TITLE PAGE

Division: Worldwide Development

Information Type: Clinical Protocol

Title:	Study HZA114971, A Multicentre Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate 50 mcg once daily on Growth Velocity in Prepubertal, Paediatric Subjects with Asthma

Compound Number: GW685698

Development Phase IV

Effective Date: 06-MAR-2019

Author(s): PPD
PPD

Revision Chronology

GlaxoSmithKline Document Number	**Date**	**Version**
2016N269987_00	2016-JUN-28	Original
2016N269987_01	2016-NOV-04	Amendment No. 1

This amendment was implemented:

- Remove the term local growth charts and replace with US CDC charts for inclusion criteria 4 and 5.
- Amend the text for inclusion criterion 7 to provide clarity on the time window used for re-scheduling the spirometry assessment at screening (Visit 1).
- Remove the term WHO growth charts and replace with North America Longitudinal Standard Growth Velocity Charts for randomization criterion 1c.
- Amended typographical error in Section 5.5.4 and to clarify that the subject will be withdrawn from study treatment (for consistency with Section 5.5.1).
- Amend the text and provide clarity on the procedure around oropharyngeal exams in Section 7.3.5.
- Amend the time and events table to show an 'x' for body weight at Visit 3 as this was missing.
- Remove word "continuously" in Section 9.1
- Add a supportive completers' analysis of growth velocity over the 1-year double-blind treatment period, based on subjects who completed the double-blind treatment period while remaining on study treatment, in Section 9.4.1.1.
- Add a summary of change in height standard deviation scores (SDS) from baseline to endpoint in Section 9.4.2.1.

2016N269987_02	2019-MAR-06	Amendment No. 2

This amendment incorporates the following changes:

- Removal of the upper limit of the FEV_1 from inclusion criterion 7 (Section 5.1).
  - ***Justification for change:*** *FEV_1 is often close to or above 100% in young children with controlled asthma. This is due to the variability of asthma with normal spirometry lung function tests (LFT) values between asthma attacks in this young population (5-9 years) with controlled asthma. For this reason, an upper limit of 95% has not been used in previous similar studies (e.g.*

Ciclesonide growth study. (2008) (paediatrics Vol 121 (1) e1-e14).

- Removal of calcitriol from exclusion criteria 3 (Section 5.2) and from the prohibited medications Table 3 (Section 6.10.2).

  - ***Justification for change:*** *Children living in regions with low sun exposure (especially in winter) can be advised to take Calcitriol (synthetic version of Vitamin D3) at prophylactic doses (e.g. 400 IU in Caucasians, 800 IU in black children) to prevent Vitamin deficiency and rickets. Excluding children taking calcitriol at prophylactic doses may remove unnecessarily subjects likely to benefit from the study drug treatment.*

- Update of text in Section 5.3 (Screening/Baseline/Run-in Failures) to allow re-screening of subjects who have failed screening.

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Regulatory Agency Identifying Number(s): IND No: 070297

INVESTIGATOR PROTOCOL AGREEMENT PAGE

- I confirm agreement to conduct the study in compliance with the protocol.
- I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described study.
- I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name: _____

Investigator Signature	Date

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1. PROTOCOL SYNOPSIS FOR STUDY HZA114971

Rationale

Growth impairment is a well-established adverse effect of glucocorticosteroids in children. Due to significantly reduced systemic exposure the potential impact of inhaled corticosteroids (ICS) on growth is small when compared with the effect observed with the use of oral corticosteroid treatments. Evidence derived from a Cochrane meta-analysis of randomised trials shows that regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm per year in linear growth velocity and 0.61 cm in change from baseline in height during a one-year treatment in children with mild to moderate persistent asthma. The effect size of ICS on linear growth velocity appears to be associated more strongly with the ICS molecule than device or dose (low to medium dose range). ICS-induced growth suppression seems to be maximal in the first year of therapy and less pronounced in the subsequent years of treatment (Zhang, 2014). Hence it is useful to assess the magnitude of growth reduction when developing a novel inhaled corticosteroid. There is a regulatory requirement to evaluate the extent of reduction (if any) of growth velocity associated with ICS containing products that are to be administered to children, and to this end there is FDA regulatory guidance [Guidance for Industry Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children, 2007]. One year is considered the minimum duration to assess growth in a robust fashion. The one-year duration minimises some confounding factors such as seasonal variations and measurement errors.

The purpose of the study is to evaluate the magnitude of effect (with a level of precision) on growth velocity of prepubertal asthmatic paediatric subjects (aged 5 to <9 years) following administration of once daily (OD) inhaled fluticasone furoate (FF) 50 mcg for one year. This study fulfils EU and US regulatory requirements for the evaluation of potential growth suppression in children.

Objectives/Endpoints

Objectives	Endpoints
Primary	
• To evaluate the magnitude of effect (with a level of precision) of inhaled FF 50 mcg versus inhaled placebo OD on growth velocity in prepubertal children over one year of treatment	**Primary** • Growth Velocity (cm/yr) over the double-blind treatment period, as determined by stadiometry **Secondary** • Proportion of subjects below the 3rd percentile of growth velocity • Change in growth velocity quartiles from baseline to endpoint • Growth velocity over the first 12 weeks of double-blind treatment period • Height standard deviation scores (SDS) at each visit
Secondary	
• To assess the safety of inhaled FF 50 mcg OD	• Incidence of adverse events • Incidence of asthma exacerbations
Other	
• To assess the effect of inhaled FF 50 mcg OD on efficacy endpoints, used as a measure of compliance to help identify non-adherence and/or poorly controlled asthma	• Change from baseline in the percentage of rescue-free 24 hour periods over the double-blind treatment period • Change from baseline in the percentage of symptom-free 24 hour periods over the double-blind treatment period • Change from baseline in AM Peak Expiratory Flow (PEF) averaged over the double-blind treatment period • Change from baseline in cACT score at the end of the double-blind treatment period

Overall Design

This is a randomised, single-blind (run-in period)/double-blind (treatment period), parallel group, placebo controlled, multicentre study to assess the effect of once daily (OD) inhaled FF 50 mcg on growth velocity in prepubertal asthmatic children on a background therapy of open-label montelukast. Study randomisation will be stratified by country.

Treatment Arms and Duration

This study will be conducted over a total duration of approximately 76 weeks: 16-week run-in period, 52-week double-blind treatment period and 8-week follow-up period.

