment or have discontinued randomized treatment early (for reasons that are NOT an indirect impact of a pandemic). Study treatment discontinuation related to an indirect impact of a pandemic will be handled with a hypothetical strategy. This corresponds to the primary estimand strategy.

The proposed sample size of 89 participants per arm has been determined using a pragmatic approach and reflects ~22% of the global Ph3a study (205715) sample size which would generally satisfy the requirement for a consistency evaluation within a global study. Please see Section 10.7.2 for further information on the selected sample size.

With this sample size, and using Bayesian dynamic borrowing with initial weight of 0.3 on the global 205715 study results (see Section 9.4.2 below), the probabilities of the study achieving a positive result for each treatment comparison under various assumptions about the true treatment difference in Chinese patients are shown in Table 4 (for further details on the a range of possible observed treatment differences in China see Statistical Appendix Section 10.7.3). These probabilities assume a between-individual SD of 350 mL for the primary endpoint (though probabilities are also shown for alternative SDs to assess the sensitivity to the assumed between participant sampling variation). This value was chosen based on results from the global asthma study 205715 (and the Japanese subset from the study) as well as global and Asian FF/VI asthma studies. It is a higher SD than observed in the global 205715 study (approximately 280-305 mL (Japanese subset (225-245 mL) based on the reported standard errors at Week 12 and Week 24), but a conservative estimate was chosen to take into account the higher variability that has been seen in other relevant asthma studies (FF/VI global and Asian studies' SD ranged approximately 300-400 mL).

The probability of a false positive result for the primary treatment comparison (assuming true treatment difference = 0 mL) is 19% (Table 4). This is higher than the typical type 1 error usually applied in fully powered registration studies, but should be considered within the context of the bridging approach. A bridging approach is proposed because of the expected similarity of the treatment difference in Chinese patients and the global population (supported by similarities in the epidemiology, pathophysiology, pharmacology and clinical management of patients and consistency of treatment differences across key demographic factors including ethnicity), and hence there is low probability of the null effect being true.

If the true treatment difference for the primary treatment comparison is 100 mL, the probability of the primary treatment comparison (FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25) meeting the definition of a positive result is 85% (equivalent to the power of the study). If a positive result for the primary treatment comparison in the testing hierarchy is achieved, the secondary treatment comparison (FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25) will be tested and the probability of meeting the definition of a positive result is 83%, assuming the true treatment difference is 100 mL.

Table 4 Probability of Success for a range of possible true treatment differences and varying standard deviation

Treatment comparison	Standard Deviation	Probability of Success[†*]			
		when the true treatment difference is 0 mL (false positive rate)	when the true treatment difference is 60 mL	when the true treatment difference is 86 mL	when the true treatment difference is 100 mL
Primary:	325 mL	19%	63%	81%	88%

Treatment comparison	Standard Deviation	Probability of Success†* when the true treatment difference is 0 mL (false positive rate)	when the true treatment difference is 60 mL	when the true treatment difference is 86 mL	when the true treatment difference is 100 mL
FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25	350 mL	19%	61%	78%	85%
	400 mL	21%	58%	74%	81%
Secondary: FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25	325 mL	16%	60%	78%	86%
	350 mL	18%	58%	76%	83%
	400 mL	19%	55%	72%	79%

†The probability of success values reported for the secondary treatment comparison (FF/UMEC/VI 200/62.5/25 compared to FF/VI 200/25) are only relelvant after obtaining a positive outcome for the primary treatment comparison (FF/UMEC/VI 100/62.5/25 compared to FF/VI 100/25).

*Results based on simulating 10,000 replicate studies and averaging the study results across replications.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	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 & run-in failures) and for the listing of AEs and SAEs for non-randomized participants
Intent-to-Treat (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 analyses. Participants will be analyzed according to the intervention they were randomized to.
Safety Population	All randomized participants who take at least 1 dose of study intervention. This will constitute the primary population for all safety analyses. Participants will be analyzed according to the intervention they actually received.

9.4. Statistical Analyses

The statistical analysis plan will be finalized prior to the lock and unblinding of the database and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.1. General Considerations

For clinic FEV1, the baseline value is the last acceptable/borderline acceptable pre-dose FEV_1 prior to randomized treatment start date (Visit 2).

9.4.2. Efficacy Analyses

Bayesian Dynamic Borrowing Design

Bayesian dynamic borrowing (BDB) provides a clinically and statistically-rigorous method to analyse this China bridging study given an explicit, pre-specified assumption about the relevance of the global 205715 study results to the Chinese population. It is expected that there is a similar benefit: risk profile in Chinese patients as compared to non-Chinese patients. This conclusion is based on the observations that:

- The disease (including its risk factors and pathophysiology) and its management are similar in Chinese and non-Chinese patients CAPG, 2016; Huang, 2019; Lin, 2018]
- Clinical data from multiple studies with the active ingredients (FF/UMEC/VI) in varying combinations and monotherapy in COPD and asthma studies have shown similar risk:benefit profiles for Chinese patients from China and non-Chinese patients [Lin, 2019; 205715 PoPPK Report; CTT11685 GSK Document Number 2017N329683_00; HZA113719 China CSR GSK Document Number 2013N169446_00; HZA113714; HZA106827 CSR GSK Document Number 2011N124014_00; HZA106829 CSR GSK Document Number 2011N128470_01]
- No clinically relevant difference in PK of FF/UMEC/VI is expected between Chinese and non-Chinese asthma patients [205715 PopPK Report GSK Document Number 2018N393131_00, CTT11685, GSK Document Number 2017N329683_00]. The safety profile of FF/ UMEC/ VI (Trelegy) is expected to be similar in Chinese and non-Chinese patients [Lin, 2019; 205715 PopPK Report GSK Document Number 2018N393131_00, Japan asthma ethnosensitivy report GSK Document Number 2019N411703_00; HZA113719 China CSR GSK Document Number 2013N169446_00; HZA106827 CSR GSK Document Number 2011N124014_00]

Using the Bayesian approach, we can test the probability that the treatment difference in change from baseline in trough FEV_1 at Week 12 is greater than 0 mL and assess the extent to which the data from this China bridging study supports the assumption of similarity with global 205715 study results, and obtain an estimate of the true treatment difference in Chinese patients based on a weighted combination of the China results and global results.

The weight given to the global 205715 study data in this estimate is commensurate with the strength of evidence of similarity provided by the China data. The BDB analysis ‘learns’ how much of the global 205715 study information to borrow based on the consistency between the observed treatment differences in the China and global studies and updates the weight on the global 205715 results accordingly.

- The stronger the evidence of consistency, the greater the increase in the updated (posterior) weight on the informative component relative to the prior weight, and hence the greater the borrowing from the global study results.
- Conversely, if the China study results are very different to the global study results, the informative component is down-weighted and final inference is based mostly on the observed data in the China study alone.
- The mechanism by which the weight is updated is entirely pre-specified and mathematically rigorous (Schmidli, 2014)

By borrowing information from the global 205715 study, the data-driven weighted average treatment difference obtained from the BDB analysis is expected to be a more precise estimate of the true treatment difference in China than the observed treatment difference in the China study alone.

