Protocol

Study ID: 107116

Official Title of Study: A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids

EudraCT Identifier: 2016-004086-87

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Approval Date of Document: 24-AUG-2020

TITLE PAGE

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Protocol Number: HZA107116/04

Short Title: A double-blind, parallel group study to evaluate the safety and efficacy of fluticasone furoate/vilanterol combination compared to fluticasone furoate in the treatment of asthma in participants (aged 5 to 17 years old inclusive)

Compound Number:	GW685698+GW642444

Sponsor Name and Legal Registered Address:

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Regulatory Agency Identifying Number(s): IND No: 077855; EudraCT No: 2016-004086-87

Approval Date: 24-AUG-2020

SPONSOR SIGNATORY:

PPD

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Clinic Respiratory

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Date

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PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Amendment 04	*24-AUG-2020*
Amendment 03	*31-JAN-2020*
Amendment 02	*10-DEC-2019* *This amendment was not implemented at clinical sites.*
Amendment 01	*19-JUN-2019* *This amendment was not implemented at clinical sites.*
Original Protocol	*22-JUN-2017*

Amendment 04: 24-AUG-2020

Overall Rationale for the Amendment: The main purpose of this amendment is to allow the option for certain visits to either be conducted at home by a qualified nurse or replaced by video-calls with the site, when appropriate and if permitted by local regulations. The screening, randomisation and Visit 6 (serial spirometry) will continue to be done in the clinic.

Challenges resulting from the COVID-19 pandemic have the potential to impact the conduct and delivery of the study due to quarantines, site closures and travel limitations. The addition of these flexible visit options will address some of the challenges faced by sites impacted by the pandemic and aid study recruitment and retention by easing the burden on site staff, subjects and parents.

This amendment also includes other minor edits including clarifications to some of the Inclusion/ Exclusion criteria and details for detecting and reporting device deficiencies have been added to Section 11.2.8 and Appendix 7.

Appendix 9 provides details of home nursing and video-calling options are outlined in detail in Appendix 9 (COVID-19 Measures) and the table below summarises the changes made in this amendment.

Section # and Name	Description of Change	Brief Rationale
Protocol Amendment and Summary of Changes Table	Document History updated to include Amendment 4. Minor edits made to the document history table. The rationale for amendment 3 replaced by the rationale for Amendment 4 The table of changes for amendment 3 moved to this Section (Appendix 10)	Updated to include Amendment 4
Table 1: Schedule of Activities	A row added to the table to indicate type of visit e.g. clinic only, home or clinic, video-call or clinic etc Footnote 1 updated to clarify the run-in period for subjects that are re-screened and revise the screening window. Footnote 2 updated to include options of a video-call at Visit 5 and 7 and home visit (if spirometry is done) at Visits. Reference to direct to patient shipment of IP has been included. Footnote 12 corrected so that it applies to the current visit options available. Footnote 15 added to clarify that the subject should be rescheduled, at the earliest opportunity, to collect serial spirometry, if it can not be done at the visit for any reason. Footnote 16 added to refer to the option of direct to patient shipment of IP that may be available to participants who will not be attending the clinic.	This Section has been updated to clarifying existing information and include the options of home visits and video-calls.
Figure 1: Study Schematic	Text below the schematic updated to reflect the home nursing and telemedicine (video-calling options)	Updated to reflect the additional options of home visits and video-calling.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Overall Study Design	Text added to clarify that the run-in period is 4 weeks from screening and remains 4 weeks, if the spirometry is re-tested. Text updated to include the home visit and telemedicine options.	Text has been updated to added clarity with regards to the run-in period and to reflect additional options of home visits and video-calling.
Section 8.1: Inclusion Criteria	The note relating to criteria 3, updated for additional clarity Criteria 6 updated to include SAMA in the definition of stable asthma therapy Criteria 7 updated to include SAMA	Some countries use SAMA instead of SABA as part of their stable asthma therapy regime.
Section 8.2: Exclusion Criteria	The unit measurement for fasting corrected for the fasting blood glucose in criteria 5	Correction of typographical error
Section 8.3: Screen Failures	Clarifying the timing of re-screens following a run-in or screen failure	Updated for clarification
Section 11.1.1: FEV1	Section updated and added to reflect the home visit options.	Updated to reflect the additional options of home visits
Section 11.1.1.1: Serial FEV1	Text added to clarify that the subject should be rescheduled, at the earliest opportunity, to collect serial spirometry, if it cannot be done at the visit for any reason.	Updated for clarification
Section 11.2.8: Medical Device Deficiencies	Section added.	To fulfil regulatory reporting obligations worldwide, this Section outlines the PI's responsibilities for the detection and documentation of events meeting the definitions of device deficiency that occur during the study.
Appendix 1: Abbreviations and Trademarks	CRO added to the list of abbreviations and RELVAR added to the trademarks table.	Updated to include an abbreviation and trademark product used in Appendix 9
Appendix 7: AEs, ADEs, SAEs, SADEs,	Appendix added.	Definition and Procedures for Recording, Evaluating,

Section # and Name	Description of Change	Brief Rationale
USADEs and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies		Follow-up, and Reporting in AEs, ADEs, SAEs, SADEs, USADEs and Device Deficiencies in medical device studies added.
Appendix 9: COVID-19 Measures	Appendix added.	This Appendix has been added to outline the changes that have been made in response to the COVID-19 pandemic
Appendix 10: Protocol Amendment History	This Section has been updated to include the changes made in Amendment 4 The Overall Rationale for Amendment 3 (including the table with the description and rationale for the changes) moved from the Protocol Amendment and Summary of Changes Table at the front of the protocol to this Section (Appendix 8) Changes made to Section 7.7.1 in Amendment 3 have been added to the table with the description and rationale in this Section (Appendix 10)	This Section includes changes made in amendment 4 Details of amendment 3 moved to this Section (Appendix 8) to maintain consistency in where changes to the protocol are being recorded In Amendment 3, changes made to Section 7.7.1 inadvertently excluded from the table of changes has been added

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1. SYNOPSIS

Protocol Title: A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old inclusive currently uncontrolled on inhaled corticosteroids

Short Title: A double-blind, parallel group study to evaluate the efficacy and safety of fluticasone furoate/vilanterol combination compared to fluticasone furoate in the treatment of asthma in participants (aged 5 to 17 years old inclusive)

Rationale:

A variety of asthma medications, generally targeting the inflammatory and/or obstructive components of the disease, may be selected for the treatment of asthma. The evidence-based asthma treatment guidelines recommend a stepwise approach to treat asthma where medications are increased or decreased when appropriate to gain and maintain disease control. For patients with persistent asthma symptoms, the preferred initiating controller medication (step 2 in the step-wise treatment paradigm) is low-dose inhaled corticosteroid (ICS) to target the inflammatory process in asthmatic airways. For children ≥5 years of age and adolescents on low-dose ICS whose asthma is uncontrolled, low-dose ICS plus adjunctive therapy (e.g. long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline) or monotherapy with medium-dose ICS, may all be considered as step 3 care. Due to the lack of comparative data for children ages 5 to 11 years, the step 3 care options are considered equivalent. This study will evaluate the efficacy and safety of fluticasone furoate/vilanterol (FF/VI) compared to fluticasone furoate (FF) in the treatment of asthma in children aged 5 to 17 years old inclusive. FF/VI has not been approved in the US in the adolescent population (12 to 17 years olds) and as a result, a cohort of adolescents is included in this study to further assess efficacy and safety in this population.

Objectives and Endpoints:

Objective	Endpoint	
Primary		
<u>Common to both 5-11 and 5-17 years population</u> • To compare the efficacy of once daily fluticasone FF/VI with once daily FF in participants with asthma. The primary estimand is that of treatment policy	**<u>Primary endpoint for 5-11 years population</u>** • Change from baseline, averaged over weeks 1-12 of the treatment period, in pre-dose (i.e. trough) morning peak expiratory flow (PEF), captured daily via electronic patient diary	**<u>Primary endpoint for 5-17 years population</u>** • Weighted mean FEV_1 (0-4 hours) at week 12. *This is the primary endpoint for the 5-17y population [required by FDA]. This is a secondary endpoint for*

Objective	Endpoint	
(effectiveness-type estimand). The secondary efficacy-type estimand will be defined for the primary and powered secondary endpoints.	*This is the primary endpoint for the 5-11y population [required by EMA]. This is a secondary endpoint for the 5-17 years population.*	*the 5-11 years population.*
	<u>Secondary endpoints common to both 5-11 and 5-17 years population:</u> • Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1-12 of the treatment period (powered secondary endpoint for 5-11 years population) captured daily via electronic patient diary. • Change from baseline in the percentage of symptom-free 24-hour periods over weeks 1-12 of the treatment period, captured daily via electronic patient diary. • Change from baseline in morning (AM) forced expiratory flow in 1 second (FEV_1) in participants who can perform the manoeuvre at week 12. • Change from baseline in Asthma Control Questionnaire (ACQ-5) at week 24. • Incidence of exacerbations over the 24 week treatment period. **<u>Other endpoints common to both 5-11 and 5-17 years population:</u>** • Change from baseline, averaged over weeks 1-12 of the treatment period in evening (PM) PEF, captured daily via electronic patient diary.	
Secondary		
<u>Common to both 5-11 and 5-17 years population</u> • To assess the safety of FF/VI in participants with asthma	• Incidence of adverse events (AEs). • Evaluation of electrocardiogram (ECG) at screening and end of treatment. • Evaluation of fasting blood glucose pre- and post-treatment.	

Overall Design:

This is a randomised, double-blind, parallel group, multicentre, stratified, study designed to evaluate the efficacy and safety of once daily FF/VI inhalation powder compared to once daily FF inhalation powder in the treatment of asthma in participants aged 5 to 17 years inclusive currently uncontrolled on inhaled corticosteroids. The study will be conducted over approximately 29 weeks.

Number of Participants:

Approximately 2900 participants will be screened to achieve a total of 870 randomised participants aged 5 to 17 years old inclusive. Of this, 652 participants will be aged 5 to 11 years (and at least 163 (25%) must be aged 5 to less than 8 years), and 218 participants will be aged 12 to 17 years inclusive.

Treatment Groups and Duration:

After completing a 4-week open-label run-in period (during which all subjects will receive fluticasone propionate (FP) 100 mcg twice daily), eligible subjects, who meet inclusion criteria for randomisation will be stratified by their age at the screening visit (5 to 11 and 12 to 17) and randomised into a 24 week double-blind treatment period followed by a 1 week follow-up period.

Subjects aged 5-11 years of age will be randomised in a 1:1 ratio to one of the following two treatments:

- FF 50 mcg once daily
- FF/VI 50/25 mcg once daily

Subjects aged 12-17 years of age inclusive will be randomised in a 1:1 ratio to one of the following two treatments:

- FF 100 mcg once daily
- FF/VI 100/25 mcg once daily

2. SCHEDULE OF ACTIVITIES (SOA)

The schedule of activities (SOA) in Table 1 details timing of procedures / assessments to be performed in this study.

The timing and number of planned study assessments may be altered during the course of the study based on newly available data to ensure appropriate monitoring.

Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the sponsor and site study files, but will not constitute a protocol amendment. The institutional review board (IRB)/independent ethics committee (IEC) will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the informed consent form (ICF).

Table 1 Schedule of Activities

Procedure	**Screening**	**Pre-randomisation**	**Randomisation**	**Treatment Period (Days, Weeks)**						**ETD**	**EW**	**FU TC (7 days post-last visit)**
Visit	**V1[1]**	**V2**	**V3**	**V4**	**V5**	**V6[15]**	**V7**	**V8**	**V9**			**V10**
Week	**-4 to Day 0**		**0**	**4**	**8[2]**	**12**	**16[2]**	**20[3]**	**24**			**25**
Day (All visits except V2 to occur within -5 to +2 days of specified day)	**-28**	**-5 (-2 to +2)**	**0**	**28**	**56**	**84**	**112**	**140**	**168**			**175**
Type of Visit	**Clinic only**	**Home or Clinic**	**Clinic only**	**Home or Clinic**	**Home[2], Video-call or Clinic**	**Clinic only**	**Video-call or clinic**	**Video-call, Phone-call or clinic**	**Home or Clinic**	**Home or Clinic**	**Home or Clinic**	**Video-call, Phone-call**
Informed consent and assent	X											
Pharmacogenetics consent and assent	←==========		==========→									
Inclusion and exclusion criteria	X[13]											
Randomisation criteria			X									
Demography	X											
Medical history	X											
Asthma history	X											
Exacerbation history	X											

Procedure	Screening	Pre-randomisation	Randomisation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post-last visit)
Visit	**V1[1]**	**V2**	**V3**	**V4**	**V5**	**V6[15]**	**V7**	**V8**	**V9**			**V10**
Week	**-4 to Day 0**		**0**	**4**	**8[2]**	**12**	**16[2]**	**20[3]**	**24**			**25**
Day (All visits except V2 to occur within -5 to +2 days of specified day)	**-28**	**-5 (-2 to +2)**	**0**	**28**	**56**	**84**	**112**	**140**	**168**			**175**
Type of Visit	**Clinic only**	**Home or Clinic**	**Clinic only**	**Home or Clinic**	**Home[2], Video-call or Clinic**	**Clinic only**	**Video-call or clinic**	**Video-call, Phone-call or clinic**	**Home or Clinic**	**Home or Clinic**	**Home or Clinic**	**Video-call, Phone-call**
Full physical exam including, height and weight	X											
EFFICACY ASSESSMENTS												
Electronic patient diary [4]	←==========					==========→				X	X	
FEV_1	X	X		X	X[2]	X				X	X[5]	
FEV_1 review of the overread only			X									
Serial FEV_1						X						
Lung function (FEV_1) reversibility testing[6]	X											
cACT/ACT	X		X									
ACQ			X			X			X			

Procedure	Screening	Pre-randomisation	Randomisation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post-last visit)
Visit	**V1[1]**	**V2**	**V3**	**V4**	**V5**	**V6[15]**	**V7**	**V8**	**V9**			**V10**
Week	**-4 to Day 0**		**0**	**4**	**8[2]**	**12**	**16[2]**	**20[3]**	**24**			**25**
Day (All visits except V2 to occur within -5 to +2 days of specified day)	**-28**	**-5 (-2 to +2)**	**0**	**28**	**56**	**84**	**112**	**140**	**168**			**175**
Type of Visit	**Clinic only**	**Home or Clinic**	**Clinic only**	**Home or Clinic**	**Home[2], Video-call or Clinic**	**Clinic only**	**Video-call or clinic**	**Video-call, Phone-call or clinic**	**Home or Clinic**	**Home or Clinic**	**Home or Clinic**	**Video-call, Phone-call**
SAFETY ASSESSMENTS												
Oropharyngeal examination	X		X						X	X	X[7]	
Concomitant medication review[2]	X		←==========→							X	X	X
12-lead ECG[14]	X								X	X	X[8]	
Vital signs	X											
AE review[2]			←==========→							X	X	X
SAE review[2]	X		←==========→							X	X	X
Exacerbation review[2]			←==========→							X	X	X
LABORATORY ASSESSMENTS												
Blood draw for fasting glucose[9]	X								X	X	X[10]	
Pregnancy Test	X								X	X	X	