Eligible subjects will receive a single-blind placebo inhaler during the 16-week run-in period. After completing the run-in period, eligible subjects will be randomly allocated to one of two treatment regimens:

- inhaled FF 50 mcg administered OD in the morning for 52 weeks

or

- inhaled placebo administered OD in the morning for 52 weeks

Each treatment will be administered via the ELLIPTA™ dry powder inhaler [formerly referred to as a novel dry powder inhaler (NDPI)].

Subjects will also receive open-label montelukast (4 mg for subjects who are 5 years old and 5 mg for subjects who are ≥6 years old). Subjects will take one tablet of montelukast each evening for the duration of the study (from the run-in period through to the end of the follow-up period). **Note:** subjects who turn 6 years old during the study, will subsequently receive 5 mg of open-label montelukast.

In addition, each subject 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.

Subjects (i.e., the child) **must** attend the clinic on the following visits for stadiometry and other key assessments:

- **Visits 1 and 3 (Screening visit and run-in period):**
    - Visit 1, subjects will attend the clinic for screening procedures. Subjects meeting the eligibility criteria will enter the 16-week run-in period.
    - Visit 3, subjects will attend the clinic for stadiometry assessment and any other assessments as indicated in the Time and Events Table (Section 7.1).
- **Visit 5 (Randomisation):**
    - Eligible subjects will be randomised to one of two treatment groups.

- Subjects will attend the clinic for stadiometry assessments and any other assessments as indicated in the Time and Events Table (Section 7.1).

- **Visits 6, 7, 8, 9, 12, 15 and 18 (Double-blind treatment period)**
  - Subjects will attend the clinic for stadiometry assessments and any other assessments as indicated in the Time and Events Table (Section 7.1).

- **Visit 20 (Follow-up period)**
  - Subjects will attend the clinic for stadiometry assessments and any other assessments as indicated in the Time and Events Table (Section 7.1).

NOTE: While the subject (ie, the child) only has to attend the clinic on the scheduled visits for stadiometry assessments (as indicated above), their parents/guardians **must** attend the clinic every month to collect/return diaries and collect/return double-blind treatment.

Type and Number of Subjects

Approximately 900 asthmatic prepubertal subjects, aged 5 to <8 years (girls) or 5 to <9 years (boys), will be screened to achieve at least 450 randomised and 406 evaluable subjects (approximately 203 evaluable subjects per treatment group).

Analysis

The primary analysis will be the comparison of the growth velocities between inhaled FF 50 mcg once daily (OD) (plus montelukast open-label) and inhaled placebo (plus montelukast open-label) over the 52-week treatment period. An analysis of covariance (ANCOVA) will be performed to estimate the mean treatment difference in growth velocity over the double-blind treatment period, adjusting for baseline growth velocity, age at Visit 1, gender and country. A 95% confidence interval will also be provided for the estimated mean treatment difference in growth velocity over the double-blind treatment period.

2. INTRODUCTION

2.1. Study Rationale

Growth impairment is a well-established adverse effect of glucocorticosteroids in children. Due to significantly reduced systemic exposure the potential impact of inhaled corticosteroids (ICS) on growth is small when compared with the effect observed with the use of oral corticosteroid treatments. Evidence derived from a Cochrane meta-analysis of randomised trials shows that regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm per year in linear growth velocity and 0.61 cm in change from baseline in height during a one-year treatment in children with mild to moderate persistent asthma. The effect size of ICS on linear growth velocity appears to be associated more strongly with the ICS molecule than device or dose (low to medium dose range). ICS-induced growth suppression seems to be maximal in the first year of therapy and less pronounced in the subsequent years of treatment (Zhang, 2014). Hence it is useful to assess the magnitude of growth reduction when developing a novel inhaled corticosteroid. There is a regulatory requirement to evaluate the extent of reduction (if any) of growth velocity associated with ICS containing products that are to be administered to children, and to this end there is FDA regulatory guidance [Guidance for Industry Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children, 2007]. One year is considered the minimum duration to assess growth in a robust fashion. The one-year duration minimises some confounding factors such as seasonal variations and measurement errors.

The purpose of the study is to evaluate the magnitude of effect (with a level of precision) on growth velocity of prepubertal asthmatic paediatric subjects (aged 5 to <9 years) following administration of once daily (OD) inhaled fluticasone furoate (FF) 50 mcg for one year.

2.2. Brief Background

Asthma is a chronic disease of the lungs characterised by airway inflammation, bronchoconstriction and increased airway responsiveness. Inhaled corticosteroids (ICS) are considered the most effective anti-inflammatory treatments for all severities of asthma [GINA, 2016; National Institutes of Health, 2007; British Guideline, 2008]. 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].

One of the well-recognised and specific adverse effects of glucocorticosteroids in children is potential growth impairment. The effects of glucocorticosteriods on the growth plate are complex. Local effects of glucocorticosteriods at the growth plate include reduction of IGF-I production, inducing IGF-I resistance and reducing production of C-type natriuretic peptide, which results in a reduction of chondrocyte proliferation, matrix synthesis and hypertrophy. These reductions in chondrocyte function result in decreased linear growth.

Although the use of inhaled corticosteroids results in lower systemic exposure than that with oral steroids, it does not completely exclude the risk of some mild degree of growth attenuation. It seems that the effect is more marked during the first year of treatment but is not sustained afterwards [Kelly, 2012]. A recent long term study has suggested that the initial decrease in attained height associated with the use of inhaled glucocorticoids in prepubertal children persisted as a reduction in adult height, although the decrease was not progressive or cumulative [Kelly, 2012].

Evidence derived from a Cochrane meta-analysis of randomised trials shows that regular use of ICS at low or medium daily doses is associated with a mean reduction of 0.48 cm per year in linear growth velocity and 0.61 cm in change from baseline in height during a one-year treatment in children with mild to moderate persistent asthma. The effect size of ICS on linear growth velocity appears to be associated more strongly with the ICS molecule than device or dose (low to medium dose range). The ICS-induced growth suppression seems to be maximal in the first year of therapy and less pronounced in the subsequent years of treatment [Zhang, 2014]. Another Cohrane review of the literature concluded that in persistent asthma, a small but statistically significant group difference in growth velocity was observed between low doses of ICS and low to medium doses of HFA-beclomethasone equivalent, favouring the use of low-dose ICS [Pruteanu, 2014]. In the four comparisons reporting linear growth over 12 months, a significant group difference was observed, clearly indicating lower growth velocity in the higher ICS dose group of 5.74 cm/y compared with 5.94 cm/y on lower-dose ICS (N = 728 school-aged children; mean difference (MD) 0.20 cm/y, 95% confidence interval (CI) 0.02 to 0.39). The authors concluded that in view of prevailing parents' and physicians' concerns about the growth suppressive effect of ICS, lack of or incomplete reporting of growth velocity in more than 86% (19/22) of eligible paediatric trials including those using beclomethasone and budesonide, is a matter of concern.