The Informative Prior and Prior Weight

The Bayesian dynamic borrowing approach will use the Week 12 results from the global 205715 study as an 'informative' prior for each of the two treatment comparisons of interest in this China bridging study. In the primary analysis for the primary treatment comparison of FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 for change from baseline in trough FEV_1 after 12 weeks in the planned China study, the global prior component is obtained from the sampling distribution of the difference in trough FEV_1 at Week 12 between the FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 arms in the global study 205715. The mean difference and its associated standard error are 86 mL and 20.1 mL, respectively, leading to a Normal distribution with mean 86 and standard deviation 20.1 as the global prior component for the primary treatment comparison.

Similarly, in the primary analysis for the secondary treatment comparison of FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 for change from baseline in trough FEV_1 after 12 weeks in the planned China study, the global prior component is obtained from the sampling distribution of the difference in trough FEV_1 at Week 12 between the FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 arms in the global 205715 study. The mean treatment difference and its associated standard error are 100 mL and 20.0 mL, respectively, leading to a Normal distribution with mean 100 and standard deviation 20.0 as the global prior component for the secondary treatment comparison.

The Week 12 data from the global study was used for the informative prior, as it is expected that the true treatment difference in Chinese participants should be similar to what was observed in the global 205715 study. A second 'weak' prior distribution assuming no knowledge of the treatment difference in China will also be specified, to allow for the possibility that the global 205715 data do not provide relevant information about the treatment difference in Chinese patients. A weighted combination of the 'informative' and 'weak' priors will be used to construct a robust mixture prior. These two components of the mixture prior will be fully pre-specified before the study starts.

In the primary analysis, a prior weight of 30% is proposed for the informative component of the robust mixture prior, with the remainder of the weight (70%) placed on the weak prior to reflect a conservative starting position regarding the assumed relevance of the global 205715 results to Chinese patients. See Statistical Appendix Section 10.7.4 for

more details on the robust mixture prior and Section 10.7.5 for details on the choice of prior weight.

The initial weight (0.3) assigned to the informative global component of the prior will be updated by the data observed in this China bridging study (as described at the start of Section 9.4.2).

Effective Sample Size

The updated weight itself is not directly interpretable as the fraction of the global study sample size that is borrowed. Instead, the effective sample size (ESS) borrowed from the global study can be quantified using the moment method implemented in the RBesT R software package v1.5-3 [Weber, 2019] Table 5 shows the expected value of the ESS borrowed from the global 205715 study for each treatment comparison when the true treatment difference in China is assumed to be 0 mL, 60 mL, 86 mL or 100 mL. This shows that, for both treatment comparisons, the ESS is comparable (in the range 91 to 118 patients' worth of information per arm) to the actual sample size in the China study (89 patients per arm) when true China treatment difference is consistent (in the range 60 mL to 100 mL) with the global study result, providing reassurance that the China data are not overwhelmed by the global study information, even when the global results are highly relevant. The ESS borrowed from the global study is less than half the sample size of the China study when true effect is null (0 mL), providing reassurance that inference would be based mostly on the China data in a scenario where the global study information was not relevant.

Table 5 Expected Effective Sample Size borrowed from the global 205715 study for a range of possible true treatment differences

Treatment comparison	Expected value of Effective Sample Size borrowed per arm from the global 205715 study			
	when the true treatment difference is 0 mL (false positive rate)	when the true treatment difference is 60 mL	when the true treatment difference is 86 mL	when the true treatment difference is 100 mL
Primary: FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25	35	107	116	113
Secondary: FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25	19	91	115	118

*Results based on simulating 10,000 replicate studies and averaging the study results across replications.

Minimum Detectable Difference

The minimum detectable difference (MDD) is the smallest treatment difference for each comparison that needs to be *observed* in this China study in order to meet the pre-specified success criteria when combined with the global 205715 study results via the Bayesian dynamic borrowing analysis. For the proposed sample size of 89 patients per arm, assumed standard deviation of the change from baseline in trough FEV_1 of 350 mL, chosen weight on the global component in the mixture prior of 0.3, and success rule that that posterior probability of the true treatment difference in China being > 0 mL is at least 95%:

- MDD for the FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 comparison is 45 mL
- MDD for the FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 comparison is 49 mL

For each treatment comparison, the MDD needed to conclude positive findings represents a threshold that is approximately 50% of the corresponding treatment difference observed in the global pivotal study 205715 (which were 86 mL and 100 mL for FF/UMEC/VI 100/62.5/25 compared to FF/VI 100/25 and FF/UMEC/VI 200/62.5/25 compared to FF/VI 200/25, respectively).

9.4.2.1. Primary Endpoint

The primary efficacy endpoint is the change from baseline in trough FEV_1 at the end of the 12-week treatment period. For each participant, the baseline value of clinic FEV_1 is the last acceptable/borderline acceptable (pre-dose) FEV_1 value obtained prior to randomization.

The primary efficacy analysis will evaluate the primary estimand in the Intent-to-Treat population (see Section 3 for details of the primary estimand), by first using a mixed-model repeated measures (MMRM) analysis of the observed China study data to get an estimate of the treatment difference for FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 as well as an estimate of the variability. These estimates will then be combined with the global 205715 study using the robust mixture prior to obtain the final posterior distribution for the China treatment difference. The following fixed effects will be included in the model: interaction between treatment group and visit, interaction between baseline trough FEV_1 and visit, pre-study ICS dosage strength (med, high), sex, baseline trough FEV_1, visit and age at screening.

The mean, median and 90% credible interval of this posterior distribution of the treatment difference will be reported, along with the probability that the true difference is greater than zero.

The following informative normal 2-component robust mixture prior will be used for Δ:

$$p(\Delta) = 0.3*N(mean=86, SD=20.1) + 0.7*N(mean=0, SD=494.97)$$

Where Δ is difference for FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 in trough FEV1 at Week 12.

Sensitivity analysis will be conducted to assess the impact of the different prior weights of the two normal components in the robust mixture prior, and the details will be specified in the SAP.

Data collected on- or post-study treatment discontinuation (with the exception of data collected after study treatment discontinuation due to an indirect impact of a pandemic) will be included in the primary efficacy analysis and no imputation of missing data are planned. Missing data are assumed Missing at Random (MAR) handled via Mixed Model Repeated Measures (MMRM) analysis. If necessary, a tipping point analysis may be conducted to assess the impact of missing data and will be detailed in the SAP.

9.4.2.2. Secondary Endpoint

The secondary treatment comparison of FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 for change from baseline in trough FEV_1 after 12 weeks will be conducted as for the primary endpoint except, for the secondary comparison the informative normal 2-component robust mixture prior is:

$$p(\Delta) = 0.3*N(mean=100, SD=20.0) + 0.7*N(mean=0, SD=494.97)$$

Where Δ is difference for FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25 in trough FEV1 at Week 12.