Procedure	**Screening**	**Pre-randomisation**	**Randomisation**	**Treatment Period (Days, Weeks)**						**ETD**	**EW**	**FU TC (7 days post-last visit)**
Visit	**V1[1]**	**V2**	**V3**	**V4**	**V5**	**V6[15]**	**V7**	**V8**	**V9**			**V10**
Week	**-4 to Day 0**		**0**	**4**	**8[2]**	**12**	**16[2]**	**20[3]**	**24**			**25**
Day (All visits except V2 to occur within -5 to +2 days of specified day)	**-28**	**-5 (-2 to +2)**	**0**	**28**	**56**	**84**	**112**	**140**	**168**			**175**
Type of Visit	**Clinic only**	**Home or Clinic**	**Clinic only**	**Home or Clinic**	**Home[2], Video-call or Clinic**	**Clinic only**	**Video-call or clinic**	**Video-call, Phone-call or clinic**	**Home or Clinic**	**Home or Clinic**	**Home or Clinic**	**Video-call, Phone-call**
Pharmacogenetic sample (saliva)[11]				X								
STUDY TREATMENT												
Dispense standardised FP run-in medication	X											
Return FP run-in medication			X									
Dispense SABA rescue inhaler	X											
Return SABA rescue inhaler									X		X	

Procedure	Screening	Pre-randomisation	Randomisation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post-last visit)
Visit	**V1[1]**	**V2**	**V3**	**V4**	**V5**	**V6[15]**	**V7**	**V8**	**V9**			**V10**
Week	**-4 to Day 0**		**0**	**4**	**8[2]**	**12**	**16[2]**	**20[3]**	**24**			**25**
Day (All visits except V2 to occur within -5 to +2 days of specified day)	**-28**	**-5 (-2 to +2)**	**0**	**28**	**56**	**84**	**112**	**140**	**168**			**175**
Type of Visit	**Clinic only**	**Home or Clinic**	**Clinic only**	**Home or Clinic**	**Home[2], Video-call or Clinic**	**Clinic only**	**Video-call or clinic**	**Video-call, Phone-call or clinic**	**Home or Clinic**	**Home or Clinic**	**Home or Clinic**	**Video-call, Phone-call**
Treatment assignment (randomisation) via IVRS			X									
Dispense double-blind study treatment via IVRS/IWRS[16]			X	X	X	X	X[12]	X				
Return double-blind study treatment				X	X	X	X	X	X	X	X	

Abbreviations: AE=adverse event; ACT=Asthma control test; cACT=Childhood asthma control test; ACQ=Asthma Control Questionnaire; ECG=electrocardiogram; ETD=early treatment discontinuation; EW=early withdrawal; FEV_1=forced expiratory volume in 1 second; FP=fluticasone propionate; FU=follow-up; IVRS=interactive Voice Response System/Interactive Web Response System; SABA= short-acting beta agonist; SAE=serious adverse event; TC=telephone call; V=Visit.

1. Prior to any study activities at Visit 1, including fasting for the blood glucose test, written informed consent should be obtained from at least one 1 parent/care giver (legal guardian) and accompanying informed assent from the participant (where the participant is able to provide assent).
   Participants who are unable to perform the pre-bronchodilator FEV_1 manoeuvre for any reason or do not provide at least 2 acceptable pre or post bronchodilator measurements [not necessarily repeatable] at Visit 1 can, at the discretion of the investigator, attend the clinic *once more* after Visit 1 to attempt to perform the pre-bronchodilator and post-

bronchodilator FEV_1 manoeuvres. This **should** be within **14 days** of Visit 1. The 4 week run-in will start after eligibility is confirmed following the spirometry re-test. The window for Screening in this case will start at the re-test.

2. Week 8 (Visit 5) and Week 16 (Visit 7) can be parent only visit or video-calls. For these visits, parents may need to come to the site to collect and return any study medication if direct to patient IP shipment is not available for any reason.. Parents should bring the diary to allow for review of concomitant medications, AEs, SAEs and exacerbations. **Note:** If the participant does attend Visit 5 with the parent (or has a home-visit) and the visit occurs during the morning (6.00am to 11.00am) then the spirometry measure **should be** performed. If only the parent attends the clinic, then the visit can be at any time of day.
3. Week 20 (Visit 8) can be a telephone call if there are no problems with compliance.
4. Asthma symptom scores, peak expiratory flow (PEF), rescue albuterol/salbutamol usage will be recorded on the electronic patient diary. To be completed every day in the morning and evening from Visit 1 through to Visit 6 only.
5. FEV_1 is not required at the Early Withdrawal Visit or Early Treatment Discontinuation Visit if these visits occurred after Visit 6.
6. Following administration of 2 to 4 inhalations of albuterol/salbutamol. Reversibility testing includes a baseline spirometry and repeat spirometry within 15 to 40 minutes after inhalation of 400 µg of salbutamol/albuterol. The reversibility test will be considered positive if participants show improvement of FEV1 ≥12% after administration of salbutamol/albuterol.
7. Oropharygneal examination is not required at the Early Withdrawal Visit if examination was performed at Early Treatment Discontinuation Visit.
8. A 12-lead ECG is not required at the Early Withdrawal Visit if it was measured at the Early Treatment Discontinuation Visit.
9. A blood draw is not required at the Early Withdrawal Visit if it was collected at the Early Treatment Discontinuation Visit.
10. A central laboratory will be used.
11. Informed consent for optional substudies, e.g. genetics consent must be obtained before collecting a sample. Sample to be obtained post-randomisation.
12. Two inhalers to be dispensed at Visit 7 as Visit 8 does not need to be in the clinic if there are no problems with compliance.
13. Participants who provide an acceptable spirometry measure at screening but who do not meet the spirometry related inclusion criteria at this visit can be re-screened (see Section 8.3).
14. Single or averaged QTc values of triplicate electrocardiograms to be obtained over a brief (e.g. 5 to 10 minute) recording period – see Section 10.1.2.
15. If the participant is unable to attend the clinic at V6 for any reason, every attempt should be made to bring the participant back to the clinic to collect serial spirometry as soon as possible between Week 12 (Visit 6) and Week 24 (Visit 9).
16. Study medication may be delivered directly to the participant, if the participant is not attending the clinic.

3. INTRODUCTION

3.1. Study Rationale

A variety of asthma medications, generally targeting the inflammatory and/or obstructive components of the disease, may be selected for the treatment of asthma. The evidence-based asthma treatment guidelines recommend a stepwise approach to treat asthma where medications are increased or decreased when appropriate to gain and maintain disease control. For patients with persistent asthma symptoms, the preferred initiating controller medication (step 2 in the step-wise treatment paradigm) is low-dose ICS to target the inflammatory process in asthmatic airways. For children ≥5 years of age and adolescents on low-dose ICS whose asthma is uncontrolled, low-dose ICS plus adjunctive therapy (e.g. long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline) or monotherapy with medium-dose ICS, may all be considered as step 3 care (Global Initiative for Asthma [GINA, 2016; National Institutes of Health NIH, 2007). Due to the lack of comparative data for children ages 5 to 11 years, the step 3 care options are considered equivalent. Fluticasone furoate/vilanterol (FF/VI) has not been approved in the US in the adolescent population (12 to less than 18 years old) and as a result, a cohort of adolescents was included in this study to assess further efficacy and safety in this population.

This study will evaluate the efficacy and safety of fluticasone furoate/vilanterol (FF/VI) compared to fluticasone furoate (FF) in the treatment of asthma. These objectives are common to the two study populations of interest: the 5-11 years (inclusive) population and the 5-17 years (inclusive) population.

The rationale for the study design is provided in Section 7.1.

3.2. Background

Asthma is a chronic disease of the lungs characterized by airway inflammation, bronchoconstriction and increased airway responsiveness. Corticosteroids are the cornerstone of anti-inflammatory therapy for persistent asthma. The goal of asthma treatment is to achieve and maintain asthma control and to reduce the future risk of exacerbations. ICS are considered the most effective anti-inflammatory treatments for all severities of persistent asthma [GINA, 2016; NIH, 2007]. The benefits of ICS include control of asthma symptoms, improvement in lung function, decrease in airway hyper-responsiveness and possibly, prevention of airway wall remodelling [Pedersen, 1997; Fanta, 2009].

FF (GW685698) as the ICS component and vilanterol (VI; GW642444) as the LABA component of the ICS/LABA combination, hereafter referred to as FF/VI, has been approved at the 100/25 mcg and 200/25 mcg dose in over 60 countries for once daily treatment of asthma. FF/VI 100/25 mcg is also indicated for the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema and to reduce exacerbations of COPD in patients with a history of exacerbation.

FF is approved in the United States of America and 10 other countries (Canada, Australia, Chile, Philippines, Switzerland, Singapore, New Zealand, South Korea, Mexico and Japan) for use as a once daily ICS for the maintenance treatment of asthma in patients aged 12 years and over.

The FF and FF/VI paediatric asthma development programmes are currently ongoing.

3.3. Benefit/Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with fluticasone furoate (FF) and fluticasone furoate/vilanterol (FF/VI) can be found in the FF and FF/VI Investigator's Brochures (GlaxoSmithKline Document Number: GM2004/00283/11, GlaxoSmithKline Document Number: RM2008/00012/09).

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

3.3.1. Risk Assessment FF and FF/VI

For FF and FF/VI, the risks associated with inhaled corticosteroids (ICS) and long-acting beta$_2$ agonists (LABA) as well as the mitigation strategy applicable to adults and adolescent asthma patients are also considered applicable to paediatric patients with asthma.

The risks are referenced in the summary of safety concerns in the most recently approved European Union Risk Management Plan (EU-RMP) for FF/VI.

The summary of data/rationale for the risks are referenced from the most currently available development safety update report (DSUR reporting period 03 July 2015 to 02 July 2016) (doc ref number: 2016N278503) and from completed clinical studies since July 2016.

Only those risks considered of clinical significance with respect to the participants included in this study are provided.

Potential risk of Clinical significance	Investigational product	Summary of data/ Rationale for the risk	Mitigation strategy
Pneumonia	FF and FF/VI	Pneumonia is a risk carried by the inhaled corticosteroids class of compounds. An increase incidence of pneumonia with higher doses of ICS cannot be ruled out; however, the absolute risk of pneumonia with FF appears to be very small and consistent with other ICS.	The risk of pneumonia in asthma patients is very low and is consistent with the risk of other ICS. Subjects are alerted to the potential risk of pneumonia in the informed consent. Investigators are informed of the risk in Section 6 Warnings and Precautions Section of the IB. Subjects with concurrent respiratory

Potential risk of Clinical significance	Investigational product	Summary of data/ Rationale for the risk	Mitigation strategy
		For FF; in an integrated analysis of 10 studies in asthma (6219 patients) the incidence of pneumonia seen with FF 100 (8.5/1000 patient years) was similar to placebo (10.8/1000 patient years) and slightly higher with FF 200 (23.6/1000 patient years). Few of the pneumonia events were serious and a similar incidence was observed across all treatment groups. An increase incidence of pneumonia with higher doses of ICS cannot be ruled out; however, the absolute risk of pneumonia with FF appears to be very small and consistent with other ICS. For FF/VI: In an integrated analysis of 18 studies in asthma (10,322 patients), the incidence of pneumonia (adjusted for exposure, due to low numbers and limited number of patients on placebo) seen with FF/VI 100/25 mcg strength (8.5/1000 patient years) was similar to placebo (9.3/1000 patient years). There was a higher incidence of pneumonia in the FF/VI 200/25 mcg strength (18.3/1000 patient years) compared to the FF/VI 100/25 microgram strength. Few of the pneumonia events led to hospitalisation with either strength, and there were no observed differences in the incidence of serious	disease are excluded from the study.

Potential risk of Clinical significance	Investigational product	Summary of data/ Rationale for the risk	Mitigation strategy
		events between the two treatment strengths.	
Hypersensitivity	FF and FF/VI	For FF and FF/VI there were few events reported in the asthma studies. As there was limited, short, exposure to placebo, any comparison is not reliable. Spontaneous reports consistent with hypersensitivity reactions to inhaled FF/VI were identified on the GSK safety database.	Subjects and their parents/guardians will be informed about the risk of hypersensitivity in the informed consent. They will be advised to seek medical treatment if any signs/symptoms of hypersensitivity occur. Subjects with milk protein allergy or known hypersensitivity to FF, the class of ICS or any ingredient of the IP preparation will be excluded from participating in the study. Investigators are informed of this in Section 6 (contra-indications) of the IB.
Systemic corticosteroid effects (adrenal suppression, effects on the eye, growth retardation)	FF and FF/VI	These are class risks carried by all inhaled corticosteroid products. Adrenal suppression No studies have shown a clinically relevant effect of FF/VI on the hypothalamic pituitary axis (HPA). This includes a formal HPA study (HZA106851), using 24 hour serum cortisol measurements, and multiple studies with COPD and asthma subjects which monitored urinary cortisol. A completed 6-week HPA axis study in children aged 5 to 11 years old did not show a clinically relevant effect of FF 50 mcg OD on adrenal function assessed by 24-hour serum cortisol profiles (HZA107118).	Subjects and their parents/ guardians will be informed about the risks in the informed consent. Investigators are made aware of the potential for these class effects in Section 6 (warnings and precautions) of the IB.

Potential risk of Clinical significance	Investigational product	Summary of data/ Rationale for the risk	Mitigation strategy
		Corticosteroid-associated ocular effects In study HZA106839 (FF/VI and FP in subjects with asthma), formal Ophthalmic assessments were conducted (including lens opacities classification system [LOCS] III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated effect on ocular disorders was observed. Growth retardation Children with asthma may experience growth retardation, which has been attributed to the delayed onset of puberty seen in asthmatics relative to non-asthmatics [GINA, 2016). A systematic review of 25 trials involving 8471 (5128 ICS-treated and 3343 control) children with mild to moderate persistent asthma showed that regular use of ICS at low or medium daily doses was associated with a statistically significant reduction in linear growth velocity (14 trials including 5717 participants; MD -0.48 cm/y, 95% confidence interval (CI) -0.65 to -0.30, P value <0.0001) and in change from baseline in height (15 trials including 3275 participants; MD-0.61	

Potential risk of Clinical significance	Investigational product	Summary of data/ Rationale for the risk	Mitigation strategy
		cm/y, 95% CI -0.83 to -0.38, p value <0.00001) during a one-year treatment period. The effect size of ICS on linear growth velocity appeared to be associated more strongly with the ICS molecule than with the device or dose. ICS-induced growth suppression seemed to be maximal during the first year of therapy and less pronounced during subsequent years of treatment. This review did not find an overall effect of ICS during the first three months of treatment [Zhang, 2014]. A recent study demonstrated a reduced mean adult height of 1.2cm (95% CI: -1.9 to -0.5) in subjects who received inhaled budesonide compared to placebo, after use of 4 to 6 years [Kelly, 2012]. A completed knemometry study did not show a clinically significant effect of FF on short term leg growth compared with placebo (HZA107112).	
Serious asthma related events	FF/VI	This is a risk carried by the class of LABA compounds. During the FF/VI studies for the asthma composite endpoint (asthma exacerbations leading to hospitalization, intubation and/or death), there was no significant difference between the FF/VI group and the ICS group or non-LABA group, demonstrating no increased risk when adding a LABA to an ICS.	Subjects with history of life-threatening asthma are excluded from the study. Inclusion criteria for the study require a subject to have their asthma disease controlled by current therapy. Subjects complete daily electronic diary entries for the symptoms of asthma, peak expiratory flow (PEF) and rescue medication use. Subjects will be advised to contact the

Potential risk of Clinical significance	Investigational product	Summary of data/ Rationale for the risk	Mitigation strategy
		Three large completed studies with ICS/LABA compounds (one in paediatric subjects) have shown no increased risk of serious asthma related events compared with ICS alone [Stempel, 2016a; Stempel, 2016b; Peters, 2016].	investigator or their physician immediately.