Therefore, there is good evidence to suggest that the first year of treatment with an inhaled corticosteroids is the most critical phase with respect to growth. In view of the seasonal variations in growth, one year is the minimum duration to reliably measure annual growth velocity [Tillmann, 2001].

Fluticasone furoate (FF) is a glucocorticoid approved in the United States of America for use as a once daily (OD) ICS for the maintenance treatment of asthma in patients aged 12 years and over (ARNUITY™ ELLIPTA). It is also the ICS component of a once daily ICS/Long Acting Beta Agonist (LABA) combination inhaler (fluticasone furoate/vilanterol) approved in over 50 countries for once daily treatment of asthma in patients aged 12 years of age and older (RELVAR™ ELLIPTA /BREO™ ELLIPTA). The fluticasone furoate/vilanterol inhalation powder, hereafter referred to as FF/VI 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. The FF and FF/VI paediatric asthma development programmes are currently ongoing.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate the magnitude of effect (with a level of precision) of inhaled FF 50 mcg versus inhaled placebo OD on growth velocity in prepubertal children over one year of treatment	**Primary** • Growth Velocity (cm/yr) over the double-blind treatment period, as determined by stadiometry **Secondary** • Proportion of subjects below the 3rd percentile of growth velocity • Change in growth velocity quartiles from baseline to endpoint • Growth velocity over the first 12 weeks of double-blind treatment period • Height standard deviation scores (SDS) at each visit
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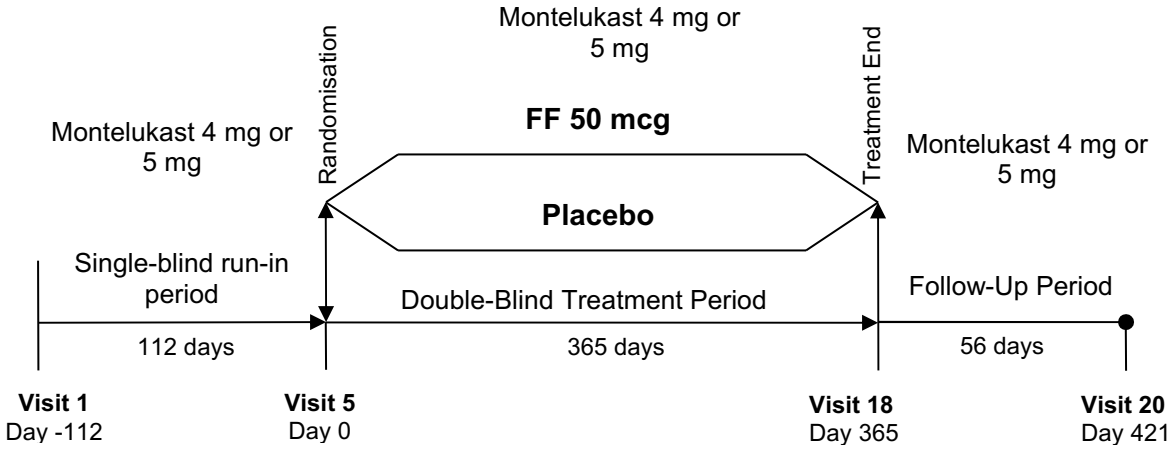
• To assess the safety of inhaled FF 50 mcg OD	• Incidence of adverse events • Incidence of asthma exacerbations
Other	
• To assess the effect of inhaled FF 50 mcg OD on efficacy endpoints, used as a measure of compliance to help identify non-adherence and/or poorly controlled asthma	• Change from baseline in the percentage of rescue-free 24 hour periods over the double-blind treatment period • Change from baseline in the percentage of symptom-free 24 hour periods over the double-blind treatment period • Change from baseline in AM PEF averaged over the double-blind treatment period • Change from baseline in cACT score at the end of the double-blind treatment period

4. STUDY DESIGN

4.1. Overall Design

This is a randomised, single-blind (run-in period)/double-blind (treatment period), parallel group, placebo controlled, multicentre study to assess the effect of FF 50 mcg OD on growth velocity in prepubertal asthmatic children on a background therapy of open-label montelukast (Figure 1). Study randomisation will be stratified by country.

Figure 1 Study Schematic



FF = Fluticasone Furoate Inhaled Powder.
*Montelukast 4mg will be provided to 5-year olds and montelukast 5 mg will be provided to children ≥ 6 years.

4.2. Treatment Arms and Duration

This study will be conducted over a total duration of approximately 76 weeks: 16-week run-in period, 52-week double-blind treatment period and 8-week follow-up period. The study randomisation will be stratified by country.

Eligible subjects will receive a single-blind placebo inhaler during the 16-week run-in period. After completing the run-in period, eligible subjects will be randomly allocated to one of two treatment regimens:

- inhaled FF 50 mcg administered OD in the morning for 52 weeks

or

- inhaled placebo administered OD in the morning for 52 weeks

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

Subjects will also receive open-label montelukast (4 mg for subjects who are 5 years old and 5 mg for subjects who are ≥6 years old). Subjects will take one tablet of montelukast each evening for the duration of the study (from the run-in period through to the end of the follow-up period). **Note:** subjects who turn 6 years old during the study, will subsequently receive 5 mg of open-label montelukast.

In addition, each subject 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.

Subjects (i.e., the child) **must** attend the clinic on the following visits for stadiometry and other key assessments:

- **Visits 1 and 3 (Screening visit and run-in period):**
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NOTE: While the subject (i.e., the child) only has to attend the clinic on the scheduled visits for stadiometry assessments (as indicated above), their parents/guardians **must** attend the clinic every month to collect/return diaries and collect/return double-blind treatment.

4.3. Type and Number of Subjects

Approximately 900 asthmatic prepubertal subjects, aged 5 to <8 years (girls) or 5 to <9 years (boys) will be screened to achieve at least 450 randomised and 406 evaluable

subjects (approximately 203 evaluable subjects per treatment group; see Section 9.2 for further details on Sample Size Considerations).

4.4. Design Justification

This study will use stadiometry to determine the effect of once daily treatment with inhaled FF 50 mcg on growth velocity in children aged 5 to <9 years of age.

All elements of study design are based on recommendations/guidelines from regulatory authorities for growth velocity studies and regulatory advice for this development programme [Guidance for Industry Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children, 2007].