Other Secondary EndpointThe other secondary endpoint of change from baseline in ACQ-7 total score at Week 12 will be analyzed in a descriptive manner with no formal hypothesis testing to be performed. The estimand will be the same as the estimand for the primary endpoint comparison except the variable is the change from baseline in ACQ-7 total score at Week 12. The treatment difference for the change from baseline in ACQ-7 total score at Week 12 will be assessed for each of below comparisons separately:

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

Each comparison will be conducted using the Mixed Model Repeated Measures (MMRM) method, including covariates for treatment group, pre-study ICS dosage strength (med, high), baseline ACQ-7 total score, visit, sex, age at screening, interaction between treatment group and visit, and interaction between baseline ACQ-7 total score and visit. The comparisons will estimate the differences between treatment groups with no p-values to be presented. The LS-means and the associated standard errors of the change from baseline values will be summarized for each treatment group. The estimated treatment difference along with corresponding standard errors and 95% CI will be presented for each of the treatment comparisons.

Full details of the analyses on all efficacy endpoints will be given in the SAP.

9.4.3. Safety Analysis

All safety analyses will be performed on the Safety Population.

Adverse events (AEs) will be coded using the standard GSK dictionary MedDRA, and grouped by body system. The number and percentage of participants experiencing at least one AE of any type, AEs within each body system and AEs within each preferred term will be presented for each treatment group. Separate summaries will be provided for all AEs, drug related AEs, fatal AEs, non-fatal SAEs, adverse events of special interest (AESIs) and AEs leading to withdrawal. Deaths and SAEs, if applicable, will be documented in case narrative format.

9.4.4. Other Analysis

Full details of the analyses to be performed as well as details of time points to be analyzed for the China only data, will be given in the SAP.

9.5. Interim Analysis

No interim analysis is planned in this study.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. 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, IB, Investigational Directions for Use (IDFU] and other relevant documents (e.g., 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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),), European Medical Device Regulation 2017/745 for clinical device research (if applicable), and all other applicable local regulations

10.1.2. 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.

10.1.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the participant or their 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 their legally authorized representative.
- Participants who are rescreened are required to sign a new ICF.
- GSK (alone or working with others) may use participant's coded study data and samples and other information to carry out this study; understand the results of this study; learn more about the study intervention or about the study disease; publish the results of these research efforts; work with government agencies or insurers to have the the study intervention approved for medical use or approved for payment coverage.
- The ICF contains a separate section that addresses the use of participant data and remaining samples for optional further research. The investigator or authorised designee will inform each participant of the possibility of further research not related to the study/disease. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any participant data and/or remaining leftover samples to be used for further research not related to the study/disease. Participants who decline further research will tick the corresponding "No" box.

10.1.4. 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 who will be required to give consent for their data to be used as described in the informed consent.
- 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.

10.1.5. Committees Structure

- Participant safety will be continuously monitored by the study team, which includes safety signal detection at any time during the study
- In particular, data will be reviewed by the Sponsor for identification of the following events that would potentially contribute to a requirement to pause the study.
  - Events considered significantly impact the safety of participants
- Enrollment will be paused during the review. If a pausing rule is met, a decision will be made, based on the review, as to whether enrollment in the study will be allowed to resume.
- Case unblinding may be performed for above reviews if necessary.

10.1.6. Dissemination of Clinical Study Data

- Where required by applicable regulatory requirements, an investigator signatory will be identified for the approval of the clinical study report. The investigator will be provided reasonable access to statistical tables, figures, and relevant reports and will have the opportunity to review the complete study results at a GSK site or other mutually-agreeable location.
- GSK will also provide all investigators who participated in the study with a summary of the study results and will tell the investigators what treatment their participants'' received. The investigator(s) is/are encouraged to share the summary results with the study participants, as appropriate.
- Under the framework of the SHARE initiative, GSK intends to make anonymized participant-level data from this trial available to external researchers for scientific analyses or to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by trial participants are used to maximum effect in the creation of knowledge and understanding. Requests for access may be made through www.clinicalstudydatarequest.com.

- GSK will provide the investigator with the randomization codes for their site only after completion of the full statistical analysis.
- The procedures and timing for public disclosure of the protocol and results summary and for development of a manuscript for publication for this study will be in accordance with GSK Policy.
- A manuscript will be progressed for publication in the scientific literature if the results provide important scientific or medical knowledge.

10.1.7. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in sponsor's TMF system or from vendor data manager.
- Quality tolerance limits (QTLs) will be pre-defined in the QTL plan to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during and at the end of the study and all deviations from the QTLs and remedial actions taken will be summarized in the clinical study report.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the [Monitoring Plan] [contracts].
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25 years from the issue of the final Clinical Study Report (CSR)/ equivalent summary 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.

10.1.8. 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.
- Definition of what constitutes source data and its origin can be found in [Source Data Acknowledgment].
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- 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.

10.1.9. Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the first participant first visit and will be the study start date.

Study/Site Termination

GSK or 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:

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 or no recruitment of participants (evaluated after a reasonable amount of time) by the investigator
- If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up

10.1.10. 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.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in Table 3 will be performed by the central laboratory.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the Protocol Amendment.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

10.3. Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. 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 intervention, whether or not considered related to the study intervention. 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 intervention.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., 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 intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention 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. "Lack of efficacy" or "failure of expected pharmacological action" also 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 (e.g., 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.

10.3.2. Definition of SAE

An SAE is defined as any serious adverse event 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 admitted (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 or significant 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 (e.g. 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. Is a suspected transmission of any infectious agent via an authorised medicinal product
g. Other situations: • Possible Hy's Law case: ALT≥3xULN AND total bilirubin ≥2xULN (>35% direct bilirubin) or international normalized ratio (INR) >1.5 must be reported as SAE • Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that 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. o Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions, or development of intervention dependency or intervention abuse.

10.3.3. Definition of Cardiovascular Events

Cardiovascular Events (CV) Definition:
Investigators will be required to fill out the specific CV event page of the CRF for the following AEs and SAEs: • Myocardial infarction/unstable angina • Congestive heart failure • Arrhythmias • Valvulopathy • Pulmonary hypertension • Cerebrovascular events/stroke and transient ischemic attack • Peripheral arterial thromboembolism • Deep venous thrombosis/pulmonary embolism • Revascularization

10.3.4. Recording and Follow-Up of AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g. hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information.
- 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 required form.
- 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 sufficient 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 intervention 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 intervention 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 submitted documents.
- The investigator will submit any updated SAE data to GSK within 24 hours of receipt of the information.

10.3.5. 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, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours. • 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 (see next section) or to the medical monitor/SAE coordinator by telephone. • Please mail to Qwy11935@gsk.com to report SAE.