3.3.2. Benefit Assessment

Inhaled corticosteroids (ICS)

The use of ICS is well established in international treatment guidelines for paediatric asthma patients [GINA, 2016]. The benefits of an ICS include control of asthma symptoms, improvement in lung function and a decrease in airway hyperresponsiveness. In addition subjects will receive SABA for use as needed for relief of asthma symptoms.

Addition of LABA to ICS

Combined treatment with ICS and LABA has been shown to be more effective than the individual components in asthma, leading to the development of fixed dose combination inhalers. The use of ICS/LABA is now well established in international treatment guidelines for patients for whom treatment with an ICS alone is no longer sufficient.

Improved compliance with once-daily treatment regimen

Data with marketed products suggests that compliance improves with less frequent administration and, therefore, it is expected that a once-daily treatment will improve compliance, which may lead to improvements in disease control and reductions in healthcare resource utilisation costs [Price, 2010; Toy, 2011; Wells, 2013].

3.3.3. Overall Benefit:Risk Conclusion

GSK has assessed this study for any potential risks that a subject may experience. The investigational products (FF and FF/VI) have acceptable safety profiles for clinical use. The risks documented for FF and FF/VI belong to the class of products to which FF and FF/VI belong. The data support a positive benefit risk balance for the product. This conclusion is supported by the results of previously conducted clinical studies with the products in healthy volunteers and subjects with asthma and COPD. A safety criterion outlining details for subject discontinuation from IP or early withdrawal is included in the protocol (Section 10). Routine safety analyses of adverse events (AEs) and serious adverse events (SAEs) from this study will be conducted by GSK.

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

For the FP/Salmeterol section, information is taken from the current approved product information of Advair. Since Advair contains an ICS and LABA, the risk mitigation strategies for FF (ICS) and VI (LABA) component will be applicable.

4. OBJECTIVES AND ENDPOINTS

<table>
<tr><th>Objective</th><th colspan="2">Endpoint</th></tr>
<tr><td>Primary</td><td colspan="2"></td></tr>
<tr><td><u>Common to both 5-11 and 5-17 years population</u>
• To compare the efficacy of once daily fluticasone FF/VI with once daily FF in participants with asthma.
The primary estimand is that of treatment policy (effectiveness-type estimand). The secondary efficacy-type estimand will be defined for the primary and powered secondary endpoints</td><td><u>Primary endpoint for 5-11 years population</u>
• Change from baseline, averaged over weeks 1-12 of the treatment period, in pre-dose (i.e. trough) morning peak expiratory flow (PEF), captured daily via electronic patient diary. This is the primary endpoint for the 5-11y population [required by EMA]. This is a secondary endpoint for the 5-17 years population.</td><td><u>Primary endpoint for 5-17 years population</u>
• Weighted mean FEV1 (0-4 hours) at week 12. This is the primary endpoint for the 5-17y population [required by FDA]. This is a secondary endpoint for the 5-11 years population.</td></tr>
<tr><td></td><td colspan="2"><u>Secondary endpoints common to both 5-11 and 5-17 years population:</u>
• Change from baseline in the percentage of rescue-free 24-hour periods over weeks 1-12 of the treatment period (powered secondary endpoint for 5-11 years population) captured daily via electronic patient diary.
• Change from baseline in the percentage of symptom-free 24-hour periods over weeks 1-12 of the treatment period, captured daily via electronic patient diary.
• Change from baseline in morning (AM) forced expiratory flow in 1 second (FEV_1) in participants who can perform the manoeuvre at week 12.</td></tr>
</table>

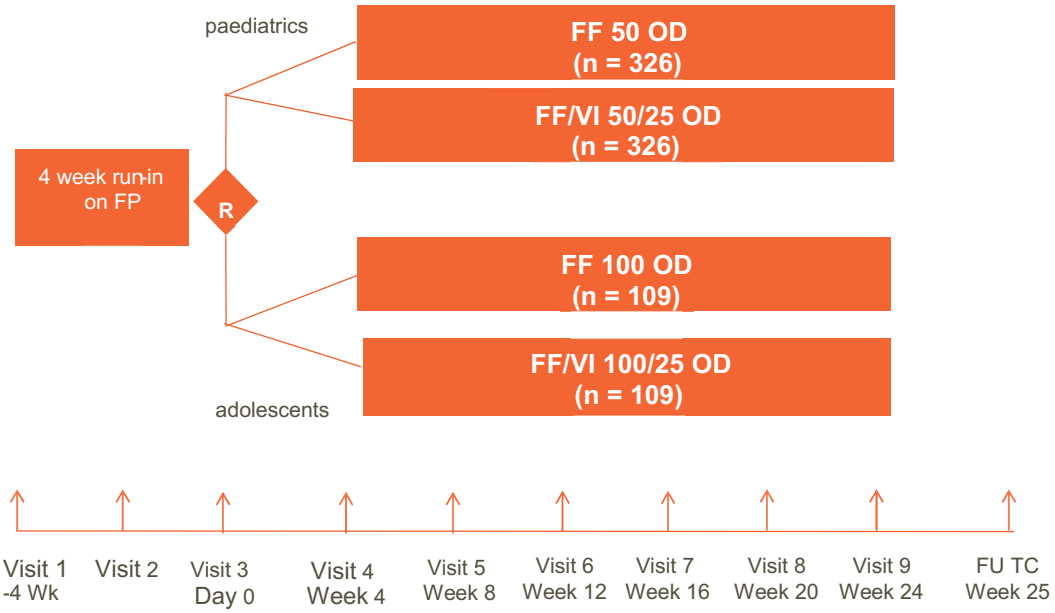
Objective	Endpoint
	• Change from baseline in ACQ-5 at week 24. • Incidence of exacerbations over the 24 week treatment period. **Other endpoints common to both 5-11 and 5-17 years population:** • Change from baseline, averaged over weeks 1-12 of the treatment period in evening (PM) PEF, captured daily via electronic patient diary.
Secondary	
Common to both 5-11 and 5-17 years population • To assess the safety of FF/VI in participants with asthma	• Incidence of adverse events (AEs). • Evaluation of fasting blood glucose pre- and post-treatment.

5. STUDY DESIGN

5.1. Overall Design

This is a randomised, double-blind, stratified, parallel group, multicentre study evaluating the efficacy and safety of once daily FF/VI inhalation powder compared to once daily FF inhalation powder in the treatment of asthma in participants aged 5 to 17 years old inclusive currently uncontrolled on inhaled corticosteroids. The overall study design is shown in Figure 1.

Figure 1 Study Schematic



Visit 1 and 3 must be done in the clinic. Spirometry for V6 must be done in the clinic. Visit 2 is for spirometry only and can be at home or clinic. Visit 5 and Visit 7 can be parent only visits or video-calls. If spirometry is done at Visit it 5, it can be done at home or clinic. Visit 4, 9, ETD and EW can be done in the home or clinic. Visit 8 can be a video-call, phone-call or clinic visit. The FU TC can be a phone-call or video-call.

This study will be conducted over a total duration of approximately 29 weeks: 4 week run-in period, 24-week double-blind treatment period and 1-week follow-up period.

Participants who meet the eligibility criteria at Visit 1 (or after spirometry re-test) will enter a 4 week open-label run-in period. During the 4 week run-in period, all subjects will receive fluticasone propionate (FP) 100mcg twice daily.

After completing the run-in period, eligible participants will be stratified by age (5 to 11 and 12 to 17) and randomised into a 24 week double-blind treatment period, as follows:

- Participants aged 5 to11 years of age will be randomised in a 1:1 ratio to one of the following two treatments:
  - FF 50 mcg once daily in the morning
  - FF/VI 50/25 mcg once daily in the morning
- Participants aged 12 to 17 years of age will be randomised in a 1:1 ratio to one of the following two treatments:
  - FF 100 mcg once daily in the morning
  - FF/VI 100/25 mcg once daily in the morning

Each treatment will be administered via the ELLIPTA dry powder inhaler (formerly referred to as a Novel Dry Powder Inhaler [NDPI]).

In addition, each participant will receive a short acting beta 2 agonist (SABA) (i.e., albuterol/salbutamol [inhalation aerosol or nebuliser]) to be used as needed throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Participants are required to attend the clinic at Visits 1, 3 and 6.. . Visit 2 is for spirometry only and can be at home or in the clinic. Visit 5 and Visit 7 can be parent only visits or video-calls. If spirometry is done at Visit it 5, it can be done at home or in the clinic. Visit 4, Visit 9, ETD and EW can be done in the home or clinic. Visit 8 can be a video-call, phone-call or clinic visit. The FU TC can be a phone-call or video-call. All spirometry (in the clinic or at home) must be started between 6am and 11am.

6. NUMBER OF PARTICIPANTS

Approximately 2900 participants will be screened to achieve a total of 870 randomised participants aged 5 to 17 years, inclusive. Of this, 652 participants will be aged 5 to 11 years (and at least 163 (25%) must be aged 5 to less than 8 years), and 218 participants will be aged 12 to 17 years inclusive.

A 70% screening failure rate is expected.

7. PARTICIPANT AND STUDY COMPLETION

A participant is considered to have completed the study if he/she has completed all visits of the study including the follow-up phone contact as shown in the SOA (Section 2).

A subject will be considered discontinued from study treatment if the subject was randomised, but intentionally and permanently stopped taking study treatment during the treatment period.

A subject will be considered withdrawn from the study if the subject left the study prior to completing all required visits and the follow-up phone contact.

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SOA.

7.1. Scientific Rationale for Study Design

The design of this study has been developed based on advice received from the Food and Drugs Administration (FDA) and the European Medicines Agency (EMA) Scientific Advice Working Party (SAWP) and subsequently agreed with the Paediatric Committee (PDCO) via a modification to the paediatric investigational plan (PIP).

This study is designed to evaluate the efficacy and safety of FF/VI in participants aged 5 to 11 years old with asthma currently uncontrolled on ICS. In addition, the study is designed to evaluate the efficacy and safety of FF/VI in participants aged 5 to 17 years old with asthma that are uncontrolled on ICS. The dose will be FF/VI 50/25 mcg for participants aged 5 to 11 years old and FF/VI 100/25 mcg for participants aged 12 to 17

years old. For each population (5-11 years and 5-17 years), the study is designed to show a statistically significant difference between FF/VI (ICS/ LABA combination therapy) and FF alone (ICS monotherapy), thereby demonstrating the contribution of the LABA (VI).

The treatment duration of the study is 24 weeks, which is considered to be sufficient to evaluate safety. Twelve weeks of treatment is considered to be sufficient to demonstrate efficacy in the proposed study population.

7.2. Dose Justification

The safety and efficacy of a fixed-dose combination of FF 50 mcg and VI 25 mcg in asthmatic children aged 5 to 11 years of age (inclusive) will be evaluated in this study. This will be compared to a dose of FF 50 mcg alone. The doses of each of the components of FF/VI were selected from the results of two Phase IIb studies dose ranging studies HZA106853 for VI and HZA106855 for FF in asthmatic participants aged 5 to 11 years of age (inclusive).

HZA106853 was a dose-ranging study that evaluated 3 doses of VI (6.25 to 25 mcg on a background of ICS) over a 4-week treatment period in children aged 5 to 11 years, who were symptomatic on a low-dose ICS. Taking the totality of the data, lung function and symptoms, into consideration, a 25 mcg dose of VI was considered the most appropriate to take forward into combination with FF in this study.

HZA106855 was a dose ranging study that evaluated 3 doses of FF (25 to 100 mcg) over 12 weeks of treatment in children aged 5 to 11 years with asthma who were symptomatic on a SABA, LTRA or low-dose ICS. Taking the totality of data into consideration, 50 mcg has been selected as the appropriate dose to take forward into combination with VI in this study.

In subjects aged 12 to 17 years of age FF 100mcg has been selected for this study as this is the starting dose currently approved for FF in subjects aged 12 years of age and older. FF/VI 100/25 mcg has been selected as the appropriate dose in this study for this age group based on the data generated from the FF and VI Phase IIb and FF/VI Phase III studies in subjects aged 12 years and older. FF/VI 100/25 is the approved starting dose in over 60 countries for the once daily treatment of asthma.

8. STUDY POPULATION

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

8.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply at Visit 1:

Age

1. Between 5 and 17 years of age inclusive, at the time of screening.

Type of Participant and Disease Characteristics

2. A history of symptoms consistent with a diagnosis of asthma for at least 6 months.
3. Pre-bronchodilator FEV_1 >50% to ≤100% predicted normal. A minimum of 2 efforts that are considered acceptable (not necessarily repeatable) are required to be eligible (see Section 11.1.1).

   NOTE: These FEV_1 measurements **must** be acceptable and **must** meet the FEV_1 inclusion limits (as stated above) and the reversibility requirements (below) to be eligible for the study. Participants who are unable to perform the pre-bronchodilator FEV_1 manoeuvre for any reason or do not provide at least 2 acceptable pre or post bronchodilator measurements [not necessarily repeatable] at Visit 1 can, at the discretion of the investigator, attend the clinic *once more* after Visit 1 to attempt to perform the pre-bronchodilator and post-bronchodilator FEV_1 manoeuvres. This **should** be within **14 days** of Visit 1 **Patients who provide an acceptable spirometry measure, but who do not meet the spirometry related criteria (Inclusion criteria 3 and 4) are considered screen failures but can be re-screened (see Section 8.3).**

4. Lung function reversibility defined as an increase of ≥12% in FEV_1 within 15 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation aerosol (or 1 nebulised treatment with albuterol/salbutamol solution). Use of a spacer is permitted.

   NOTE: Participants who meet inclusion criteria 3 with a technically acceptable pre-bronchodilator FEV_1 manoeuvre at Visit 1, but are then unable to perform the technically acceptable post-bronchodilator FEV_1 needed for reversibility can, at the discretion of the investigator, attend the clinic *once more* after Visit 1 to attempt to perform both the pre-bronchodilator and post-bronchodilator FEV_1 manoeuvres again. This **should** be within **14 days** of Visit 1. These FEV_1 measurements must be acceptable and must meet the FEV_1 inclusion limits and the reversibility requirements to be eligible for the study. **Patients who provide an acceptable spirometry measure, but who do not meet the spirometry related criteria (3 and 4) can be re-screened (see Section 8.3).**

5. Uncontrolled asthma, with a cACT/ACT score ≤19.

6. Receiving stable asthma therapy (SABA or SAMA inhaler plus ICS [total daily dose ≤FP 250 mcg or equivalent])for at least 4 weeks prior to Visit 1 (i.e., screening).