The duration of the double-blind treatment period (52 weeks) is considered sufficient to determine an effect of inhaled corticosteroids on growth velocity. This duration is considered sufficient to minimise measurement errors and seasonal variations.

In order to optimise the accuracy of growth assessments, repeated measurements will be taken approximately every 3 months with more frequent measurements at the start of therapy. Previous studies have shown that the greatest effect tends to be within the first few months [Roizen, 2012; Price, 2002; Pruteanu, 2014].

All subjects will be on a background of open-label montelukast tablets to avoid a "no treatment" arm. This should reduce the risk of uncontrolled asthma in the placebo group, hence minimising the rate of drop-outs, the negative growth effect of poor asthma control and confounding of concomitant corticosteroid used to treat exacerbations.

To ensure blinding throughout the study, subjects will receive single-blind inhaled placebo during the run-in period and all subjects will receive inhaled FF or inhaled placebo OD via the ELLIPTA dry powder inhaler during the double-blind treatment phase.

Furthermore, all children will be pre-pubertal to avoid the pubertal growth spurt, which is an important confounding factor in the assessment of paediatric growth.

The randomisation will be stratified by country to account for possible differences in medical practices and growth velocity across the countries.

4.5. Dose Justification

The 50 mcg is proposed as the FF dose for this study. In the phase 2b dose-ranging study HZA106855 statistically significant improvements in lung function (peak flow) and asthma control (rescue free days) were seen for the 50 mcg FF dose compared to placebo in children with asthma. Furthermore, there was no statistically significant reduction in urinary cortisol associated with FF when compared to placebo.

4.6. Benefit:Risk Assessment

Summaries of findings from both clinical and non-clinical studies conducted with fluticasone furoate (FF) can be found in the FF Investigator's Brochure [GlaxoSmithKline Document Number GM2004/00283/10].

For montelukast, information is taken from the label of SINGULAIR [SMPC, Summary of Product Characteristics, May 2016 (5 mg) and February 2016 (4 mg)].

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

4.6.1. Risk Assessment

For FF, the following risks related to inhaled corticosteroid use (ICS) as applicable to adult and adolescent asthma patients were taken from the risk table for ongoing risks for FF in the development safety update report 2015; (GlaxoSmithKline Document Number 2015N240433). The data/ rationale for the risks were derived from the literature, 2015 Investigator's Brochure [GlaxoSmithKline Document Number GM2004/00283/10] and from an integrated analysis of key FF studies as well as information for FF/VI.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Investigational Product (IP) [Fluticasone furoate (GW685698)]		
Pneumonia	For FF; in an integrated analysis of 10 studies in asthma (6219 patients) the rate 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 rate was observed across all treatment groups. An increased 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.	Subjects and their parents/guardians will be informed about the risk of pneumonia in the informed consent. Subjects and their parent/guardian will be advised to seek medical treatment if any signs of pneumonia occur. Investigators are informed of the risk in Section 6 (Contraindications) of the Investigator Brochure (IB).
Hypersensitivity	For FF there were few events reported in the asthma studies. As there was limited, short, exposure to placebo, any comparison is not	Subjects and their parents/guardians will be informed about the risk of hypersensitivity in the informed consent. Subjects and their

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	reliable. There are post-marketing reports of hypersensitivity to FF/VI. Adverse reactions may include anaphylaxis, angiodema, urticaria and rash.	parent/guardian will be advised to seek medical treatment if any signs 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 the risk in Section 6 (Contraindications) of the Investigator Brochure (IB).
Adrenal suppression	This is considered a class effect of ICS. Preclinical studies showed that FF effects are comparable with other corticosteroids. No studies have shown a clinically relevant effect of FF/VI on the hypothalamic-pituitary adrenal axis (HPA) at the 100/25 mcg strength. 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.	Subjects and their parents/guardians will be informed about the risk of adrenal suppression in the informed consent. Investigators are made aware of the potential for this class effect in Section 6 (Warnings and Precautions) of the IB. If systemic symptoms appear, investigators should implement an appropriate treatment while observing the subject's asthma symptoms.
Corticosteroid associated eye disorders	This is considered a class effect of ICS. Preclinical studies showed FF at high dose comparable to other high dose corticosteroids. In study HZA106839 (FF/VI, FF and FP in subjects with asthma), formal ophthalmic assessments were conducted (including LOCS III evaluations for ocular opacities) throughout the study. This study showed no apparent effects on lens	Subjects and their parents/guardians will be informed about the risk of corticosteroid associated eye disorders in the informed consent. Subjects will be advised to seek medical treatment if any signs of eye disorder occur. Investigators are made aware of the potential for this class effect in Section 5.3.2.2. (Adverse Effects) of the IB.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	opacification, compared to baseline. During studies in both subjects with asthma and COPD, no associated effect on ocular disorders was observed.	
Growth suppression	Preclinical studies have shown that the effects of FF at high doses are comparable with those of other corticosteroids. No clinical data is currently available in children. Children with asthma may experience growth retardation (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% 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 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	The protocol will explore the potential risk of reduction in growth velocity.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	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).	
Study Procedures		
Spirometry procedures	Shortness of breath, coughing, light-headedness or fainting, and/or chest tightness	If any of these symptoms should occur spirometry will be stopped and the subject will receive medical treatment.

4.6.2. Risk Assessment for Montelukast

Montelukast is a marketed drug with two dose strengths for the paediatric population:

- 2 to 5 years old: 4 mg chewable tab
- 6 to 14 years old: 5 mg chewable tab

In this study, montelukast will be used in line with the recommendations provided in the product label. A summary of the risks associated with montelukast is as follows:

Table 1 Common adverse reactions (≥1/100 to <1/10) in paediatric patients treated with montelukast

Body System Class	Paediatric Patients 6 to 14 years old (one 8-week study; n=201) (two 56-week studies; n=615)	Paediatric Patients 2 to 5 years old (one 12-week study; n=461) (one 48-week study; n=278)
Nervous system disorders	Headache	-
Gastrointestinal disorders	-	Abdominal pain
General disorders and administration site conditions	-	Thirst

1. Adapted from SINGULAIR Paediatric Granules SMPC, Summary of Product Characteristics, May 2016 (5 mg) and February 2016 (4 mg).