SAE Reporting to GSK via Paper Data Collection Tool
• Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the **medical monitor or the SAE coordinator**. • 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 data collection tool within the designated reporting time frames. • Please mail to Qwy11935@gsk.com to report SAE.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions:

Woman of Childbearing Potential (WOCBP)

Women in the following categories are considered WOCBP (fertile):

1. Following menarche
2. From the time of menarche until becoming post-menopausal unless permanently sterile (see below)

Notes:

- 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, confirmation with more than one FSH measurement [insert threshold if required (>40 IU/L or mIU/mL) or remove to allow for flexibility with different local thresholds for defining postmenopausal state] is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen 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.
- Permanent sterilization methods (for the purpose of this study) include:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Woman of Nonchildbearing Potential (WONCBP)

Women in the following categories are considered WONCBP:

1. Premenopausal female with permanent infertility due to one of the following (for the purpose of this study):
   a) Documented hysterectomy
   b) Documented bilateral salpingectomy
   c) Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

2. 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, confirmation with more than one FSH measurement [insert threshold if required (>40 IU/L or mIU/mL) or remove to allow for flexibility with different local thresholds for defining postmenopausal state] is required.
- Females on HRT and whose menopausal status is in doubt must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance:

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly Effective Methods[b] That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Implantable progestogen-only hormone contraception associated with inhibition of ovulation[c]
Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)[c]
Bilateral tubal occlusion
Azoospermic partner (vasectomized or due to a to medical cause)

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days. Note: documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Highly Effective Methods [b] That Are User Dependent Failure rate of <1% per year when used consistently and correctly.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulationc • oral • intravaginal • transdermal • injectable
Progestogen-only hormone contraception associated with inhibition of ovulationc • oral • injectable
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 intervention. 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*
a. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly. c. Male condoms must be used in addition to hormonal contraception. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. Note: Periodic abstinence (calendar, sympto-thermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction)

10.5. Appendix 5: Liver Safety: Required Actions and Follow-up Assessments

Phase III-IV 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).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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

Liver Chemistry Stopping Criteria	
ALT-absolute	ALT ≥ 8xULN
ALT Increase	ALT ≥ 5xULN but <8xULN persists for ≥2 weeks ALT ≥ 3xULN but <5xULN 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 ≥ 5xULN but <8xULN and cannot be monitored weekly for ≥2 weeks ALT ≥ 3xULN but <5xULN 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	
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) • As restart/rechallenge is **not allowed**, permanently discontinue study treatment	• Viral hepatitis serology[4] • Obtain INR and recheck with each liver chemistry assessment until the transaminases values show downward trend • Only in those with underlying chronic Hepatitis B at study entry (identified by positive Hepatitis B surface antigen) quantitative Hepatitis B Deoxyribonucleic acid (DNA) and Hepatitis delta antibody[5]. • Obtain blood sample for pharmacokinetic (PK) analysis, within 28 days after last dose[6]

Liver Chemistry Stopping Criteria	
and continue participant in the study for any protocol specified follow up assessments **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	• 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 medications. • Record alcohol use on the liver event alcohol intake case report form (CRF) page **<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 high performance liquid chromatography (HPLC) assay (quantifies potential acetaminophen contribution to liver injury in participants with definite or likely acetaminophen use in the preceding week [James, 2009]). **NOTE: 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 (HbsAg) and Hepatitis B Core Antibody (IgM); Hepatitis C Ribonucleic acid (RNA); Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody
5. If Hepatitis delta antibody assay cannot be performed, it can be replaced with a PCR of Hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for 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 PK 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 III-IV liver chemistry increased monitoring criteria with continued therapy

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
ALT ≥5xULN and <8xULN **and** bilirubin <2xULN **without** symptoms believed to be related to liver injury or hypersensitivity, **and** who can be monitored weekly for 2 weeks. OR 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 ALT decreases from ALT ≥5xULN and <8xULN to ≥3xULN but <5xULN, continue to monitor liver chemistries weekly. • If, after 4 weeks of monitoring, ALT <3xULN and bilirubin <2xULN, monitor participants twice monthly until liver chemistries normalize or return to within baseline.

10.6. Appendix 6: AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with ISO 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable).
- Both the investigator and the sponsor will comply with all local medical device reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all GSK medical devices provided for use in the study.

10.6.1. Definition of Medical Device AE and ADE

Medical Device AE and ADE Definition
• An AE is any untoward medical occurrence, in a clinical study participant, users, or other persons, temporally associated with the use of study intervention whether or not considered related to the investigational medical device. 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 an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved. • An adverse device effect (ADE) is an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

10.6.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**
a. Led to death
b. Led to serious deterioration in the health of the participant, that either resulted in: • A life-threatening illness or injury. 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. • A permanent impairment of a body structure or a body function.

• Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE. • Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect
d. Is a suspected transmission of any infectious agent via a medicinal product
SADE definition
• A SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. • Any device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.
Unanticipated SADE (USADE) definition
• An USADE (also identified as UADE in US Regulations 21 CFR 813.3), is a serious adverse device effect that by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see Section 2.3).

10.6.3. Definition of Device Deficiency

Device Deficiency Definition
• A device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

10.6.4. Recording and Follow-Up of AE and/or SAE and Device Deficiencies

AE, SAE and Device Deficiency Recording
• When an AE/SAE/device deficiency occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The investigator will then record all relevant AE/SAE/device deficiency information in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form.

- It is not acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by medical monitor. 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 medical monitor.
- 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.
- For device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
    - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a device deficiency. This includes any amendment to the device design to prevent recurrence.

Assessment of Intensity

- The investigator will make an assessment of intensity for each AE/SAE/device deficiency reported during the study and assign it to one 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 sufficient 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 used for rating the intensity of an event; both AEs and SAEs 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.
- Other measures to evaluate AEs and SAEs may be utilized (e.g., National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]).

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/device deficiency
- 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 intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or IDFU or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE/device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/device deficiency 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/SAE/device deficiency

- 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/SAE/device deficiency 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.

10.6.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next table) in order to report the event within 24 hours. • 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 offline 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 (see next section) or to the GSK medical monitor or the SAE coordinator by telephone. • Contacts for SAE reporting can be found in SRM and Investigator Site File.

SAE Reporting to GSK via Paper Data CollectionTool
• Facsimile transmission of the SAE data collection tool is the preferred method to transmit this information to the GSK medical monitor or the SAE coordinator. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper 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 paper data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in SRM and the Investigator Site File.

10.6.6. Reporting of SADEs

SADE Reporting to GSK
NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies. • Any device deficiency that is associated with an SAE must be reported to GSK within 24 hours after the investigator determines that the event meets the definition of a device deficiency.

- GSK will review all device deficiencies and determine and document in writing whether they could have led to an SAE. These device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in SRM and the Investigator Site File.

10.7. Appendix 7: Statistical Appendix

10.7.1. Choice of posterior probability

A 95% posterior probability that the true treatment difference in trough $FEV_1 > 0$ mL represents a high level of confidence for declaring a positive treatment benefit in Chinese patients in the context of a bridging study where substantial evidence of treatment benefit in global (non-Chinese) patients already exists and is aligned with examples of Bayesian decision criteria given in the FDA draft guidance on Complex Innovative Designs [https://www.fda.gov/media/130897/download]. This represents a more rigorous evidentiary threshold than is typically provided by a 'positive trend 'design, which requires only that the *observed* treatment difference > 0.