7. Able to replace their current SABA/SAMA treatment with salbutamol/albuterol aerosol inhaler at Visit 1 for use as needed for the duration of the study. Salbutamol/albuterol metered dose inhaler (MDI) will be administered with or without a spacer, to be used as determined by the investigator. The use or non-use of the spacer should be consistent for an individual participant throughout the study.

Sex

8. Male or female participants

   Females of reproductive potential must agree to follow 1 of the options listed (which include abstinence) in the Modified List of Highly Effective Methods for Avoiding Pregnancy in Females of Reproductive Potential (FRP) (see Section 14.4) from 30 days prior to the first dose of study medication and until at least five terminal half-lives OR until any continuing pharmacologic effect has ended, whichever is longer after the last dose of study medication and completion of the follow-up call. The investigator is responsible for ensuring that participants understand how to properly use these methods of contraception.

   Note: Any female participant who is lactating (breastfeeding) will **not** be included in the study.

Informed Consent

9. Written informed consent from at least 1 parent/care giver (legal guardian) and accompanying informed assent from the participant (where the participant is able to provide assent) prior to admission to the study.
   - If applicable, participant must be able and willing to give assent to take part in the study according to the local requirement. The study investigator is accountable for determining a child's capacity to assent to participation in a research study, taking into consideration any standards set by the responsible IEC.
   - Participant and their legal guardian(s) understand that the study requires them to be treated on an outpatient basis.
   - Participant and their legal guardian(s) understand that they must comply with study medication and study assessments including recording of PEF and rescue SABA use, attending scheduled study visits, and being accessible by a telephone call.

8.2. Exclusion Criteria

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

Medical Conditions

1. A history of life threatening asthma defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea, respiratory arrest or hypoxic seizures.
2. Any asthma exacerbation requiring the use of oral steroids within 6 weeks of Visit 1, systemic or depot corticosteroids within 12 weeks of Visit 1, OR ER attendance within 3 months of Visit 1 OR hospitalisation within 6 months of Visit 1.

3. A culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that has not resolved within 4 weeks of Visit 1 and which 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.
4. Clinical visual evidence of oropharyngeal candidiasis.
5. Fasting blood glucose at screening >100 mg/dl (5.6mmol/L). **NOTE:** Participants who have a value that is above >100 mg/dl can have a repeat test before Visit 2.
6. Severe obesity (BMI above the 99th centile based on the CDC charts).
7. Any significant abnormality or medical condition identified at the screening medical assessment (including serious psychological disorder) that in the investigator's opinion, preclude entry into the study due to risk to the participant or that may interfere with the conduct and/or outcome of the study.
8. QT interval corrected using Fridericia's formula (QTcF) >450 msec or QTcF >480 msec in participants with bundle branch block or any other clinically significant abnormality in the Screening 12-lead ECG.

Notes:

- For purposes of data analysis, QT interval corrected for heart rate according to Bazett's formula (QTcB), Fridericia's formula (QTcF), another QT correction formula, or a composite of available values of QTc will be used as specified in the Reporting and Analysis Plan (RAP).

Prior/Concomitant Therapy

9. Use of any prohibited medications listed in Section 9.7.1.

Relevant Habits

10. Present use of any tobacco products including e-cigarettes and vaping.

Contraindications

11. Drug allergies: any adverse reaction including immediate or delayed hypersensitivity to any beta 2-agonists, sympathomimetic drug or any intranasal, inhaled, or systemic corticosteroid therapy. Known or suspected sensitivity to the constituents of the ELLIPTA Inhaler (i.e. lactose or magnesium stearate).
12. Milk Protein Allergy: history of severe milk protein allergy.

Diagnostic Assessments and Other Criteria

13. Participated in a clinical trial and has received an investigational product within the following time period prior to the first dosing day in the current study: 30 days, five half-lives or twice the duration of the biological effect of the study treatment (whichever is longer).
14. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.

15. An affiliation with the investigator site: the parents/guardians or child is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
16. The parent or guardian has a history of psychiatric disease, intellectual deficiency, substance abuse or other condition (e.g. inability to read, comprehend or write) which may affect:
    - validity of consent to participate in the study
    - adequate supervision of the participant during the study
    - compliance of participant with study medication and study procedures (e.g. completion of daily diary, attending scheduled clinic visits)
    - participant safety and well-being
17. Children in care: children who are wards of the government or state are not eligible for participation in this study.

8.3. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomised in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Participants who fail any of the screening or run-in criteria for any reason may be re-screened *once* **after a period of at least 1 month** from the date of screen failure or run-in failure.

Any re-screened subject must satisfy all of the protocol specified inclusion/exclusion requirements at the re-screening visit. Re-screened subjects should be assigned a new subject number at the time of re-screening.

8.4. Randomisation Criteria

Subjects must meet the following criteria to be eligible for randomisation:

8.4.1. Inclusion Criteria for Randomisation to Treatment

1. **Asthma control:** uncontrolled asthma, with a cACT/ACT score ≤19.
2. A technically acceptable pre-bronchodilator FEV_1 >50% to ≤100% predicted normal at Visit 2. A minimum of 2 efforts that are considered acceptable and repeatable following the overread are required to be eligible (see Section 11.1.1).
3. **Symptoms and rescue use:** demonstrated and reported in a daily diary symptoms of asthma (a score of ≥1 on the day-time or night-time asthma symptom scores) and/or

daily albuterol/salbutamol on at least 3 of the last 7 consecutive days of the run-in period (not including the date of randomisation).

4. **Compliance with run-in medication:** compliance is defined as use of run-in medication on at least 4 of the last 7 consecutive days of the run-in period (not including the date of randomisation) recorded in the electronic patient diary.
5. **Compliance with completion of the daily diary reporting:** defined as completion of all questions on 4 out of the last 7 days during the run-in period (not including the date of randomisation).

8.4.2. Exclusion Criteria for Randomisation to Treatment

1. Changes in asthma medication that occur after screening.
2. 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.
3. Evidence of an exacerbation, defined as a:
   - deterioration of asthma requiring the use of oral corticosteroids for at least 3 days, or
   - a depot corticosteroid injection, or
   - an in-patient hospitalisation due to asthma that required systemic corticosteroids between screening and randomisation.
4. Clinical visual evidence of oropharyngeal candidiasis at the Randomisation Visit.
5. Unable to use the ELLIPTA inhaler correctly.

9. TREATMENTS

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

Investigational product will be supplied by the Clinical Trial Supply group. The frequency at which the investigational product will be supplied to each individual site will be adapted to the availability of investigational product, recruitment capacity of that site, and to the expiry date of the investigational product.

9.1. Treatments Administered

Details of study treatments that will be administered in this study are detailed in Table 2.

Table 2 Study Treatments

Study Treatment Name:	Fluticasone Furoate / Vilanterol 50/25 mcg dry powder inhaler*	Fluticasone Furoate / Vilanterol 100/25 mcg dry powder inhaler*	Fluticasone Furoate 50 mcg dry powder inhaler**	Fluticasone Furoate 100 mcg dry powder inhaler**
Dosage formulation:	Dry powder inhaler	Dry powder inhaler	Dry powder inhaler	Dry powder inhaler
Unit dose strength(s)/Dosage level(s):	FF 50 mcg & VI 25 mcg per actuation	FF 100 mcg & VI 25 mcg per actuation	FF 50 mcg per actuation	FF 100 mcg per actuation
Route of Administration:	Inhaled	Inhaled	Inhaled	Inhaled
Dosing instructions:	Inhale once in the morning	Inhale once in the morning	Inhale once in the morning	Inhale once in the morning
Device:	Ellipta	Ellipta	Ellipta	Ellipta
Method of individualizing dosage:	Inhalation (oral)	Inhalation (oral)	Inhalation (oral)	Inhalation (oral)

*Dual Strip; **Single Strip

Fluticasone propionate mulitdose powder inhaler (100 mcg twice daily) will be supplied by the Clinical Trial Supply group for use during the run-in period.

SABA inhalation aerosol (albuterol/salbutamol) will be provided locally for symptomatic relief of asthma symptoms during the study.

9.1.1. Medical Devices

Peak flow meters will be provided by GSK for use in this study; however these devices are not manufactured by, or on behalf of GSK.

Any malfunctions with the Ellipta inhaler should be reported and defective inhalers should be returned (see SRM for further details).

9.2. Dose Modification

Not applicable.

9.3. Method of Treatment Assignment

Participants are required to meet the inclusion criteria for randomisation to treatment detailed in Section 8.4. Participants meeting exclusion criteria for randomisation to treatment will not be randomised to treatment.

Participants will be randomised to 1 of 2 treatment arms using Interactive Voice/Web Response System (IVRS/IWRS).

Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS will be provided to each site.

Study treatment will be dispensed (according to treatment assigned using IVRS) at the study visits summarised in SOA. Returned study treatment should not be re-dispensed to the participants.

9.4. Blinding

This is a double-blind study and the following will apply:

- The IVRS/IWRS will be programmed with blind-breaking instructions. The blind may be broken if, in the opinion of the investigator, it is in the participant's best interest for the investigator to know the study treatment assignment. GSK must be notified before the blind is broken unless identification of the study treatment is required for a medical emergency in which the knowledge of the specific blinded study treatment will affect the immediate management of the participant's condition (eg, antidote is available). In this case, GSK must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form (CRF), as applicable.
- The date and reason for the unblinding must be fully documented in the CRF and source documentation.
- A subject may continue in the study if that subject's treatment assignment is unblinded by GSK Global Clinical Safety and Pharmacovigilance (GCSP) personnel. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.
- GSK's GCSP staff may unblind the treatment assignment for any participant with an SAE. If the SAE requires that an expedited regulatory report be sent to 1 or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

9.5. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

- Only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation, and final disposition records).

- Further guidance and information for the final disposition of unused study treatment are provided in the study reference manual (SRM).

- Under normal conditions of handling and administration, study treatment is not expected to pose significant safety risks to site staff. Take adequate precautions to avoid direct eye or skin contact and the generation of aerosols or mists. In the case of unintentional occupational exposure, notify the monitor, Medical Monitor and/or GSK study contact.

- A Material Safety Data Sheet (MSDS)/equivalent document describing occupational hazards and recommended handling precautions either will be provided to the investigator, where this is required by local laws, or is available upon request from GSK.

9.6. Treatment Compliance

Subject compliance with double-blind study medication will be assessed from Visit 3 (Randomisation visit) through to Visit 9 (End of Treatment Period) by reviewing the following:

1. ELLIPTA dose counter assessment at each visit.

Subjects whose compliance falls below 80% during the study should be re-trained on appropriate dosing of study drug, and may be required to attend the clinic for an unscheduled visit.

9.7. Concomitant Therapy

Any medication that is not prohibited in Inclusion/Exclusion criteria section (see Section 8.1 and Section 8.2) is allowed during the study, as long as the dose remains constant wherever possible and their use is not expected to affect the outcome of the study assessments.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrolment or receives during the study must be recorded along with:

- reason for use

- dates of administration including start and end dates
- dosage information including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

The study site will supply salbutamol/albuterol aerosol inhaler at Visit 1 for use as needed for the duration of the study. Salbutamol/albuterol MDI will be administered with or without a spacer, to be used as determined by the investigator. The use or non-use of the spacer should be consistent for an individual participant throughout the study.

SABA (inhalation aerosol or nebuliser) use should be withheld for 4 hours prior to the FEV_1 measurement at screening and at all future visits where FEV_1 is measured.

9.7.1. Prohibited Medications and Non-Drug Therapies

Note: Participants should be treated as appropriate for asthma exacerbations without requirement to withdraw the participant from the study.

Steroids will be an exclusion from randomisation if administered during the run-in period (apart from FP). However, they should never be withheld if deemed necessary.

Use of the following medications is prohibited according to the timeframes indicated unless they are deemed necessary to treat an asthma exacerbation or another condition appropriately:

- **From screening visit (Visit 1) to Visit 9**: LTRAs, ketotifen, nedocromil sodium, orally inhaled sodium cromoglycate, SABA/short-acting muscarinic antagonist (SAMA) combinations (e.g. Combivent), and inhaled corticosteroids (except for FP which is given during the run-in).

- **Within 4 weeks of Visit 1**: participants who have changed their asthma medication.

- **Within 4 weeks of Visit 1, or any time between Visit 1 to 9**: theophyllines, oral long-acting beta 2-agonists (e.g. bambuterol), inhaled long-acting beta 2-agonists (e.g. salmeterol, formoterol), combination products containing inhaled long-acting beta 2-agonists (e.g. Seretide, Symbicort, Dulera) and inhaled long-acting anticholinergics (e.g. tiotropium). Potent cytochrome P450 3A4 (CYP3A4) inhibitors (e.g. clarithromycin). Prescription or over-the-counter medication that would significantly affect the course of asthma or change in asthma medication, or interact with study drug including (but not limited to): anticonvulsants (barbiturates, hydantoins, carbamazepine); polycyclic anti-depressants; oral, systemic or transdermal beta-adrenergic blocking agents; phenothiazines and monoamine oxidase inhibitors.

- **Within 6 weeks of Visit 1 or any time between Visit 1 to 9**: Oral corticosteroids. **NOTE:** During the double-blind treatment period subjects who require limited courses of oral corticosteroids should remain on study treatment.

- **Within 12 weeks of Visit 1 or any time between Visit 1 to 9**: systemic or depot corticosteroids, anti-immunoglobulin E (IgE) (e.g. Xolair), anti-interleukin (IL)5 (e.g. Nucala) immunosuppressive medications (immunotherapy for the treatment of allergies is allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the participant remains in the maintenance phase throughout the study).

- **Other:** a participant must not have used any inhaled SABA within 4 hours of Visit 1.

9.8. Treatment after the End of the Study

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

The investigator is responsible for ensuring that consideration has been given to the post-study care of the subject's medical condition, whether or not GSK is providing specific post-study treatment.

10. DISCONTINUATION CRITERIA

10.1. Discontinuation of Study Treatment

Participants that permanently stop study treatment are encouraged to remain in the study. Participants have the right to discontinue study treatment before the end of the study. Participants who discontinue from study treatment prematurely (for any reason) should continue to be followed-up as per protocol until the completion of the follow-up assessments. The investigator must make every effort to keep the participant in the study to collect efficacy and safety data.

Participants may be discontinued from study treatment at any time by the investigator if it is considered to be detrimental for them to continue on study treatment. Specifically, a participant will be discontinued from study treatment if he/she meets any of the following criteria outlined below:

- A participant becomes pregnant.

- Female participants who reach menarche after Visit 1 and who do not agree to follow one of the options listed in the Modified List of Highly Effective Methods for Avoiding Pregnancy in FRP (which includes abstinence) as outlined in Section 14.4.

- A participant meets the liver stopping criteria (see Section 10.1.1).

- A participant meets the QTc stopping criteria (see Section 10.1.2).

A participant may discontinue study treatment at any time at his/her own request. An Early Treatment Discontinuation Visit should be conducted within approximately 24 hours of the participant stopping study medication. In the event a participant discontinues study treatment at or during a scheduled visit, an Early Treatment Discontinuation Visit is not required; however, all study procedures scheduled at an Early

Treatment Discontinuation Visit must be performed at this visit instead and reasons for treatment discontinuation should be collected. These participants will not be allowed to restart study treatment; however, participants will be asked to continue to follow the regular visit schedule, including the completion of the daily electronic patient diary (until Visit 6), and attending the clinic at Visit 6 to obtain serial FEV_1 measurements. The investigator should prescribe appropriate asthma medication to participants who discontinue study treatment and elect to continue in the study. After treatment discontinuation, the prohibited medications listed in exclusion criterion 7 are no longer applicable. Every effort will be made to contact participants who do not attend the End of Treatment Visit to collect information on any AEs, SAEs and exacerbations, and to collect the e-diary.