Table 2 Adverse reactions reported in post-marketing use of montelukast

System Organ Class	Adverse Experience Term	Frequency Category*
Infections and infestations	upper respiratory infection†	Very Common
Blood and lymphatic system disorders	increased bleeding tendency	Rare
Immune system disorder	hypersensitivity reactions including anaphylaxis	Uncommon
	hepatic eosinophilic infiltration	Very Rare
Psychiatric disorders	dream abnormalities including nightmares, insomnia, somnambulism, anxiety, agitation including aggressive behaviour or hostility, depression, psychomotor hyperactivity (including irritability, restlessness, tremor§)	Uncommon
	disturbance in attention, memory impairment	Rare
	hallucinations, disorientation, suicidal	Very Rare

System Organ Class	Adverse Experience Term	Frequency Category*
	thinking and behaviour (suicidality)	
Nervous system disorder	dizziness, drowsiness, paraesthesia/hypoesthesia, seizure	Uncommon
Cardiac disorders	palpitations	Rare
Respiratory, thoracic and mediastinal disorders	epistaxis	Uncommon
	Churg-Strauss Syndrome (CSS)	Very Rare
	pulmonary eosinophilia	Very Rare
Gastrointestinal disorders	diarrhoea‡, nausea‡, vomiting‡	Common
	dry mouth, dyspepsia	Uncommon
Hepatobiliary disorders	elevated levels of serum transaminases (ALT, AST)	Common
	hepatitis (including cholestatic, hepatocellular, and mixed-pattern liver injury).	Very Rare
Skin and subcutaneous tissue disorders	rash	Common
	bruising, urticaria, pruritus	Uncommon
	angiooedema	Rare
	erythema nodosum, erythema multiforme	Very Rare
Musculoskeletal, connective tissue and bone disorders	arthralgia, myalgia including muscle cramps	Uncommon
General disorders and administration site conditions	pyrexia	Common
	asthenia/fatigue, malaise, oedema,	Uncommon

*Frequency Category: Defined for each Adverse Experience Term by the incidence reported in the clinical trials data base: Very Common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1000 to <1/100), Rare (≥1/10,000 to <1/1000), Very Rare (<1/10,000).
†This adverse experience, reported as Very Common in the patients who received montelukast, was also reported as Very Common in the patients who received placebo in clinical trials.
‡This adverse experience, reported as Common in the patients who received montelukast, was also reported as Common in the patients who received placebo in clinical trials.
§ Frequency Category: Rare

1. Taken from SINGULAIR Paediatric Granules SMPC, Summary of Product Characteristics, May 2016 (5 mg) and February 2016 (4 mg).

4.6.3. Benefit Assessment

4.6.3.1. Fluticasone Furoate

The use of ICS is now well established in international treatment guidelines for paediatric asthma patients. The benefits of an ICS include control of asthma symptoms, improvement in lung function and a decrease in airway hyper-responsiveness. In addition subjects will receive short-acting beta2 agonists (SABA) for use 'as needed' for relief of asthma symptoms.

All subjects will undergo medical assessment at screening and over the treatment period. Subjects will have frequent clinic visits for the evaluation of their asthma during the study period. Subjects will have an assessment of FEV_1 at screening and there will be a review of a daily diary during the study. The diary will contain PEF measurements, rescue albuterol/salbutamol usage, daily symptom scores, and any medical problems experienced and if any medication was required.

4.6.3.2. Leukotriene receptor antagonists

Leukotriene receptor antagonists are established in international treatment guidelines for paediatric asthma patients [GINA, 2016]. Montelukast is an orally active compound which binds with high affinity and selectivity to the cysteinyl leukotriene ($CysLT_1$) receptor. In children under 5 years of age, montelukast improved parameters of asthma control compared with placebo irrespective of concomitant controller therapy (inhaled/nebulized corticosteroids or inhaled/nebulized sodium cromoglycate) [SMPC, 2016]. Benefits of treatment in children 6-14 years of age include an improvement in lung function and decreased "as-needed" β-agonist use [SMPC, 2016]. GINA guidance 2014 states than LTRA are less effective than ICS but may be appropriate for initial controller treatment for patients unwilling or unable to use ICS, or for patients with intolerable side effects to ICS or for patients with concomitant allergic rhinitis.

4.6.4. Overall Benefit:Risk Conclusion

GlaxoSmithKline (GSK) has assessed this study for any potential risks that a subject may experience. The investigational product (IP) FF has an acceptable safety profile for clinical use and there are no significant associated risks. This conclusion is supported by the results of previous clinical studies with the products in healthy volunteers and subjects with Asthma and COPD that can be found within the FF IB GlaxoSmithKline Document Number GM2004/00283/10] and the FF/VI IB [GlaxoSmithKline Document Number RM2008/00012/07. Safety criteria outlining details for subject withdrawal is included in the protocol (Section 5.5, Withdrawal Criteria). A thorough summary and evaluation of the available pre-clinical data can be found in the IB [GlaxoSmithKline Document Number GM2004/00283/10].

Montelukast is an authorised product for the treatment of paediatric asthma and as such it is generally accepted that the benefits of treatment outweigh the risks. It has been included in this study to ensure all subjects have at least one asthma controller medication

throughout the study, therefore reducing the risk of worsening asthma symptoms for subjects randomised to the placebo inhaler treatment arm.

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

5. SELECTION OF STUDY POPULATION AND WITHDRAWAL CRITERIA

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

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

5.1. Inclusion Criteria

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

DEMOGRAPHICS
1. Male or female subjects. 2. Age: a. Males between 5 and <9 years old b. Females between 5 and <8 years old 3. Subjects must be pre-pubertal (Tanner Stage 1). 4. Height centile between 3% and 97% based on US CDC charts. 5. Subjects with body weight and body mass index that is between 3rd and 97th centile based on the US CDC charts (provided in the Study Reference Manual [SRM]).

TYPE OF SUBJECT AND DIAGNOSIS INCLUDING DISEASE SEVERITY
6. A documented history of symptoms consistent with a diagnosis of asthma for at least 6 months prior to Visit 1. 7. A pre-bronchodilatory FEV_1 at Visit 1 (Screening) of ≥60%. There should be no SABA use within 4 hours of this measurement. **NOTE:** Only subjects who are unable to perform the FEV_1 manoeuvre at their Visit 1 can, at the discretion of the investigator, attend the clinic to perform the manoeuvre **once more** on another day before Visit 2. This repeat FEV_1 manoeuvre **must** be acceptable (as defined in the SRM) and **must** meet the FEV_1 inclusion limits to be eligible for the study. 8. Able to replace their current SABA treatment with study supplied rescue

albuterol/salbutamol provided at Visit 1 for use as needed for the duration of the study.