10.7.2. Choice of Sample size

A total sample size of 356 participants (89 per arm) is considered an achievable sample size for a bridging study, taking into consideration: i) the feasibility of enrollment and the regulatory guidelines for sample size that would generally be required for consistency evaluation in an MRCT global study; and ii) the aim of getting medicines to Chinese patients as quickly as possible in a setting where there is a strong expectation based on clinical and epidemiological data that efficacy in Chinese patients should be similar to that already demonstrated in non-Chinese patients.

10.7.3. A range of possible observed treatment differences in China

The observed treatment differences considered have been selected to represent the following scenarios:

- 0 mL (no difference observed between FF/UMEC/VI and FF/VI)
- 60 mL (this was the minimum detectable difference *in the global 205715 study* that was needed to meet the primary success rule *in the global study 205715* for mean difference in change from baseline trough FEV_1 for both the FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 comparison and the FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 comparison)
- 86 mL (this is the mean difference in change from baseline in trough FEV_1 for FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 at week 12 that was observed in the global 205715 study)
- 100 mL (this is the mean difference in change from baseline in trough FEV_1 for FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 at week 12 that was observed in the global 205715 study)

10.7.4. Overview of the proposed robust mixture prior and analysis strategy

In order to formally incorporate the global 205715 study data in this bridging study, informative robust mixture priors (Schmidli, 2014) for the differences of FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg and FF/UMEC/VI 200/62.5/25 µg vs. FF/VI 200/25 µg will be constructed. These priors will be updated with the China study data to derive the posterior distributions that will be used to test the primary and secondary hypotheses in the hierarchical testing strategy. The priors are a mixture of two normal distributions:

- Component 1 is an informative prior based on change from baseline in trough FEV1 results at week 12 from the global study 205715, referred to as the "global prior".
- Component 2 is a "vague" prior added to enable the prior to down-weight the information from global data in case of conflict between the observed results in the China and global populations.

Denoting the difference (FF/UMEC/VI - FF/VI) as $\Delta\ ^{\delta_P}$, the prior has the form:

$$p(\Delta) = w \cdot p_1(\Delta) + (1\text{-}w) \cdot p_2(\Delta)$$

where $p_1(\Delta)$ $p_1(\delta_P)$is the component containing the information from the global study prior, $p_2(\Delta)$ $p_2(\delta_P)$is the vague component. There is a prior for each of the treatment comparisons of interest.

The Informative (Global) Prior

For the primary treatment comparison of FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 for change from baseline in trough FEV_1 after 12 weeks in this study, the global prior component is obtained from the sampling distribution of the difference in trough FEV_1 at Week 12 between the FF/UMEC/VI 100/62.5/25 vs FF/VI 100/25 arms in the global study 205715 (formally, it is the posterior distribution of this difference obtained by combining the sampling distribution of the observed treatment difference from 205715 with a flat prior distribution). The mean difference and its associated standard error are 86 mL and 20.1 mL, respectively, leading to a Normal distribution with mean 86 and standard deviation 20.1 as the global prior component for the primary treatment comparison.

Similarly, for the secondary treatment comparison of FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 for change from baseline in trough FEV_1 after 12 weeks in this study, the global prior component is obtained from the sampling distribution of the difference in trough FEV_1 at Week 12 between the FF/UMEC/VI 200/62.5/25 vs FF/VI 200/25 arms in the global 205715 study. The mean treatment difference and its associated standard error are 100 mL and 20.0 mL, respectively, leading to a Normal distribution with mean 100 and standard deviation 20.0 as the global prior component for the secondary treatment comparison.

Figure 2 and Figure 3 show density plots of the global priors for each FF dose. The prior probability that the difference is larger than zero is >99% for both treatment comparisons.

Figure 2 Density Plot of Global Prior for Difference in Change from Baseline Trough FEV_1 (FF/UMEC/VI 100/62.5/25 – FF/VI 100/25) at Week 12 (mL)

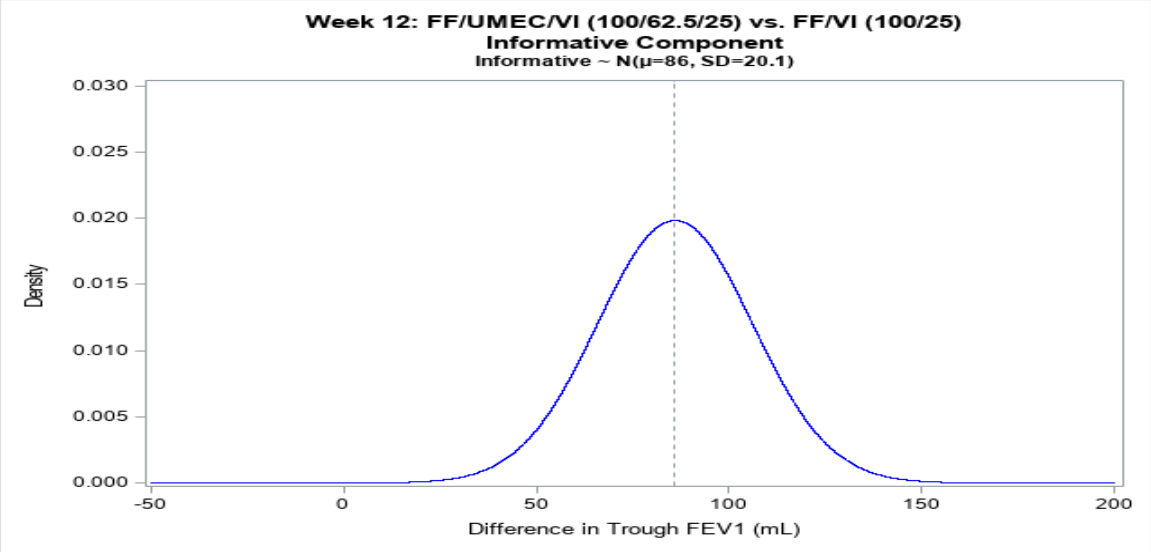
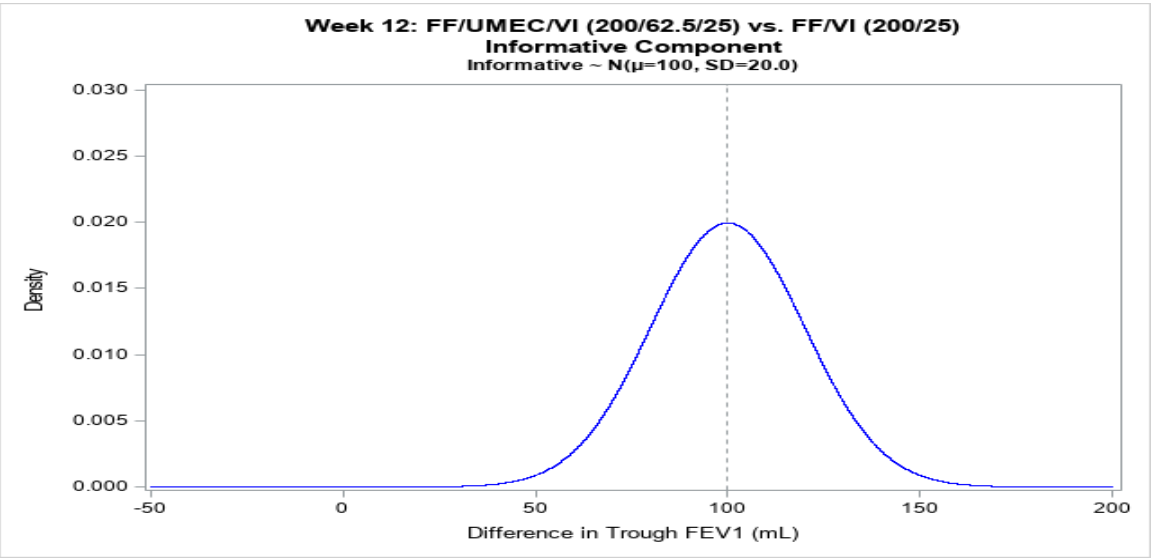