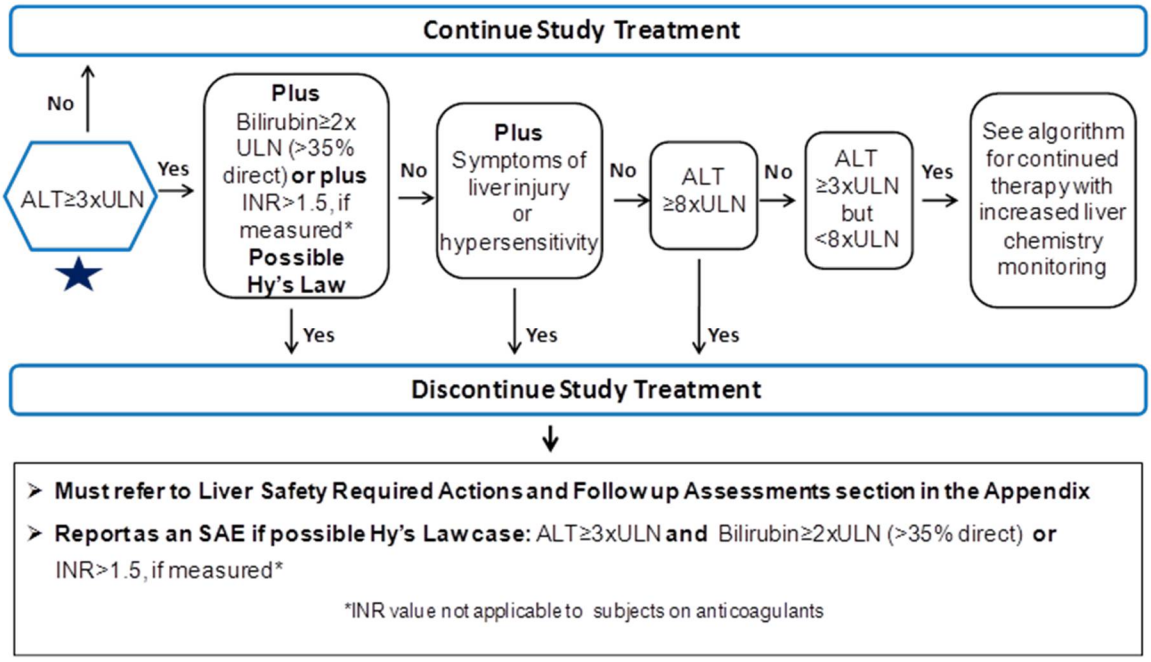
10.1.1. Liver Chemistry Stopping Criteria

There are no scheduled blood tests in this study, apart from the collection of a fasting glucose blood sample. If however the participant has a routine blood test during the study and the results suggest abnormal liver function, then the liver stopping criteria will apply.

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

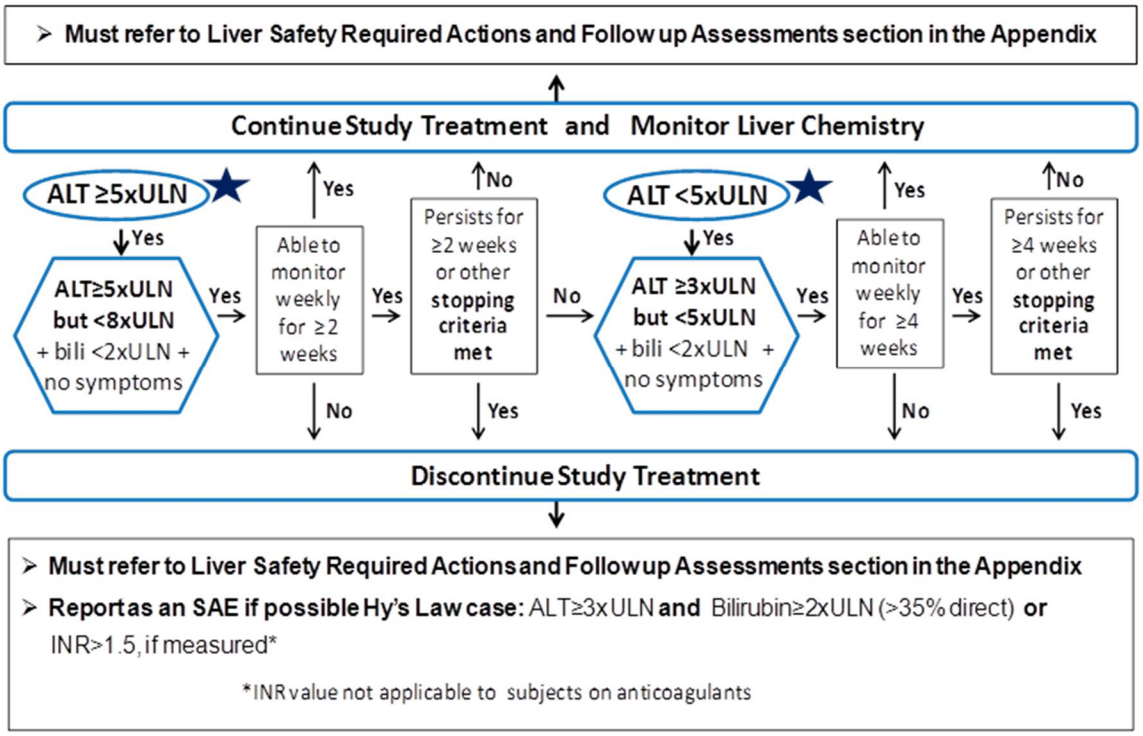
Discontinuation of study treatment for abnormal liver tests should be considered by the investigator when a participant meets one of the conditions outlined in the algorithm or if the investigator believes that it is in the best interest of the participant.

Algorithm A: Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

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



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 6.

10.1.2. QTc Stopping Criteria

ECGs will be performed as outlined in the SOA (Table 1). QTcF will be used for each individual participant to determine eligibility for and discontinuation from the study.

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

A participant who meets the bulleted criteria based on the average of triplicate ECG readings will be withdrawn from study treatment:

- QTcF > 500 msec OR Uncorrected QT > 600 msec
- Change from baseline of QTcF > 60 msec

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

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

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

10.2. Withdrawal from the Study

- A participant may withdraw from the study at any time at his/her own request or at the request of his/her legal guardian(s),or may be withdrawn at any time at the discretion of the investigator for safety, behavioural, or administrative reasons.
- If the participant withdraws assent or if his/her legal guardian(s) withdraw 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 (e.g. saliva) taken and not tested, and the investigator must document this in the site study records.
- Refer to the SOA (Table 1) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.

If the participant chooses to withdraw from the study, all study-related medications and other study related materials should be returned to the site by the participant. An Early Withdrawal Visit should be conducted within approximately 24 hours of the participant stopping study medication. In the event a participant withdraws at or during a scheduled visit, an Early Withdrawal Visit is not required; however, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead. A follow-up phone contact or video-call should be made 7 days after the Early Withdrawal Visit. The primary reason for study treatment discontinuation or study withdrawal will be recorded in the electronic case report form (eCRF) and any data collected up until the point of withdrawal will be used in the data analyses.

10.3. 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 or legal guardian(s) (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarised in the SOA (Table 1).
- 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 treatment.
- 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 (eg, 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.
- A 2mL blood sample will be collected for the assessment of fasting blood glucose from each participant at Visits 1 and 9 (and ETD/DW, and if repeat test is required at Visit 1).

11.1. Efficacy Assessments

The timing of all efficacy assessments is provided in the SOA.

11.1.1. FEV_1

Spirometry at Visit 2, Visit 4, Visit 5 (if applicable), ETD and EW may be collected at home or in the clinic. At-home spirometry must be done using a Masterscope provided by the spirometry vendor, ERT (with central over-read). Home nurses will be experienced in spirometry and will be trained by ERT.

Spirometry at Visit 1 and Visit 6 must be done in the clinic.

Spirometry will be performed to assess FEV_1. It will be measured using a standardised calibrated spirometer. At least 3 spirometry manoeuvres (from a maximum of 8 attempts) should be achieved on each occasion that spirometry assessments are performed. For all spirometry data collected, best spirometry effort will be selected from a measurement that meets the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines.

For both the pre-bronchodilator and post-bronchodilator time points at screening (Visit 1), there must be a minimum of 2 spirometry efforts that are considered acceptable (not necessarily repeatable) to be eligible for the study.

At the pre-randomisation visit (Visit 2), there must be a minimum of 2 spirometry efforts that are considered acceptable and repeatable (available and reviewed at Visit 3) in order to be eligible for randomisation.

For all data (including both pre-dose and serial FEV_1) collected during the treatment period (Visits 4 and 6, and where collected at Visit 5) and ETD/EW, there must be a minimum of 2 efforts that are considered acceptable (not necessarily repeatable).

Predicted FEV_1 values will be based on Quanjer (GLI2012) [Quanjer, 2012].

For all visits and time points, spirometry will be subject to a central overread. The final value after the overread is the value that will be databased and analysed. This is also the value that will be used to determine eligibility for the spirometry at Visits 1 and 2.

Participants **must** withhold from using salbutamol/albuterol (inhalation aerosol or nebuliser) for 4 hours prior to FEV_1 measurements. In addition, participants **must not** take their study drug (if applicable) prior to the visit and performing their pre-dose FEV_1 measurement.

Pre-dose FEV_1 will be measured in the morning between 6.00am and 11.00am.

11.1.1.1. Serial FEV_1

Serial FEV_1 measurements at Visit 6 will occur at 15 minutes pre-dose and 30, 60, 120,180, and 240 minutes post dose.

If the participant is unable to attend the clinic at Visit 6 for any reason, every attempt should be made to bring the participant back to the clinic to collect serial spirometry as soon as possible between Visit 6 (Week 12) and Visit 9 (Week 24).

Any serial measurements that are collected after week 12 will be used in the primary analysis, which is considered acceptable as the drug effect is expected to have reached a plateau by 3 months post-randomisation, and should not significantly change afterwards.

11.1.1.2. Reversibility

At Visit 1, to check eligibility, reversibility in FEV_1 will be assessed.

FEV_1 will be measured within 15 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol (a spacer device may be used if required) or one nebulised treatment with albuterol/salbutamol solution. Subjects who fail to demonstrate a ≥12% increase in FEV_1 will not be eligible to take part in the study (see Section 8.1. for further information).

Percent reversibility will be calculated as follows:

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

11.1.2. Electronic Daily Diaries

Participants will be issued with an electronic patient diary and instructed on how to complete it. The following parameters will be recorded in the electronic patient diary from Visits 1 to 6 only:

- Daily PEF (morning and evening) (see Section 11.1.2.1 for further details)
- Daily asthma symptom scores (morning and evening) (see Section 11.1.2.2 for further details)
- Number of inhalations of rescue albuterol/salbutamol inhalation aerosol used during the day and night. **Note:** Rescue medication taken as preventative treatment before exercise will be excluded from this count and should not be entered into the daily eDiary.

11.1.2.1. Daily PEF

PEF will be measured in the morning and evening using a peak flow meter that will be issued to participants at Visit 1. The best of three attempts will be recorded in the electronic patient diary.

PEF will be measured prior to any study medication and any rescue albuterol/salbutamol inhalation aerosol use.

11.1.2.2. Asthma Symptom Scores

The following should be recorded in the electronic patient diary in the evening at bedtime (PM) before taking any rescue or study medication and before PEF measurements:

- Day-time Symptom Score:
  - CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.
  - [redacted]
  - [redacted]
  - [redacted]

- CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

The following will be recorded every day in the eDiary in the morning (AM) upon rising before taking any rescue medication and before PEF measurement:

- Night-time Symptom Score:
  - CCI - This section contained Clinical Outcome Assessment data collection questionnaires or indices, which are protected by third party copyright laws and therefore have been excluded.

11.1.3. Questionnaires

Questionnaires should be completed before any procedures are performed on the participant to avoid influencing the participant's response. To avoid biasing responses, the participants should not be told the results of diagnostic tests prior to completing the questionnaires and it is recommended that the questionnaires be administered at the same time of day during each visit (as applicable). 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.

11.1.3.1. Childhood Asthma Control Test and Asthma Control Test

The Childhood Asthma Control Test (cACT) or Asthma Control Test (ACT) will be completed at Visit 1 and Visit 3 only as part of the eligibility and randomisation criteria. The cACT will be completed by participants aged 5 to 11 years old and the ACT will be completed by participants 12 to 17 years old.

The cACT is a 7-item questionnaire to measure asthma control in children. It is designed for completion by the participant and by the participant's parent/legal guardian. The child should complete questions 1-4 as independently as possible; however, if a child has difficulty with completion, the parent/legal guardian can provide assistance. The parent/legal guardian should complete questions 5-7 without letting their child's responses influence their answers. The investigator or designated study site personnel should encourage the child not to skip questions on the cACT or take breaks during the completion of the paper questionnaire.

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

11.1.3.2. Asthma Control Questionnaire ACQ-5

The ACQ-5 is a five-item questionnaire, which has been developed as a measure of participants' asthma control that can be quickly and easily completed [Juniper, 2005a]. The questions are designed to be self-completed by the participant.

Participants will complete the ACQ-5 at Visits 3, 6 and 9. The ACQ 5 includes five questions (concerning nocturnal awakening, waking in the morning, activity limitation, shortness of breath and wheeze) which enquire about the frequency and/or severity of symptoms over the previous week. The response options for all these questions consist of a zero [CCI redacted] to six [CCI redacted]) scale. A score of <0.75 indicates well-controlled asthma and a score ≥1.5 indicates poorly controlled asthma [Juniper, 2006]. A change of ≥0.5 in score suggests a clinically important change in score [Juniper, 2005b].

11.1.4. Asthma exacerbation

An exacerbation is defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or a single depot corticosteroid injection or an in-patient hospitalisation or emergency department visit due to asthma that required systemic corticosteroids. Investigators should follow current asthma management guidelines in the evaluation of patients with worsening of asthma and in the management of acute exacerbations. Asthma exacerbations should not be recorded as an AE, unless they meet the definition of an SAE. For the purposes of this study, asthma exacerbations will be collected and recorded on the exacerbations log in the eCRF. The treatment details must also be recorded in the eCRF.

11.2. Adverse Events

The definitions of an AE or SAE can be found in Appendix 3.

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the participant to discontinue the study treatment study (see Section 10).

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

- All SAEs will be collected from signing of the ICF until the follow-up call at the time points specified in the SOA (Section 2).

- All AEs will be collected from the start of treatment until the follow-up call at the time points specified in the SOA (Section 2).
- Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.
- All SAEs will be recorded and reported to the sponsor or designee within 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 AEs or SAEs in former study participants. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must promptly notify the sponsor.
- The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

11.2.2. 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.

11.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, [and non serious AEs of special interest (as defined in Section 3.3)], will be followed until the event is resolved, stabilized, otherwise explained, or the participant is lost to follow-up (as defined in Section 10.3). Further information on follow-up procedures is given in Appendix 3.