9. A cACT score of >19.

10. Patients should have required at least one course of corticosteroid for their asthma (inhaled or oral) in the past year.

    - There **must** be no ICS use within 6 weeks of Visit 1 (Screening).
    - There **must** be no oral corticosteroids use within 12 weeks of Visit 1 (Screening)

11. Using one or more of the following asthma therapies prior to entry into the study:

    - Short acting beta-agonist (SABA) inhaler alone (e.g. salbutamol) on an as needed basis and/or
    - Regular non-ICS controller medications for asthma (e.g. cromones or leukotriene receptor antagonists).

INFORMED CONSENT

12. Written informed consent from at least one parent/care giver (legal guardian) and accompanying informed assent from the subject (where the subject is able to provide assent) prior to admission to the study.
    - If applicable, subject must be able and willing to give assent to take part in the study according to local requirement. The study investigator is accountable for determining a child's capacity to assent for participation in a research study, taking into consideration any standards set by the responsible IEC.
    - Subject and their legal guardian(s) understand that they must comply with study medication administration regimens and study assessments including recording of symptom scores and rescue albuterol/salbutamol use, attending all study visits, and being accessible by telephone.

5.2. Exclusion Criteria

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

CONCURRENT CONDITIONS/MEDICAL HISTORY

1. Growth Criteria:

a. Any previous or current condition that affects growth, including sleep disorders, endocrine disorders, skeletal dysplasia, Turner and Noonan syndromes, Marfan, Beckwith–Wiedeman and Sotos syndromes, Klinefelter's syndrome, coeliac disease, inflammatory bowel diseases and renal failure or any significant abnormality or medical condition that is identified at the screening medical assessment (including serious psychological disorder) that is likely to interfere

with the conduct of the study.

b. Subjects with premature adrenarche (further details will be provided in the SRM).

c. A child who is unable to stand, or who finds standing difficult due to illness or physical disabilities should be excluded.

2. **Disease Criteria:**
   a. Subjects with a history of asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or use of a depot corticosteroid injection within 3 months or those requiring hospitalisation for asthma (within 6 months) prior to screening.
   b. Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of Visit 1 and led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study.
   c. Clinical visual evidence of candidiasis at Visit 1 (Screening).
   d. Any significant abnormality or medical condition identified at the screening medical assessment that in the Investigator's opinion, preclude entry into the study due to risk to the subject or that may interfere with the outcome of the study.

CONCOMITANT MEDICATIONS
3. **General:** a. Prior use of any medication or treatment that might affect growth including, but not limited to: amphetamines, anticonvulsants, biphosphonates, calcitonin, erythropoietin, growth hormone, methylphenidate, phosphate binders, antithyroid drugs (e.g., Methimazole) or thyroid hormone. 4. Use of any of the prohibited medications listed in Section 6.10.2.

CONTRAINDICATIONS
5. **Hypersensitivity:** Known hypersensitivity to corticosteroids, leukotrienes, or any excipients in the ELLIPTA inhaler and study tablets. 6. **Milk Protein Allergy:** History of severe milk protein allergy.

DIAGNOSTIC ASSESSMENTS AND OTHER CRITERIA
7. The subject has 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, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer).

8. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day.
9. Children who are an immediate family member of the participating Investigator, sub-Investigator, study coordinator, or employee of the participating Investigator.
10. The Parent or Guardian has a history of known or suspected 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 subject during the study
    - compliance of subject with study medication and study procedures (e.g.completion of daily diary, attending scheduled clinic visits)
    - subject safety and well-being
11. Children in care: Children who are wards of the government or state are not eligible for participation in this study.

5.3. Screening/Baseline/Run-in Failures

Screen failures are defined as subjects who consent to participate in the clinical trial, are assigned a subject number, and complete at least one study procedure but are not subsequently entered into the run-in period. Subjects who enter the run-in period but are not randomised are considered run-in failures. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required which may include Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events relating to study participation.

Re-screening of screen failures is permitted. Individuals who do not meet the criteria for participation in this study (i.e., are a screen failure) may be re-screened up to one additional time if the investigator judges the subject can meet the eligibility criteria. 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.

Re-screening of run-in failures **is not** permitted.

5.4. Randomisation Criteria

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

1. Growth

a. **Prepubertal**: Subjects must be pre-pubertal (Tanner Stage 1).

b. **Body weight and body mass index**: Between the 3rd and 97th percentile based on the US CDC standard statistics or any local standards outside the US. The US CDC standards are provided in the SRM.

c. **Baseline growth velocity**: Between the 3rd and 97th percentile based on North America Longitudinal Standard Growth Velocity charts.

d. **Bone age**: Within 2 years of subject's chronological age as determined by hand/wrist x-ray during the baseline period.

2. **Disease Changes**

a. **Prohibited Diseases**: No new medical conditions that would have been exclusionary at Visit 1.

3. **Medications**

a. **Corticosteroid Use:** No corticosteroid use during the baseline period that would likely have a systemic effect.

b. **Prohibited Medications**: No use of any medications during the baseline period that are detailed in the inclusion/exclusion criteria during the baseline period for worsening asthma symptoms.

4. **Study Compliance**:

a. **Responsibility:** Subject/parent/guardian has demonstrated the ability to comply with all study procedures during the run-in study period, including proper study drug administration during the randomisation visit.

b. **Single-blind treatment:** Compliance with single-blind placebo treatment as recorded in the daily diary and based on the dose counter. Subjects who have not taken their inhaler at least 80% of the time during the last 30 days of the run-in period will not be eligible for randomisation.

5. **Assessments:** Able to use the ELLIPTA inhaler correctly.

5.5. Withdrawal/Stopping Criteria

5.5.1. Subject Withdrawal by Investigator or Self-withdrawal

The following criteria will cause a subject to be discontinued from study treatment but every effort should be made to keep the subject in the study:

1. **Non-Compliance**: A subject is significantly non-compliant with the requirements of the protocol (see Section 6.7).

2. **Adverse Event**: A subject has an adverse event that, in the investigator's judgement, makes continued study treatment an unacceptable risk.

3. **Study Blinding Revealed:** The treatment blind is broken for any subject other than by GSK GCSP personnel.

4. If during the study the subject has a blood sample taken and the results meet the liver chemistry stopping criteria (see Section 5.5.3).

5. If during the study the subject has an ECG and the results meet the QTc stopping criteria (see Section 5.5.4).

In addition to the reasons above, a subject may be discontinued from study treatment at any time at the discretion of the investigator for safety, behavioural or administrative reasons.