Figure 3 Density Plot of Global Prior for Difference in Change from Baseline Trough FEV_1 (FF/UMEC/VI 200/62.5/25 – FF/VI 200/25) at Week 12 (mL)



The Vague Prior

The vague prior has a mean of 0 mL (i.e. centred at the null hypothesis of no effect in China). The SD of this prior was chosen so that it contains a minimal amount of information equivalent to the sampling distribution of the mean treatment difference derived from a single observation per arm with the assumed SD in the China population. The SD of change from baseline in trough FEV_1 in China is assumed to be 350 mL (see below), and therefore the SD of the vague prior is:

$$\sqrt{\frac{2 \times 350^2}{1}} = 494.97\ mL$$

For both FF/UMEC/VI 100/62.5/25 compared to FF/VI 100/25 and FF/UMEC/VI 200/62.5/25 compared to FF/VI 200/25, the prior probability under this vague prior that the difference is larger than zero is 50%. Note that the assumption about the SD of change from baseline in trough FEV_1, which determines the SD of the vague prior, will not be revisited once the China data is observed. In other words, the two components of the mixture prior will be fully pre-specified before the study starts.

Initial weight on informative (global) prior component and effective sample size borrowed from the global 205715 study

A initial (prior) weight of 30% is proposed (for both treatment comparisons) for the informative global component of the robust mixture prior, with the remainder of the weight (70%) placed on the weak prior to reflect a conservative starting position regarding the assumed relevance of the global 205715 results to Chinese. Combining the two components and their respective weights gives the following 2-component mixture normal:

For FF/UMEC/VI 100/62.5/25 µg vs. FF/VI 100/25 µg:

$p(\Delta) = 0.3*N(mean=86, SD=20.1) + 0.7*N(mean=0, SD=494.97)$

For FF/UMEC/VI 200/62.5/25 µg vs. FF/VI 200/25 µg:

$p(\Delta) = 0.3*N(mean=100, SD=20.0) + 0.7*N(mean=0, SD=494.97)$

Figure 4 and Figure 5 show density plots of the mixture prior for each treatment comparison using the initial weight of 0.3, overlaid on top of the density plots of the two individual components (global and vague). According to these mixture priors, the prior probability that the true treatment difference in China is larger than zero is 65% for both comparisons. (Note that the x-axis in the plots has been truncated (at -50 mL and 200 mL) to focus on the range of values for the true treatment difference that are

supported by the global prior component; the vague prior and the overall mixture prior have long 'tails' with small but non-zero probability of the true treatment difference being greater or less than the range of x-axis values shown).

Figure 4 Density Plot of Mixture Prior and Individual Components for FF/UMEC/VI 100/62.5/25 vs. FF/VI 100/25 in Change from Baseline Trough FEV_1 at Week 12 (mL)

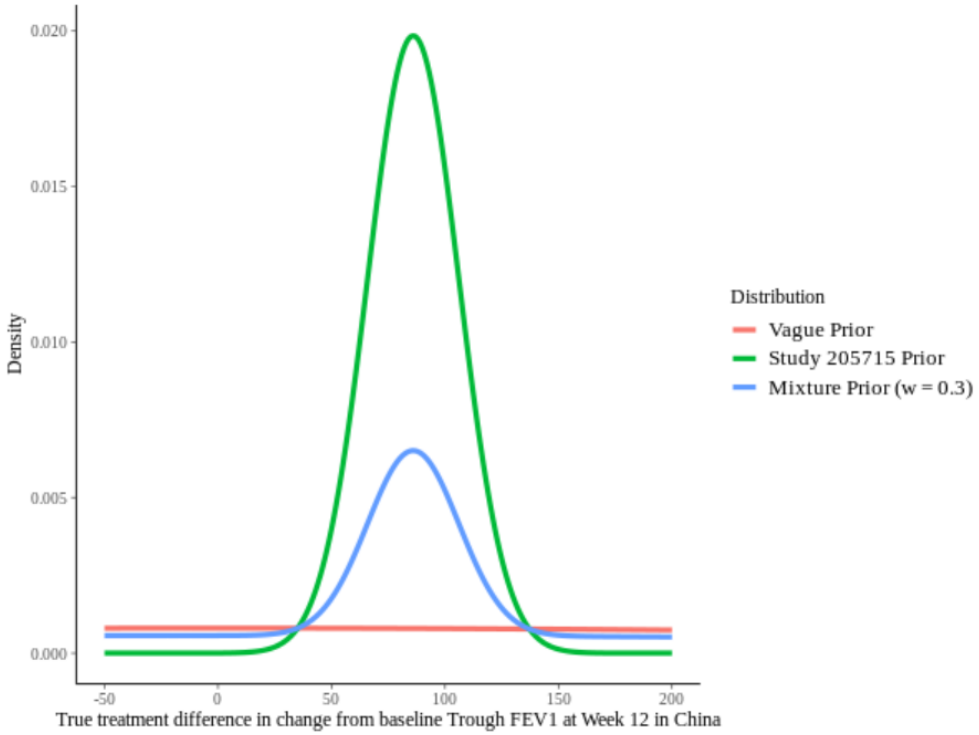
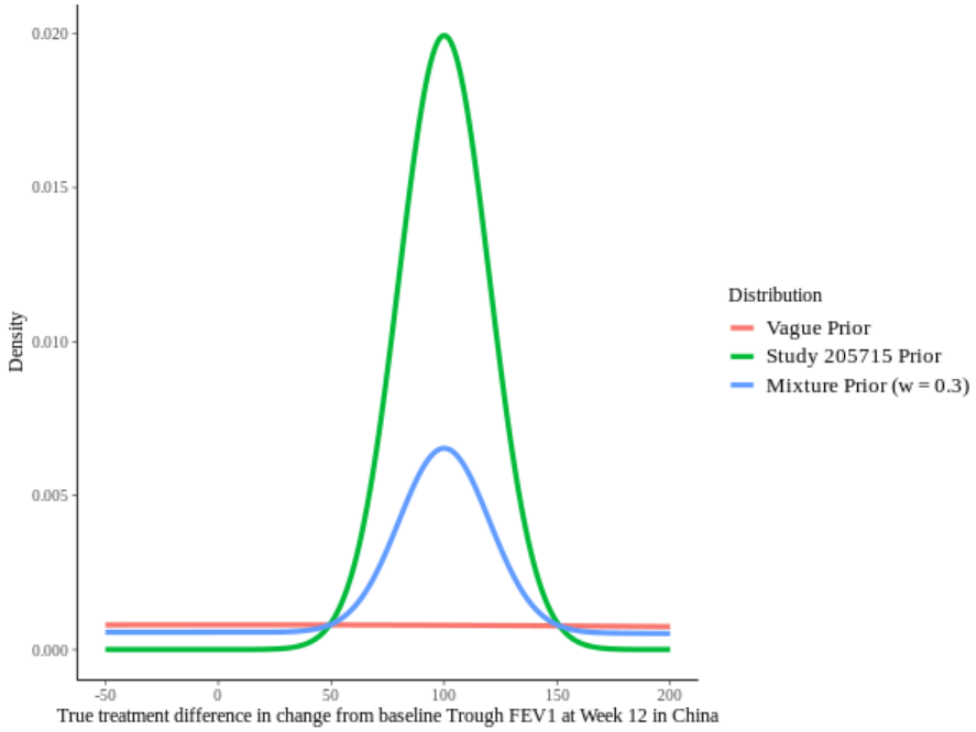