11.2.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g. summary or listing of SAE) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

11.2.5. Death Events

For all deaths, whether or not they are considered SAEs, specific 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 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 1 week of when the death is reported.

11.2.6. Pregnancy

- Details of all pregnancies in female participants will be collected after the start of study treatment and until the last follow-up visit.
- If a pregnancy is reported, the investigator should inform the CRO within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAE.

11.2.7. Treatment of Overdose

For this study, any dose of FF/VI combination or FF that is more than that permitted by the protocol within a 24-hour time period that results in clinical signs or symptoms will be considered an overdose.

GSK does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for AE/SAE and laboratory abnormalities including a morning cortisol (to be assessed based on the duration and magnitude of the overdose) until FF and / or VI (depending on treatment group) can no longer be detected systemically (at least 5 days from last dose administered).
3. Obtain a plasma sample for PK analysis within 1 to 5 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis).
4. Document the quantity of the excess dose as well as the duration of the overdosing in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

11.2.8. Medical Device Deficiencies

Medical devices are being provided for use in this study. To fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of device deficiency that occur during the study with such devices.

The definition of a Medical Device Deficiency can be found in Section 14.7 Appendix 7.

NOTE: Deficiencies fulfilling the definition of an AE/SAE will also follow the processes outlined in Appendix 7 of the protocol.

11.2.8.1. Time Period for Detecting Medical Device Deficiencies

- Medical device deficiencies that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any device deficiency at any time after a participant has been discharged from the study, and such device deficiency is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.
- The method of documenting Medical Device Incidents is provided in Appendix 7.

11.2.8.2. Follow-up of Medical Device Deficiencies

- Follow-up applies to all participants, including those who discontinue study intervention or the study.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

11.2.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a device deficiency.
- The Medical Device Deficiency Report Form will be sent to the CRO by the electronic data collection tool. If the electronic data collection tool is unavailable, then the paper SAE data collection tool should be utilized.

- The CRO will be the contact for the receipt of device deficiency reports.

11.2.8.4. Regulatory Reporting Requirements for Medical Device Incidents

- The investigator will promptly report all deficiencies occurring with any medical device provided for use in the study in order for the sponsor to 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.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

11.3. Safety Assessments

Planned time points for all safety assessments are provided in the SOA.

11.3.1. Physical Examination

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

11.3.2. Oropharyngeal Examination

Oropharyngeal examination for visual evidence of oral candidiasis will be carried out at as outlined in the SOA. If the visual oropharyngeal examination is abnormal prior to randomisation the participant must not be randomised.

If there is any visual clinical evidence of oral candidiasis during the double-blind treatment period of the study, subjects may continue in the study and appropriate anti-infective therapy should be instituted at the discretion of the investigator. If the subject requires therapy with a medication prohibited by the protocol, the subject should be treated appropriately and discontinued from study treatment. All visual clinical evidence of candidiasis must be reported as an AE.

The results of the oropharyngeal examinations and any relevant pharmacotherapy will be recorded in the subject's clinic notes and eCRF.

11.3.3. Vital Signs

Vital signs (systolic and diastolic blood pressure and heart rate) will be measured at Screening only. The measurement will be taken after 5 minutes rest prior to spirometry. One reading of blood pressure and pulse will be taken and will only be repeated if out of the normal range.

11.3.4. Electrocardiograms

12-Lead electrocardiogram measurements will be performed at Visit 1, Visit 9, and the Early Treatment Discontinuation/Early Withdrawal Visit.

The 12-lead ECG will be recorded at 25 mm/sec and will consist of a recording of leads I, II, III, aVR, aVL, aVF and V1 to V6 and 10 seconds recording of lead II (rhythm strip). At least 3 complete evaluable complexes per lead will be recorded. The following ECG parameters will be determined. Single 12-lead ECG will be obtained as outlined in the SOA using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QTc intervals. Refer to Section 10.1.2 for QTc withdrawal criteria and additional QTc readings that may be necessary.

Further details on ECG measurements will be provided in the SRM.

11.3.5. Clinical Safety Laboratory Assessments

No clinical laboratory tests will be performed in this study, except for the collection of a 2 ml fasting glucose blood sample at the Screening Visit (Visit 1) and Visit 9 (End of Treatment) or at the ETD/EW visit if applicable. A central laboratory will be used.

If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (eg, SAE or AE or dose modification), then the results must be recorded in the CRF.

11.4. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

11.5. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

11.6. Genetics

A 2 mL saliva sample for deoxyribonucleic acid (DNA) isolation will be collected from participants who have consented to participate in the genetics analysis component of the study. Participation is optional. Participants who do not wish to participate in the genetic research may still participate in the study.

In the event of DNA extraction failure, a replacement genetic sample may be requested from the participant. Signed informed consent will be required to obtain a replacement sample unless it was included in the original consent.

See Appendix 5 for information regarding genetic research. Details on processes for collection and shipment and destruction of these samples can be found in the SRM.

11.7. Biomarkers

Biomarkers are not evaluated in this study.

11.8. Health Economics OR Medical Resource Utilization and Health Economics

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

12. STATISTICAL CONSIDERATIONS

12.1. Sample Size Determination

12.1.1. Sample Size Assumptions

Approximately 870 participants will be randomised in this study in a ratio of 1:1 giving 435 randomised participants per arm in the 5-17 years old population. There will be 652 randomised participants who will be 11 years old or less at screening, giving 326 randomised participants per arm in the 5-11 years old population.

12.1.1.1. Sample Size Assumptions for 5-17 Years Old Population

The sample size calculation for the 5-17 years old population is based on the primary efficacy endpoint of weighted mean FEV_1 (0-4 hours). The sample size allows for up to 20% of participants to not contribute to the primary endpoint giving a total of 348 evaluable participants per arm.

The standard deviation is assumed to be 280mL for 5-11 year olds and 500mL for 12-17 year olds based on previous studies. Using the assumed representation across the age ranges (652 and 218 randomized participants, respectively), a standard deviation of 348mL has been assumed for the 5-17 years old population based on a weighted average of the variances (i.e. assuming equal means).

The sample size has 93% power, based on a true population difference of 90mL and significance declared at the two-sided 5% significance level. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 52mL.

12.1.1.2. Sample Size Assumptions for 5-11 Years Old Population

The sample size calculation for the 5-11 years old population is based on the primary efficacy endpoint of AM PEF and on the nominated powered secondary endpoint of change from baseline in rescue-free 24-hour periods. The sample size allows for up to 4% of participants to not contribute to either endpoint giving a total of 312 evaluable participants per arm.

For the primary endpoint of AM PEF, a standard deviation of 30 L/min is assumed, based on previous studies. The sample size has 91% power, based on a true population

difference of 8 L/min and significance declared at the two-sided 5% significance level. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 4.7 L/min.

For the nominated powered secondary endpoint of change from baseline in rescue-free 24-hour periods, a standard deviation of 30% is assumed, based on previous studies. The sample size has 99% power, based on a true population difference of 10% and significance declared at the two-sided 5% significance level. The smallest observed effect predicted to result in a statistically significant difference between treatment groups is 4.7%.

Assuming a correlation of 0.1 between the primary endpoint and the nominated powered secondary endpoint, the overall power for both endpoints in the 5-11 years old population is 90%.

12.1.2. Sample Size Sensitivity

The standard deviation assumptions are based on estimates from previous studies. Table 3 presents the power achieved for the FF/VI versus FF treatment comparison in the 5-17 years old population with the proposed sample size, should the assumption around the standard deviation of the data change. Table 4 presents the power achieved for the FF/VI versus FF treatment comparison in the 5-11 years old population with the proposed sample, should the assumptions around the standard deviation of the data change. In each case, the actual assumptions used in the sample size calculations are shaded in grey.

Table 3 Impact of Standard Deviation on Power for 5-17 Years Old Population

	Standard Deviation	Power (%)
Weighted Mean FEV_1 (0-4 hours):	300mL	98
	325mL	95
	348mL	93
	375mL	89
	400mL	84

Table 4 Impact of Standard Deviation on Power for 5-11 Years Old Population

	Standard Deviation	Power (%) for Individual Endpoints	Overall Power (%) Across Both Endpoints
AM PEF: % Rescue-free 24 hr periods:	20 L/min 20%	>99 >99	>99
AM PEF: % Rescue-free 24 hr periods:	25 L/min 25%	98 >99	98
AM PEF: % Rescue-free 24 hr periods:	30 L/min 30%	91 99	90
AM PEF: % Rescue-free 24 hr periods:	35 L/min 35%	82 95	77

	Standard Deviation	Power (%) for Individual Endpoints	Overall Power (%) Across Both Endpoints
AM PEF: % Rescue-free 24 hr periods:	40 L/min 40%	70 88	62

12.1.3. Sample Size Re-estimation

No sample size re-estimation is planned.

12.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Total Population	The Total Population will comprise all participants screened and for whom a record exists on the study database and will be used for the tabulation and listings of reasons for withdrawal before randomisation.
ITT (5-17 Years Old) Population	The ITT (5-17 Years Old) Population will comprise all participants randomised to treatment and who received at least 1 dose of study medication. Randomised participants will be assumed to have received study medication unless definitive evidence to the contrary exists. Outcomes will be reported according to the randomised treatment allocation. This will constitute one of the two primary populations for all efficacy measures and safety measures.
ITT (5-11 Years Old) Population	The ITT (5-11 Years Old) Population will be a subset of the ITT (5-17 Years Old) Population for subjects aged 11 years old or younger at screening. Outcomes will be reported according to the randomised treatment allocation. This will constitute one of the two primary populations for all efficacy measures and safety measures.

12.3. Statistical Analyses

12.3.1. Hypotheses

The primary efficacy endpoint for the 5-17 years old population is weighted mean FEV_1 (0-4 hours). For the 5-11 years old population the primary efficacy endpoint is the change from baseline in AM PEF and the nominated powered secondary endpoint is the change from baseline in rescue-free 24-hour periods. For each of these endpoints there will be a single inequality comparison of FF/VI versus FF. Demonstration of efficacy for each of these inequality comparisons will be based on a hypothesis testing approach, whereby the null hypothesis is that there is no difference between treatment groups for the endpoint of

interest and the alternative hypothesis is that there is a difference between treatment groups.

A 2-sided 5% risk associated with incorrectly rejecting any of the null hypotheses (significance level) is considered acceptable for this study. As the comparisons on the 5-17 years old population and the 5-11 years old population are being made for different purposes they will each have distinct multiple testing strategies which will be assessed separately.

For each of the two populations, in order to account for multiplicity across the key endpoints, a step-down closed testing procedure will be applied to the inequality comparison of FF/VI versus FP whereby this comparison will be required to be significant at the 0.05 level for the primary endpoint in order to infer on the secondary endpoints and inference for a test in the pre-defined hierarchy of secondary endpoints is dependent upon statistical significance having been achieved for the previous comparison in the hierarchy of secondary endpoints. If a given statistical test fails to reject the null hypothesis of no treatment difference at the significance level of 0.05, then all tests lower down in the hierarchy will be interpreted as descriptive only.

Figure 2 Statistical Testing Strategy for 5-17 Years Old Population

Testing of each endpoint is dependent on significance at the 0.05 level having been achieved on the previous endpoint in the hierarchy.	
Primary Efficacy Endpoint	
1) Weighted mean FEV_1 (0-4 hours):	FF/VI vs. FF
Secondary Efficacy Endpoints	
2) Rescue-free 24 hour periods:	FF/VI vs. FF
3) Symptom-free 24 hour periods:	FF/VI vs. FF
4) AM FEV_1:	FF/VI vs. FF
5) AM PEF:	FF/VI vs. FF
6) ACQ:	FF/VI vs. FF

Figure 3 Statistical Testing Strategy for 5-11 Years Old Population

Testing of each endpoint is dependent on significance at the 0.05 level having been achieved on the previous endpoint in the hierarchy.	
Primary Efficacy Endpoint	
1) AM PEF:	FF/VI vs. FF
Secondary Efficacy Endpoints	
2) Rescue-free 24 hour periods:	FF/VI vs. FF
3) Symptom-free 24 hour periods:	FF/VI vs. FF
4) AM FEV_1:	FF/VI vs. FF
5) ACQ:	FF/VI vs. FF
6) Weighted mean FEV_1 (0-4 hours):	FF/VI vs. FF

The treatment comparisons defined as part of the multiple testing strategy will be limited to the specified key comparisons shown in Figure 2 and Figure 3. Analyses of other efficacy measures in either population for the FF/VI versus FF treatment comparison are nested under the secondary efficacy measures and no multiplicity adjustment is planned for these other efficacy endpoints.

In each population, if significance is achieved for the FF/VI versus FF treatment comparison on the primary efficacy endpoint, then the secondary endpoints will be tested in a closed-testing manner using the hierarchy of comparisons. If significance is also achieved for each of the secondary efficacy endpoints, then all other efficacy endpoints will be tested for the FF/VI versus FF treatment comparison without further multiplicity adjustment.

12.3.2. Treatment Comparisons

12.3.2.1. Primary Comparison of Interest

The primary treatment comparison for the 5-17 years old population will be FF/VI versus FF for the primary efficacy endpoint of weighted mean FEV_1 (0-4 hours) at week 12.

The primary treatment comparison for the 5-11 years old population will be FF/VI versus FF for the primary efficacy endpoint of change from baseline in AM PEF averaged over weeks 1-12.

12.3.2.2. Other Comparisons of Interest

The primary treatment comparison of FF/VI versus FF will also be performed for the secondary and other efficacy endpoints.

12.3.3. Key Elements of Analysis Plan

The FF/VI 50/25 mcg and FF/VI 100/25 mcg treatment groups will be combined into one FF/VI treatment group for the purpose of reporting. Similarly, the FF 50 mcg and FF 100 mcg treatment groups will be combined into one FF treatment group for the purpose of reporting.

In this study, every effort will be made for participants who withdraw from study medication to remain in the study and continue with the normal visit schedule providing all of the expected data. The main analysis for all efficacy endpoints will evaluate the primary de facto estimand of treatment policy (effectiveness-type estimand): the mean difference between treatment groups for the time point of interest regardless of whether the participant remained on-treatment. This means that for any given endpoint, all available data for a participant will be used including any data that was collected after the participant was withdrawn from study medication. Specific details for inclusion will be detailed in the reporting and analysis plan (RAP), but in general the minimum data required will be a baseline evaluation and at least one post-baseline evaluation. For the powered endpoints only, a secondary de jure efficacy-type estimand will be evaluated by using only on-treatment data.

Endpoints relating to daily diary assessments will be calculated from all available data over the time period of interest. In addition to the weeks 1-12 time period, smaller time periods will also be defined in order to perform sensitivity analyses. However for any given time-period that is defined, no imputations will be performed on missing daily diary data within that time period. Any defined time period for a diary data endpoint will be considered missing if less than 2 days (i.e., 24-hr periods) are recorded in that time period.

For the derivation of the percentage of symptom-free 24-hour periods, a given 24-hour period will be considered as missing if both the day-time and night-time data are missing or if one is symptom-free but the other is missing. However, if either the daytime or the night-time has symptoms then the 24-hour period will be considered not symptom-free. The same principals will be applied to the derivation of the percentage of rescue-free 24-hour periods.