If a subject discontinues study treatment, the subject will not automatically be considered as being withdrawn from the study but will be encouraged to stay in the study. An Early Treatment Discontinuation Visit should be conducted within approximately 24 hours of the subject stopping study medication (Section 7.1). In the event a subject 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. These subjects will not be allowed to restart study treatment, however, will be asked to continue to follow the regular visit schedule (Section 7.1). Reasons for treatment discontinuation will be collected and, where possible, every effort will be made to collect growth measurements throughout the intended study period (with particular focus on obtaining the end of the 52-week treatment period height measurement) and recorded in the CRF as planned. After the Early Treatment Discontinuation Visit the subjects will no longer be required to complete the e-diary. The investigator should prescribe appropriate asthma medication to subjects who discontinue study treatment and elect to continue in the study. After treatment discontinuation, the prohibited medications listed in Section 6.10.2 are no longer applicable.

A subject may withdraw from the study at any time at his/her own request (or at the request of his/her parents/guardians). In this case, all study-related medications and other study related materials should be returned to the site by the subject. An Early Withdrawal Visit should also be scheduled within approximately 24 hours of the subject withdrawing from the study (Section 7.1). In the event a subject withdraws at or during a scheduled visit, an Early Withdrawal Visit is not required; however, all study procedures scheduled at an Early Withdrawal Visit must be performed at this visit instead. The primary reason of withdrawal from the study will be recorded in the CRF. If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the study records.

The only reasons for study withdrawal are patient withdrawal of consent to contribute additional outcome information and loss to follow-up.

5.5.2. Subjects Lost to Follow-up

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

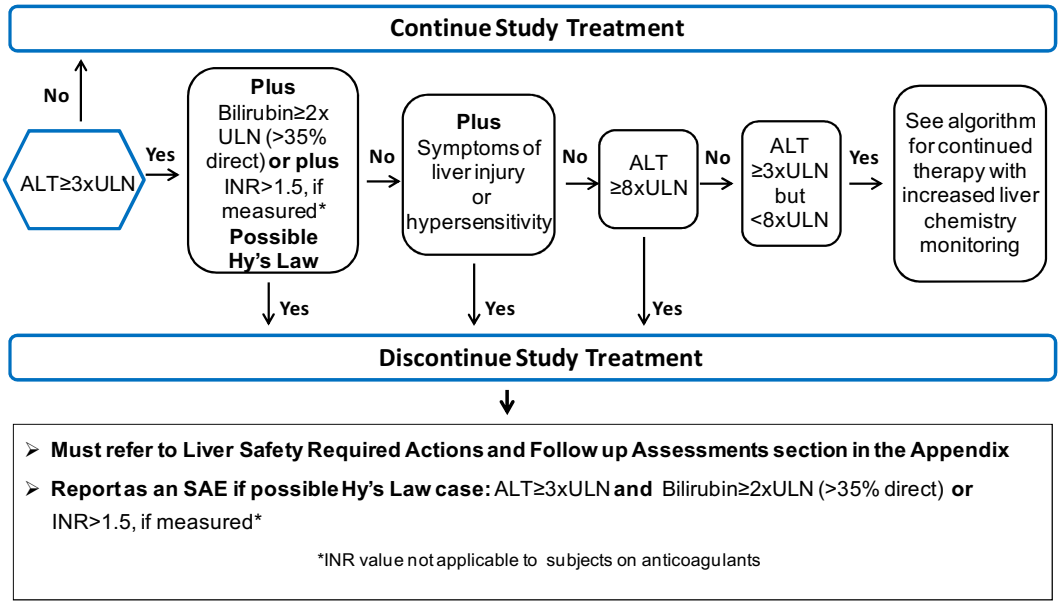
- The site must attempt to contact the parent/subject and re-schedule the missed visit as soon as possible.
- The site must counsel the parent/subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
-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

5.5.3. Liver Chemistry Stopping Criteria

Clinical laboratory tests are not planned at Screening or during this study. However, if a subject has a blood test taken during the study the following stopping criteria apply.

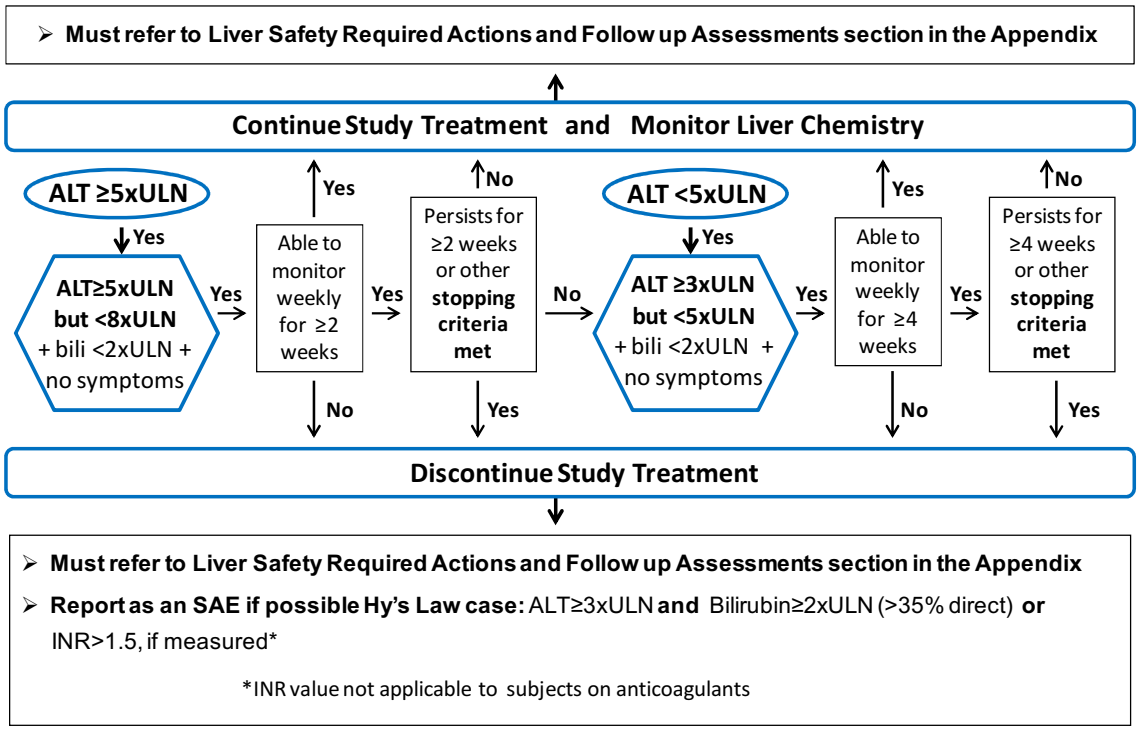
Liver chemistry stopping and increased monitoring criteria have been designed to assure subject safety and evaluate liver event etiology (in alignment with the FDA premarketing clinical liver safety guidance).
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Phase III-IV Liver Chemistry Stopping and Increased Monitoring Algorithm



Liver Safety Required Actions and Follow up Assessments Section can be found in Appendix 2.