Figure 5 Density Plot of Mixture Prior and Individual Components for FF/UMEC/VI 200/62.5/25 vs. FF/VI 200/25in Change from Baseline Trough FEV1 at Week 12 (mL)



10.7.5. Choice of weights

The scientific grounds for expecting similar benefit:risk profile in China and global study patients justifies a high initial weight on the informative component. However, based on an extensive review of the impact of the prior weight specified for the global 205715 study (prior weights explored were: 0.0, 0.1, 0.2, 0.3, … , 0.9, 1.0) on the operating characteristics of the BDB design, a more conservative prior weight of 30% was felt to provide an acceptable trade-off between the risks of a false positive result and a false negative result, and to enable meaningful gains in precision due to borrowing information from the global study whilst ensuring that the prior does not dominate the posterior completely but allows the observed data in Chinese patients to contribute to the inference from the study.

10.8. Appendix 8: Abbreviations and Definitions and Trademarks

Abbreviations

ACQ	Asthma Control Questionnaire
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Transaminase
AM	Morning
AST	Aspartate Transaminase
ATS	American Thoracic Society
BDB	Bayesian Dynamic Borrowing
BMI	Body Mass Index
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CPAP	Continuous Positive Airway Pressure
CPK	creatine phosphokinase
CV	Cardiovascular
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
EU	European Union
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
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HbO2	Oxyhemoglobin
hCG	Human Chorionic Gonadotropin

HIV	Human Immunodeficiency Virus
HPA	Hypothalamic Pituitary Axis
HR-QoL	Health-Related Quality of Life
HRT	Hormone Replacement Therapy
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroids
IDFU	Investigational Directions for Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	international normalized ratio
IOP	Intraocular Pressure
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to Treat
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IVD	*in vitro* diagnostic
kg	Kilogram
L/min	Liters per minute
LABA	Long-Acting Beta-2-Agonists
LAMA	Long-Acting Muscarinic Antagonist
LAR	legally authorized representative
LDH	lactate dehydrogenase
LOCS III	Lens Opacities Classification System III
LRTI	Lower Respiratory Tract Infection
LTRA	Leukotriene Receptor Antagonist
MACE	Major Adverse Cardiac Event
MAOI	Monoamine Oxidase Inhibitors
MDD	Minimum Detectable Difference
MedDRA	Medicinal Dictionary for Regulatory Activities
mcg (μg)	Microgram
MCV	Mean Corpuscula Volume
MCH	Mean Corpuscular Haemoglobin
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
pH	potential of Hydrogen

PK	Pharmacokinetic
PM	Afternoon
prn	As needed
QD	Once daily
QTLs	Quality tolerance limits
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
RAMOS NG	Registration and Medication Ordering System Next Generation
RBC	Red Blood Cell
RNA	Ribonucleic acid
SABA	Short-Acting Beta-2-Agonists
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGPT	Serum Glutamic-Pyruvic Transaminase
SGOT	Serum Glutamic-Oxaloacetic Transaminase
SPC	Summary of Product Characteristics
SoA	Schedule of Activities
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
WOCBP	Woman of Childbearing Potential
WONCBP	Woman of Nonchildbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline group of companies
NONE

10.9. Appendix 9: 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. 28-Apr-2021

The amendment is substantial.

Overall Rationale for the Amendment:

The amendment is made to meet the requirement from CDE that secondary endpoints need to be added to support the evaluation of the efficacy of treatment, and some additional amendments are also made to provide more clear information.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	The change from baseline of ACQ-7 is added as other secondary endpoint.	The secondary endpoint is added to meet the requirement of CDE to provide more information on efficacy of FF/UMEC/VI to support the assessment.
Section 1.3 Schedule of Activities (SoA)	ACQ is added in the SOA in the "Efficacy assessment", and will be evaluated at V1, 2, 3, 4 & EW. Footnote 8 is newly added to provide more information on how and when the ACQ will be evaluated. Footnote 18: the visit number is revised from "visit 3" to "visit 2".	As ACQ-7, 6&5 are added as endpoints, the activities related to the evaluation of ACQ are added in the SOA. Content in the footnote 8 is added to provide clear instruction. Visit number in footnote 18 is corrected.
Section 3. OBJECTIVES AND ENDPOINTS	The change from baseline of ACQ-7 is added as other secondary endpoint. And other measurement related to ACQ 7, 6 & 5 are also added.	These secondary and exploratory endpoints are added to meet the requirement of CDE to provide more information on efficacy of FF/UMEC/VI to support the assessment.
Section 5.5. Criteria for Randomisation	"At the end of the run-in period (Visit 1)" is changed to "At the end of the run-in period".	The removal of "visit 1" is to avoid confusion.
Section 8.1.4. Questionnaires	This section is removed, and relevant content is combined in Section 8.2.2.	To avoid repetition with the content in Section 8.2.2.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 8.2.2. Asthma control Questionnaire	This section is newly added to provide the introduction of ACQ.	As ACQ is added as a study endpoint, the introduction of this questionnaire is added under efficacy assessment section.
Section 8.2.4. Alerts	Add the threshold for the alerts related to use of rescue mediations.	This is added to specify the threshold for the alert in the eDiary.
Section 8.4.9 Medical Device	Add some content to specify that the definition of a Medical Device Deficiency can be found in Section 10.6, and also the reporting requirement.	To provide information on where to find the definition of Medical Device Deficiency.
Section 9.4.2.2. Secondary Endpoint	Add the content of the analysis method of ACQ-7.	This is to describe the method to be applied for the analysis for ACQ-7.
Section 10.6 Appendix 6 AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies	This section is newly added per GSK's policy.	To provide clear information on the medical device related AEs.
Others	Replace "subject" with "participant" in the document.	To comply with GSK's policy.