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

It is anticipated that a large number of centers will participate in the study. Therefore, it is likely that many centers will enroll very small number of participants. Consequently, all centers within the same country will be pooled. In addition, if there are any countries enrolling very small numbers in total (<12), these countries will be pooled with another country within a similar geographical region. All amalgamations will be finalized and documented prior to unblinding the treatment codes. These amalgamations will be used wherever region is incorporated into the analysis.

Baseline values for each endpoint will be those used as appropriate from either Visit 2 or Visit 3 for clinic visit endpoints or derived from the last 7 days of the run-in daily diary prior to the randomisation of the patient.

12.3.3.1. Primary Efficacy Analyses

12.3.3.1.1. Primary Efficacy Analyses for 5-17 Years Old Population

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5-17 Years Old) population will include data from all participants regardless of whether or not they were on-treatment at the time of their week 12 serial FEV_1 measurements.

To address the secondary efficacy-type estimand, the analysis will be repeated using only on-treatment data.

The primary endpoint of weighted mean FEV_1 (0-4 hours) at week 12 will be derived using the post-dose assessments (after 30 minutes and 1, 2, 3, 4 hours) with their actual times and using the pre-dose assessment as the 0 hour measurement. The weighted mean will be calculated as the average area under the curve using the trapezoidal rule, and dividing by the relevant time interval (i.e. the time between the actual time of dose and the actual time of the last FEV_1 measurement being used).

The weighted mean will be analysed using an analysis of covariance (ANCOVA) model with effects due to baseline pre-dose FEV_1, region, sex, age and treatment group. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison will be presented together with 95% confidence intervals for the difference and a p-value for the treatment comparison.

12.3.3.1.2. Primary Efficacy Analyses for 5-11 Years Old Population

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5-11 Years Old) population will include all available AM PEF data from weeks 1-12, regardless of whether the participant was still on-treatment at the time of the measurement.

To address the secondary efficacy-type estimand, the analysis will be repeated using only on-treatment data.

The primary endpoint of change from baseline in AM PEF averaged over weeks 1-12 will be calculated for each participant using only data that are from the first 84 calendar days after randomisation.

The primary analysis will be performed using an ANCOVA model with effects due to baseline AM PEF, region, sex, age and treatment group. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison will be presented together with 95% confidence intervals for the difference and a p-value for the treatment comparison.

A sensitivity analysis for the primary effectiveness-type estimand will be performed including all data from weeks 1-12 (regardless of treatment state). For this analysis, the

weeks 1-12 time period will be split into 6 separate time periods: Weeks 1-2, Weeks 3-4, Weeks 5-6, Weeks 7-8, Weeks 9-10 and Weeks 11-12. The data will then be analysed using a mixed model repeated measures (MMRM) model, which will allow for effects due to baseline AM PEF, region, sex, age, time period and treatment group. This model will also contain a time period-by-baseline interaction term and a time period-by-treatment interaction term. Missing data are not implicitly imputed in this analysis. However, all non-missing data for a participant will be used within the analysis to estimate the average treatment effect over Weeks 1-12.

12.3.3.2. Secondary Efficacy Analyses

Change from Baseline in the Percentage of Rescue-free 24-Hour Periods for the ITT (5-11 Years Old) Population

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5-11 Years Old) population will include all available data from weeks 1-12, regardless of whether the participant was still on-treatment at the time of the question.

To address the secondary efficacy-type estimand, the analysis will be repeated using only on-treatment data.

The powered secondary endpoint of change from baseline in the percentage of rescue-free 24 hour periods over weeks 1-12 will be calculated for each participant using only data that are from the first 84 calendar days after randomisation.

The primary analysis will be performed using an ANCOVA model with effects due to baseline, region, sex, age and treatment group. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison will be presented together with 95% confidence intervals for the difference and a p-value for the treatment comparison.

A sensitivity analysis for the primary effectiveness-type estimand will be performed including all data from weeks 1-12 (regardless of treatment state). For this analysis, the weeks 1-12 time period will be split into 6 separate time periods: Weeks 1-2, Weeks 3-4, Weeks 5-6, Weeks 7-8, Weeks 9-10 and Weeks 11-12. The data will then be analysed using a mixed model repeated measures (MMRM) model, which will allow for effects due to baseline, region, sex, age, time period and treatment group. This model will also contain a time period-by-baseline interaction term and a time period-by-treatment interaction term. Missing data are not implicitly imputed in this analysis. However, all non-missing data for a participant will be used within the analysis to estimate the average treatment effect over Weeks 1-12.

Change from Baseline in the Percentage of Rescue-free 24-Hour Periods for the ITT (5-17 Years Old) Population

The change from baseline in the percentage of rescue-free 24 hour periods over weeks 1-12 is a secondary endpoint for the 5-17 years old population and will be calculated for each participant using only data that are from the first 84 calendar days after

randomisation. The primary analysis will be performed using an ANCOVA model with effects due to baseline, region, sex, age and treatment group.

Change from Baseline in the Percentage of Symptom-free 24-Hour Periods

The change from baseline in the percentage of symptom-free 24 hour periods over weeks 1-12 will be calculated for each participant using only data that are from the first 84 calendar days after randomisation. The primary analysis will be performed using an ANCOVA model with effects due to baseline, region, sex, age and treatment group.

Change from Baseline in AM FEV_1

Change from baseline in AM FEV_1 at week 12 will be defined using the pre-dose FEV_1 assessment at the Week 12 clinic visit. Analysis will be performed using an MMRM model, which will allow for effects due to baseline FEV_1, region, sex, age, visit and treatment group. This model will also contain a visit-by-baseline interaction term and a visit-by-treatment interaction term. Missing data are not implicitly imputed in this analysis. However, all non-missing pre-dose data for a participant taken at scheduled visits 3, 4 and 5 (weeks 4, 8 and 12) will be used within the analysis to estimate the week 12 treatment effects.

Change from Baseline in ACQ-5

Change from baseline in ACQ-5 at week 24 will be analysed using an MMRM model, which will allow for effects due to baseline, region, sex, age, visit and treatment group. This model will also contain a visit-by-baseline interaction term and a visit-by-treatment interaction term. Missing data are not implicitly imputed in this analysis. However, all non-missing data for a participant taken at scheduled visits 5 and 8 (weeks 12 and 24) will be used within the analysis to estimate the week 24 treatment effects.

Weighted Mean FEV_1 (0-4 hours) for 5-11 Years Old Population

Weighted mean FEV_1 (0-4 hours) at week 12 is a secondary endpoint for the 5-11 years old population. It will be analysed using an analysis of covariance (ANCOVA) model with effects due to baseline FEV_1, region, sex, age and treatment group.

Change from Baseline in AM PEF for 5-17 Years Old Population

The change from baseline in PM PEF over weeks 1-12 is a secondary endpoint for the 5-17 years old population and will be calculated for each participant using only data that are from the first 84 calendar days after randomisation. The primary analysis will be performed using an ANCOVA model with effects due to baseline, region, sex, age and treatment group.

Change from Baseline in PM PEF

The change from baseline in PM PEF over weeks 1-12 will be calculated for each participant using only data that are from the first 84 calendar days after randomisation. The primary analysis will be performed using an ANCOVA model with effects due to baseline, region, sex, age and treatment group.

12.3.3.3. Other Analyses

The reporting and analysis of other endpoints as specified in the protocol will be provided in the RAP.

12.3.4. Interim Analyses

There are no interim analyses planned during this study.

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14. APPENDICES

14.1. Appendix 1: Abbreviations and Trademarks

ACQ	Asthma Control Questionnaire
AE	Adverse event
AM	Ante meridiem (morning)
ANCOVA	Analysis of covariance
ATS	American Thoracic Society
BID	Twice daily
BMI	Body Mass Index
cACT	Childhood asthma control test
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract Research Organisation
CYP3A4	Cytochrome P450 3A4
dl	Decilitre
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EMA	European Medicines Agency
ERS	European Respiratory Society
ETD	Early treatment discontinuation
EW	Early withdrawal
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FF/VI	Fluticasone furoate/vilanterol
FP	Fluticasone propionate
FRP	Females of reproductive potential
FU	Follow-up
GCSP	Global Clinical Safety and Pharmacovigilance
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
HPA	Hypothalamic-pituitary adrenal axis
ICF	Informed consent document
ICS	Inhaled corticosteroid
IEC	Independent ethics committee
IgE	Immunoglobulin E
IL	Interleukin
IRB	Institutional review board
ITT	Intent-to-treat

IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
L/Min	Litre per Minute
LABA	Long-acting beta agonist
LOCS	Lens opacities classification system
LTRA	Leukotriene receptor antagonist
mcg	Microgram
MDI	Metered dose inhaler
mol/L	Mole per Litre
MMRM	Mixed model repeated measures
MSDS	Material Safety Data Sheet
msec	Millisecond
NIH	National Institutes of Health
PDCO	Paediatric Committee
PEF	Peak expiratory flow
PIP	Paediatric investigational plan
PM	Post meridiem (evening)
QTcB	QT interval corrected for heart rate according to Bazett's formula
QTcF	QT interval corrected for heart rate according to Fridericia's formula
RAP	Reporting and Analysis Plan
SABA	Short-acting beta agonist
SDS	Standard Deviation Score
SAE	Serious adverse event
SAMA	Short-acting muscarinic antagonist
SAWP	Scientific Advice Working Party
SOA	Schedule of activities
SRM	Study reference manual
SUSAR	Suspected unexpected serious adverse reactions
TC	Telephone call
V	Visit
VI	Vilanterol
WOCBP	Woman of Childbearing Potential

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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Xolair

14.2. Appendix 2: Study Governance Considerations

Regulatory and Ethical Considerations

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

Financial Disclosure

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

Informed Consent Process

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

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

Data Protection

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

Committees Structure

Not applicable.

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 multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

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

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

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

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

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 (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICF, pertaining to the conduct of this study must be retained by the investigator for 25years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

Source Documents

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

Study and Site Closure

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

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

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

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

14.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of a study treatment, whether or not considered related to the study treatment. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study treatment.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (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 (ie, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AE. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Recording AE and SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to GSK in lieu of completion of the GSK /AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficiently discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AE and SAE can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AE and SAE
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by GSK to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide GSK with a copy of any post-mortem findings including histopathology. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to t GSK within 24 hours of receipt of the information.

Reporting of SAE to GSK

SAE Reporting to GSK via Electronic Data Collection Tool
• The primary mechanism for reporting SAE to GSK will be the electronic data collection tool. • If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next Section). • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next Section) or to the medical monitor by telephone. • Contacts for SAE reporting can be found in the SRM.

SAE Reporting to GSK via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the **medical monitor**. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.

- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SRM.

14.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Woman of Childbearing Potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with ONE of the following:

- Documented hysterectomy
- Documented bilateral salpingectomy
- Documented bilateral oophorectomy

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

3. Postmenopausal female

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

Contraception Guidance

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 5.

Table 5 Highly Effective Contraceptive Methods

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

NOTES:

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

b. Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case two highly effective methods of contraception should be utilized during the treatment period and for at least X, corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential after the last dose of study treatment

Pregnancy Testing

- WOCBP should only be included after a confirmed menstrual period and a negative highly sensitive urine pregnancy test

- Additional pregnancy testing is not required during the treatment period corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential after the last dose of study treatment and as required locally
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected
- Pregnancy testing, with a sensitivity of 5, 10, 25 mIU/mL will be performed and assayed in a certified laboratory OR and assayed in the central laboratory OR using the test kit provided by the central laboratory / provided by the sponsor /approved by the sponsor and in accordance with instructions provided in its package insert

Collection of Pregnancy Information

Female Participants who become pregnant

- Investigator will collect pregnancy information on any female participant, who becomes pregnant while participating in this study.
- Information will be recorded on the appropriate form and submitted to GSK within 24 hours of learning of a participant's pregnancy.
- Participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow up information on participant and neonate, which will be forwarded to GSK Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date.
- Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE.
- A spontaneous abortion is always considered to be an SAE and will be reported as such.
- Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to GSK as described in Appendix 3. 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 will discontinue study treatment

14.5. Appendix 5: Genetics

USE/ANALYSIS OF DNA

- Genetic variation may impact a participant's response to therapy, susceptibility, severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a saliva sample will be collected for deoxyribonucleic acid (DNA) analysis.
- DNA samples will be used for research related to [FF/VI or FF] or [asthma] and related diseases. They may also be used to develop tests/assays including diagnostic tests) related to [FF/VI or FF] (or study treatments of this drug class), and [asthma]. Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome [or analysis of the entire genome] (as appropriate).
- DNA samples will be analyzed if it is hypothesized that this may help further understand the clinical data.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on [FF/VI or FF] (or study treatments of this class) or [asthma] continues but no longer than [15] years or other period as per local requirements.

14.6. Appendix 6: 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 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) • **Do not restart/rechallenge** participant with study treatment unless allowed per protocol	• 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 DNA and Hepatitis delta antibody[5]. • Obtain blood sample for pharmacokinetic (PK) analysis, within insert time interval recommended by clinical

Liver Chemistry Stopping Criteria	
and GSK Medical Governance approval **is granted.** • If restart/rechallenge **not allowed or not granted**, permanently discontinue study treatment 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	pharmacokinetics representative after last dose[6] • 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 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.

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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.

14.7. Appendix 7: 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 (see Section 9.1.1. for the list of GSK medical devices).

14.7.1. 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.

14.7.2. Definition of Medical Device SAE, SADE and USADE

A Medical Device SAE is any serious adverse event **that:**	
g.	Led to death
h.	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
i. Led to fetal distress, fetal death or a congenital abnormality or birth defect
j. 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 3.3).

14.7.3. 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.

14.7.4. 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 the CRO in lieu of completion of the CRO/AE/SAE/device deficiency form.
- There may be instances when copies of medical records for certain cases are requested by the CRO. 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 the CRO.
- 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) 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 the CRO 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 the CRO within 24 hours of receipt of the information.

14.7.5. Reporting of SAEs

SAE Reporting to GSK via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the CRO 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 medical monitor by telephone.
- Contacts for SAE reporting can be found in the SRM.

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 medical monitor. • 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 the SRM.

14.7.6. 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 the CRO within 24 hours after the investigator determines that the event meets the definition of a device deficiency. • The CRO 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 the SRM.

14.8. Appendix 8: Country-specific requirements

For Germany only exclusion criterion 8 will be as follows:

Exclusion of participants with QTc > 450 msec or those with any other significant abnormality in the screening 12-lead ECG.

14.9. Appendix 9: COVID-19 Measures

Protocol Title: A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids

Protocol Number: HZA107116/04 Amendment 4

Compound Number or Name: GW685698+GW642444

Brief Title: A double-blind, parallel group study to evaluate the safety and efficacy of fluticasone furoate/vilanterol combination compared to fluticasone furoate in the treatment of asthma in participants (aged 5 to 17 years old inclusive)

Study Phase: IIIA

Approval Date: 24-AUG-2020

THIS APPENDIX APPLIES TO ALL CURRENT APPROVED VERSIONS OF PROTOCOL HZA107116

Overall Rationale for this Appendix

COVID-19 pandemic may impact the conduct and delivery of clinical studies. Challenges may arise from quarantines, site closures, travel limitations and/or interruptions to the supply chain for the investigational product. These challenges may lead to difficulties in meeting protocol-specified procedures, including administering or using the investigational product, adhering to protocol-mandated visits, laboratory/diagnostic testing and study timelines.

HZA107116 is included in the Paediatric Investigation Plan (PIP) for Relvar™ Ellipta™, with a commitment to deliver to agreed European Medicines Agency (EMA) timelines. The COVID-19 pandemic may delay study timelines due to low recruitment rates as a result of site closures and travel limitations and may lead to a greater number of early withdrawals.

This protocol appendix outlines measures that may be applicable for any site impacted by the COVID-19 pandemic and to ease the burden on site staff, subjects and parents by allowing flexibility in the way the visits are conducted in an attempt to counter the impact of COVID-19 pandemic on recruitment and retention. The purpose of the appendix is to provide information on the measures to be taken to protect participants' safety, welfare and rights, promote data integrity and deliver the study within the agreed timelines of the PIP.

These measures will remain in place until study completion.

Study Procedures During COVID-19 Pandemic

During the special circumstances caused by the current COVID-19 pandemic, sites should consider specific public health guidance, the impact of any travel restrictions implemented by local/regional health authorities and local institutions, and individual benefit /risk when making enrollment and treatment decisions for trial participants.

Clinical investigators should document in site files and in source data, how COVID related restrictions or challenges may have impacted study conduct for any participants. Missing or delayed protocol required data/visits due to COVID-19 should be noted in participant notes and recorded as a COVID-19 protocol deviation.

Protocol Defined Procedures/Visits:

Where applicable country and local regulations and infrastructure for home healthcare allow, home healthcare may take place at a location other than the clinical trial site to perform study assessments, which may include collection of blood and urine samples, measurement of vital signs, weight, spirometry and dispensation and collection of study drug (at the discretion of the Investigator). It is the responsibility of the investigator to inform the CRO when this occurs and to document in source notes.

- Remote visits may be performed at the participant's home by qualified study personnel, unless the Investigator deems that a site visit is necessary.

- Additional unscheduled safety assessments such as routine blood sampling may be performed at the discretion of the Investigator including in the participant's home, if deemed necessary. Biological samples may be collected at a different location, other than the study site (e.g., at participant's home) by qualified study personnel or at a local medical facility according to standard operating procedures and applicable regulations (see note). Biological samples should not be collected if they cannot be processed in a timely manner or appropriately stored until the intended use.

- Spirometry may be collected by a home health nurse, at visits indicated in the SOA, to alleviate the burden on subjects of frequent visits to the study site. The spirometry must be done using a Masterscope provided by the spirometry vendor, ERT (with central over-read). Nurses will be experienced in spirometry and will be trained by ERT.

  NOTE: Serial spirometry at Visit 6 must be done in the clinic.

- If visits to a site/home are not feasible, then the medical evaluation of asthma may take place by telemedicine which will use secure video conferences, phone calls, and a web portal and/or mobile application as a way of communicating with and monitoring the participant's progress. The CRO will be accountable for working with Science 37 (the vendor) to ensure the site has the required equipment, training and support for this model and should be notified as soon as possible by the investigator that the service is required.

- As part of this model, study visits are completed using the Science 37 platform, which is a software interface that connects participants to their investigators and study teams through either a study-issued smartphone or participant's own device (BYOD) model in addition to providing a data collection platform. This technology may be used in combination with visits from mobile study personnel (e.g. mobile nurses) to participants' homes for various lab collections and designated study procedures.

- The study investigator is responsible for ensuring that the identification, management, and reporting of AEs and SAEs are completed in accordance with the protocol and applicable regulations. AEs are first reported by participants to the investigator/study team or may be identified by the study team during interactions with the participants via telemedicine encounters. In addition, mobile nurses may identify AEs as well and report them to the investigator for evaluation. Additionally, AEs may be identified from lab reports, imaging or ECG reports, and other records. As determined by the investigator, the appropriate medical intervention, therapeutic intervention, and/or support measures are instituted, as necessary. Provision of a study-issued smartphone or the Science 37 app on a participant's own device allows for study participants to report AEs at any time. Participants can also request a timely secure videoconference with the investigator and/or site staff.

- The participant should be informed of the plan and any potential risks associated with the virtual medium and sign a revised Informed Consent Form if required. IRB/Ethics committee should be informed and/or approve of this change in approach and the process documented in study files.

- The schedule of study activities is provided in Table 1.

Study Intervention(s)

If allowed by country regulation/ethics, then study intervention (including rescue study medication and ancillary supplies related to IMP administration) can be shipped direct-to-patient (DTP) from the investigational site to the participant's home address. The process for this shipment must be agreed with the CRO who will provide the relevant documentation and links to courier sites required to ensure shipments are adequately temperature controlled (if required) throughout transportation.

The Principal Investigator assumes Good Clinical Practice (GCP) responsibilities for IMP handling and the medical control for dispensing to patients. Site Staff should document the

dispensing in the Dispensing/Accountability Logs adding a comment that this was a DTP dispensing.

Compliance with provisioning and collection of study drug will be verified through observation by study staff or trained home healthcare professionals.

In some cases, trial participants who no longer have access to investigational product or the investigational site may need additional safety monitoring (e.g., on withdrawal of an active investigational treatment).

Data Management/Monitoring

The eDiary device provided to the participant may be returned to the home nurse after Visit 9)/ETD/EW or the participant should be instructed to maintain the device and to return them to the site when a visit to the site will be allowed.]

If on-site monitoring is no longer permitted, the CRO will consider remote Source Data Verification/Source Document Review (SDV/SDR) where permitted by the clinical site/institution. Remote SDV/SDR will be proposed to study sites to meet a patient and/or critical quality need, e.g., to assess participant safety or to ensure data integrity. In case of remote SDV/SDR, the CRO will work with the site to ensure subject privacy.

eCRF/CRF Final or Interim Sign off Process: The Principal Investigator (PI) is responsible for ensuring that the data within the eCRF casebook and any other data sources utilized during the study for each study participant is complete and consistent with source documents throughout the study (ICH GCP 4.9.1 4.9.2). The PI may sign/re-sign the eCRF from any computer/location by accessing the eDC platform using his/her unique eCRF log-in credentials. The PI may delegate this activity to another medically qualified and trained sub-investigator and this must be documented on the Delegation of Responsibilities (DoR) Log. It is recommended that the PI identifies a sub-investigator as a back-up for eCRF signatures. The sub-investigator must be appropriately trained on the protocol and eCRF requirements (with training documented), and the DoR log updated accordingly.

Essential Document Sign Off Process: If an investigator is unable to print and sign essential documents such as Protocol /Amendment signature page then Email approval can be accepted by replying to the relevant email that is sent by the CRO.

14.10. Appendix 10: Protocol Amendment History

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

The Protocol Amendment Summary of Changes for the previous amendments (Amendment 01 and Amendment 02) is provided below.

Amendment 01 19-JUN-2019

Overall Rationale for the Amendment: The aim of this amendment is to aid in the recruitment of participants in this study. The changes will allow flexibility to perform spirometry manoeuvres are screening especially in the younger participants.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signature Page	Amended to indicate new sponsor signatory	Amended as there is a change in sponsor signatory.
Synopsis and Section 4 Objectives and Endpoints	Added clarity around the primary endpoint to indicate which was required by the FDA and EMA.	To provide clarity based on regulatory feedback.
Section 6.1 Inclusion criteria	Inclusion criterion 3 – Prebronchodilator FEV1. The note to this criterion has been amended to allow participants who are unable to perform their prebronchodilator FEV1 at Visit 1 another attempt that can be within 7 days of this visit.	This was amended to allow flexibility to the younger participants in this study, who may find it challenging to perform spirometry for the first time at the screening visit.
Section 6.1 Inclusion criteria	Inclusion criterion 4: Reversibility This criterion has been amended to reflect that the waiting time after SABA will be within 15 and 40 minutes instead of 10 and 40 minutes as in the original protocol.	This was amended to allow more time for the SABA to take effect and allow participants a better chance of demonstrating reversibility.
Section 6.1 Inclusion criteria	Inclusion criterion 8: Male and Female participants A note has been added to clarify that females who are lactating are not to be included.	Added based on feedback that was received when the original protocol was issued. An administrative letter was produced for sites at the time.
Section 6.2 Exclusion criteria	Exclusion criterion 6: Obesity This criterion has been amended to ensure that severely obese participants (ie, participants who have a BMI above the 99th) are excluded rather than	Amended to ensure that severely obese participants were excluded as severe obesity has an impact on respiratory function.

Section # and Name	Description of Change	Brief Rationale
	those who classed as obese (ie, had a BMI at the 97th centile as in the original protocol).	
Section 6.2 Exclusion criteria	Exclusion criterion 8: QTc This criterion has been amended to indicate that only QTc(F) will be used for eligibility purpose.	Amended to provide clarity and to ensure that sites are consistently using one QTc formula when assessing a participant's eligibility.
Section 6.2 Exclusion criteria	Exclusion criterion 10: Relevant habits (Tobacco use) This criterion has been amended to indicate that participants using e-cigarettes and who are vaping are also excluded.	Amended to ensure that all tobacco or smoking-related use was not allowed.
Section 6.3 Screen Failures	This was amended to allow for re-screening of screen failures up to one additional time.	Amended to help with recruitment of a difficult to recruit population.
Section 9.1.1 Efficacy Assessments - FEV1	Added that predicted FEV1 values are based on ERT standards for spirometry.	Added for clarity
Section 10.1.1.1. Sample Size Assumptions for 5-17 Year Old Population	Corrected an error and added more detail regarding the standard deviation assumed for the primary endpoint for the 5-17 years old population.	Added following a regulatory request from the FDA for more information.
Section 12.7 Appendix related to country-specific changes	Added a change in exclusion criterion 8 that is applicable to participants in Germany only.	Added based on feedback that was received when the original protocol was issued. An administrative letter was produced for sites at the time.

Amendment 02 10-DEC-2019

Overall Rationale for the Amendment: Asthma is a variable condition especially in children. Additionally, spirometry is a procedure that is often challenging to perform in this population and children may have symptomatic asthma even when they appear to have normal lung function. The changes in this amendment take into account the variability in asthma by allowing re-screening, and also by increasing the maximum permitted FEV_1 at screening and randomisation to 100% predicted normal. These changes are expected to help with recruitment of this population.

Section # and Name	Description of Change	Brief Rationale
Schedule of Activities (SOA)	Visit 4 and Visit 5 will become optional parent only visits, and as a result FEV_1 measure will only need to be done if the participant attends the clinic. A footnote is added to indicate this. Also, the footnote states if the participant does come to the clinic with the parent, and the visit occurs in the morning (6.00am to 11.00am) then the spirometry measurement should be performed. If only the parent attends, then this can be at any time of day.	This was amended to give participants the option of not attending to reduce burden on younger participants having to miss more school days and come to the site. Parents will need to come to collect study treatment.
Section 5.1, Overall Study Design	Figure 1 – Study Schematic updated to add footnotes relating to Visits 4 and 5 Last paragraph in Section updated with details around Visits 4 and 5. And amended wording to indicate which visits need to be morning visits.	Changes made for consistency and clarity.
Section 6.1 Inclusion criteria	Inclusion criterion 1 – Age Changed 'at the time of signing the informed consent' to 'at the time of screening'.	This was amended for consistency as participants are stratified by age at screening.
Section 6.1 Inclusion criteria	Inclusion criterion 3 – Prebronchodilator FEV_1. The upper limit of the range has been changed from ≤90% to ≤100%	This was amended to reflect that the younger population often have a pre-bronchodilator FEV_1 predicted that is normal but they may still have symptomatic asthma. This change was therefore to aid recruitment of symptomatic asthma participants who demonstrate reversibility but who may have normal lung function.
Section 6.1 Inclusion criteria	Inclusion criterion 3 – Prebronchodilator FEV_1. The note to this criterion has been amended to allow participants who are unable to perform their FEV_1 at Visit 1 another attempt that can be within 14 days of this visit. This is extended from the 7 days that was allowed in amendment 1.	This was amended to allow flexibility to the younger participants in this study, who may be unfamiliar with the procedure and may find it challenging to perform spirometry for the first time at the screening visit.

Section # and Name	Description of Change	Brief Rationale
Section 6.1 Inclusion criteria	Inclusion criterion 3 – Reversibility. The note to this criterion has been amended to allow participants who are unable to attempt to perform their FEV_1 at Visit 1 another attempt that can be within 14 days of this visit.	This was amended to allow flexibility to the younger participants in this study, who may be unfamiliar with the procedure and find it challenging to perform spirometry for the first time at the screening visit.
Section 6.3 Screen Failures	This was amended to allow for re-screening of screen failures.	Asthma is a variable condition especially in children, thus participants who have screen-failed could be re-screened at a later date if the severity of their asthma has changed. This will help recruitment of younger participants.
Section 8.1.2	Amended text to indicate that only QTcF is used for the ECG. A footnote was added to the SOA to indicate that the QTc should be based on a single or averaged QTc values of triplicate ECGs.	Amended for clarity.
Section 9.1.1	• Amended the visits in 4th paragraph. • Removed reference to ERT in 5th paragraph.	• Standardise wording • Added Quanjar (2012) for calculation of predicted normal FEV_1.
General throughout	Added Albuterol.	Standardise wording to reflect the fact that salbutamol is known as albuterol in USA and some other countries.

Amendment 03 31-JAN-2020

Overall Rationale for the Amendment: As Visit 4 is the first visit after randomisation to study treatment, it is considered an important visit at which to collect clinical data.

Section # and Name	Description of Change	Brief Rationale
Sponsor Signatory	Change to the sponsor signatory department details	Revision made due to organisational changes.
Schedule of Activities (SOA)	Visit 4 will no longer be an optional parent only visit.	As Visit 4 is the first visit after randomization to study treatment, it was considered

Section # and Name	Description of Change	Brief Rationale
	The participant will need to attend this visit where clinical assessments as indicated in the schedule of activities will need to be assessed. Thus 'Footnote 2' has been amended to remove Visit 4.	by the regulators to be an important visit at which to collect clinical data.
Section 5.1, Overall Study Design	Figure 1 – Study Schematic updated to remove reference to Visit 4 being an optional parent only visit. Last paragraph in this Section amended to correctly reference Visit 4.	Changes made for consistency and clarity.
Section 7.7.1, Prohibited Medications and Non-Drug Therapies	The changes made to Section 7.7.1 included the addition of the following note and new text (red text denotes new text): •Note: Participants should be treated as appropriate for asthma exacerbations without requirement to withdraw the participant from the study. Steroids will be an exclusion from randomisation if administered during the run-in period (apart from FP). However, they should never be withheld if deemed necessary. •Use of the following medications is prohibited according to the timeframes indicated unless they are deemed necessary to treat an asthma exacerbation or another condition appropriately: •From screening visit (Visit 1) to Visit 9: LTRAs, ketotifen, nedocromil sodium, orally inhaled sodium cromoglycate, SABA/short-acting muscarinic antagonist (SAMA) combinations (e.g. Combivent), and inhaled corticosteroids (except for FP which is given during the run-in).	To provide further clarity on the use of steroids.
Section 9.1.1 FEV1	Fourth paragraph amended text to correctly reference Visit 4.	Changes made for consistency and clarity.