11. REFERENCES

American Heart Association. Classes of Heart Failure. Available at: http://www.heart.org/HEARTORG/Conditions/HeartFailure/AboutHeartFailure/Classes-of-Heart-Failure_UCM_306328_Article.jsp (4 May 2016).

China Guideline for the prevention and treatment of bronchial asthma (CAPG) (2016 version). Chin J Tuberc Respir Dis, 2016,39(9):1-24.

FF/UMEC/VI Japan asthma ethnosensitivy report 2019N411703_00: FF/UMEC/VI Single Inhaler Triple Therapy in Japanese Participants with Asthma: Japan Subgroup Analyses of 205715, 04-September-2019

Fluticasone furoate (GW685698) + Umeclidinium (GSK573719) + Vilanterol (GW642444) Investigator's Brochure. Version 10; Document Number 2012N131935_10, 09-SEP-2020.

Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention, 2020. Available from: http://www.ginasthma.org/

Global Strategy for the Diagnosis, Management and Prevention of COPD, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2016. Available from: http://www.goldcopd.org/

GSK Document Number 2017N329683_00 Clinical Pharmacology Study Report: Population Pharmacokinetic Modeling report for Fluticasone Furoate, Umeclidinium and Vilanterol using Pooled Data from three Phase III studies (200812, CTT116853 and CTT116855) in adults with Chronic Pulmonary Obstructive Disease (208059), 10-Jan-2018.

GSK Document Number 2018N393131_00: 205715 PopPK report: Population Pharmacokinetic Modeling of Fluticasone Furoate, Umeclidinium Bromide and Vilanterol Using Data From a Phase III Study (205715) in Subjects with Inadequately Controlled Asthma, 20-August-2019.

Huang K, Yang T, Xu J, Yang L, Zhao JP, Zhang XY, et.al. For the China Pulmonary Health (CPH) Study Group Prevalence, risk factors, and management of asthma in China: a national cross-sectional study. Lancet 2019; 394: 407–18

HZA106827 CSR: GSK Document Number 2011N124014_00: HZA106827: A randomised, double-blind, placebo-controlled (with rescue medication), parallel group multi-centre study of Fluticasone Furoate/GW642444 Inhalation Powder and Fluticasone Furoate Inhalation Powder alone in the treatment of persistent asthma in adults and adolescents, 10-APR-2012

HZA106829 CSR: GSK Document Number 2011N128470_01: HZA106829: A Randomised, Double-Blind, Parallel Group, Multicentre Study of Fluticasone Furoate/GW642444 Inhalation Powder, Fluticasone Furoate Inhalation Powder Alone,

and Fluticasone Propionate Alone in the Treatment of Persistent Asthma in Adults and Adolescents, 30-APR-2012

HZA113714 China CSR: GSK Document Number 2013N161713_00: A Randomized, Double-Blind, Double-Dummy, Parallel Group Study to Evaluate the Efficacy and Safety of Fluticasone Furoate/Vilanterol Trifenatate (FF/VI) Inhalation Powder Delivered Once Daily Compared to Fluticasone Propionate Delivered Twice Daily in the Treatment of Asthma in Adolescent and Adult Subjects of Asian Ancestry Currently Treated with High-Strength Inhaled Corticosteroids or Mid-Strength ICS/LABA Combination Therapy, 20-JUN-2013.

HZA113719 China CSR: GSK Document Number 2013N169446_00: A Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Multicentre Study to Evaluate the Efficacy and Safety of Fluticasone Furoate /Vilanterol Trifenatate (FF/VI) Inhalation Powder Delivered Once Daily for 12 Weeks in the Treatment of Asthma in Adolescent and Adult Subjects of Asian Ancestry Currently Treated with Low To Mid-Strength Inhaled Corticosteroid or Low-Strength Combination Therapy, 23-OCT-2013.

James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen* overdose and acute liver failure. Drug Metab Dispos 2009;37:1779-1784.

Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee. Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. Respir Med 2006;100:616-621.

Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. Eur Respir J 1999;14:902-907.

Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. Respir Med 2005;99:553-558.

Kerstjens H, Casale T, Bleecker E, Meltzer E, Pizzichini E, Schmidt O, et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials. Lancet Respir Med 2015;3:367-76.

Kerstjens HAM, Engel M, Dahl R, Paggiaro P, Beck E, Vandewalker M, et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med 2012;367:1198-207.

Kerstjens HAM, J Maspero, KR Chapman, van Zyl-Smit R, Hosoe M, Tanse A, et al. Once-daily, single-inhaler mometasone–indacaterol–glycopyrronium versus mometasone–indacaterol or twice-daily fluticasone–salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study.Lancet Respir Med (2020)published online July 9.

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

Lin J, Dong Yang, Mao Huang, et.al. Chinese expert consensus on diagnosis and management of severe asthma. J Thorac Dis. 2018 Dec; 10(12): 7020–7044.

Lin J, Huanying Wan, Jian Kang , et. al. Add-on Tiotropium in Chinese Patients With Moderate Asthma: A Pooled Subgroup Analysis of MezzoTinA-Asthma 1 and 2. Allergy Asthma Immunol Res. 2019 Jul;11(4):519-528.

Miller MR et al. Standardization of Lung Function Testing. Eur Resp J 2005;26:153-161.

Price D, Fletcher M, van der Molen T. Asthma control and management in 8,000 European patients: the REcognise Asthma and Link to Symptoms and Experience (REALISE) survey. NPJ Prim Care Respir Med. 2014;24:14009;

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

Roche N., Plaza V., Backer, V. van der Palen V, Cerveri I, Gonzalez C, et al. Asthma control and COPD symptom burden in patients using fixed-dose combination inhalers (SPRINT study). npj Prim. Care Respir. Med. 30, 1 (2020).

Schmidli , H., Gsteiger , S., Roychoudhury , S., O'Hagan , O., Spiegelhalter , D. J., & Neuenschwander , B. (2014). Robust meta-analytic-predictive priors in clinical trials with historical control information. *Biometrics*, 70: 1023-32.

Spiriva Respimat Summary of Product Characteristics, Boerhringer Ingelheim, March 2016. Available from: http://www.medicines.org.uk/emc/medicine/20134/SPC

Weber, S. (2019). RBesT: R Bayesian Evidence Synthesis Tools. R package version 1.5.3. https://CRAN.R-project.org/package=RBesT.

Wyrwich KW, Khan SA, Navaratnam P, Nolte H, Gates Jr DF. Validation and agreement across four versions of the asthma control questionnaire in patients with persistent asthma. Resp Med 2011;105:698-712.

Signature Page for 214263 TMF-14804664 v1.0

Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 18-Jul-2022 16:02:13 GMT+0000

Signature Page for TMF-14804664 v1.0