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 2.

5.5.3.1. Study Treatment Restart or Rechallenge

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

5.5.4. QTc Stopping Criteria

ECGs are not planned at Screening or during this study. However, if during the study a subject has an ECG performed the following stopping criteria apply.

A subject who meets the bulleted criteria below will be withdrawn from the study treatment:

- QTc > 500 msec OR Uncorrected QT > 600 msec

5.6. Subject and Study Completion

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

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

6. STUDY TREATMENT

6.1. Investigational Product and Other Study Treatment

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

	Study Treatment		
Product name:	**FF (GW685698) 50mcg Dry Powder Inhaler***	**Placebo***	**Montelukast (open label)**
Formulation description:	Dry Powder Inhaler	Dry Powder Inhaler	4 mg chewable tablet (5 year old subjects) 5 mg chewable tablet (≥6 year old subjects) **Note:** subjects who turn 6 years old during the study, will subsequently receive 5 mg of open-label montelukast.
Dosage form:	Dry Powder Inhaler	Dry Powder Inhaler	Chewable tablet
Unit dose strength(s)/Dosage level(s):	50 mcg per blister	Lactose	4 mg or 5 mg
Route of Administration	Inhaled	Inhaled	Oral
Dosing instructions:	Inhale once daily in the MORNING	Inhale once daily in the MORNING	Once daily in the EVENING
Physical description:	Dry White Powder	Dry White Powder	Chewable tablet
Storage conditions	Store up to 25°C (77°F)	Store up to 25°C (77°F)	Per commercial Label: 59°F to 86°F (15°C to 30°C).
Device:	ELLIPTA	ELLIPTA	N/A
Method for individualizing dosage:	Inhalation (oral)	Inhalation (oral)	Chewable tablet

*Single Strip

During the run-in period, all eligible subjects will receive a single-blind placebo ELLIPTA inhaler.

Each subject will also receive an 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.

6.2. Medical Devices

Medical devices (peak flow meters and stadiometers) will be provided by GSK for use in this study. However, none of the devices provided are manufactured by, or on behalf of GSK.

6.3. Treatment Assignment

All subjects will receive a single-blind placebo inhaler during the 16-week run-in period.

Subjects will be stratified by country and be assigned to double-blind treatment (either inhaled FF 50 mcg or inhaled placebo) in accordance with the randomisation schedule generated prior to the start of the study, using validated software.

6.4. Blinding

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

- The investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency** OR in the event of a serious medical condition when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject as judged by the investigator.
- Investigators have direct access to the subject's individual study treatment.
- It is preferred (but not required) that the investigator first contacts the Medical Monitor or appropriate GSK study personnel to discuss options **before** unblinding the subject's treatment assignment.
- If GSK personnel are not contacted before the unblinding, the investigator must notify GSK as soon as possible after unblinding, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study.
- The date and reason for the unblinding must be fully documented in the CRF and source documentation.

A subject may continue in the study if that subject's treatment assignment is unblinded by GSK GCSP Personnel. The primary reason for discontinuation (the event or condition which led to the unblinding) will be recorded in the CRF.

- GSK's Global Clinical Safety and Pharmacovigilance (GCSP) staff may unblind the treatment assignment for any subject with an SAE. If the SAE requires that an expedited regulatory report be sent to one or more regulatory agencies, a copy of the report, identifying the subject's treatment assignment, may be sent to investigators in accordance with local regulations and/or GSK policy.

6.5. Packaging and Labelling

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

6.6. Preparation/Handling/Storage/Accountability

- Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure environmentally controlled and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e. receipt, reconciliation and final disposition records).
- Further guidance and information for final disposition of unused study treatment are provided in the 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.

6.7. Compliance with Study Treatment Administration

Subject compliance with single-blind treatment will be assessed during the run-in period (Visits 1 to 5) by reviewing the dose counter and daily e-diaries.

Subject compliance with double-blind study medication will be assessed at Visit 5 (Randomisation visit) through to Visit 20 (Follow-up visit/Early Withdrawal) by reviewing the following:

1. ELLIPTA dose counter assessment at each visit.

2. Daily e-diary recordings of treatment adherence.

Compliance with open-label montelukast will be assessed throughout the study (Visit 1 to Visit 20 [Follow-up visit/Early Withdrawal]) by reviewing the daily e-diaries.

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. In the instance of significant and repeated non-compliance, the subject may be withdrawn after discussion with the Medical Monitor.

6.8. Treatment of Study Treatment Overdose

For this study, any dose of 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.

1. Contact the Medical Monitor immediately
2. Closely monitor the subject for adverse events (AEs)/serious adverse events (SAEs) and laboratory abnormalities until FF can no longer be detected systemically (at least 5 days for FF from the date of the last dose of study treatment)
3. Obtain a plasma sample for pharmacokinetic (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 subject.

6.9. Treatment after the End of the Study

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

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

6.10. Concomitant Medications and Non-Drug Therapies

6.10.1. Permitted Medications and Non-Drug Therapies

Any medication that is not prohibited in the Inclusion/Exclusion criteria or in the Prohibited Medications section 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. In addition, the following guidelines apply for specific medications:

- Immunotherapy: Immunotherapy for the treatment of allergies is allowed during the study if it was initiated 30 days prior to Visit 1 and there are no significant changes in the dose, concentration or dilution during the study.

6.10.2. Prohibited Medications and Non-Drug Therapies

Use of the following medications is prohibited according to the timeframes below:

Table 3 Prohibited Medications

Within 2 weeks prior to Visit 1 and at any time during the study
Theophyllines
Administration of prescription or over-the-counter medication that would significantly affect the course of asthma, or interact with study drug.
Within 6 weeks prior to Visit 1 and at any time during the study
Intranasal, inhaled and high potency topical (dermatological) corticosteroids **NOTE:** During the double-blind treatment period subjects who require limited courses of inhaled and/or intranasal corticosteroids should remain on study treatment.
Oral long-acting beta2-agonists (e.g. bambuterol) and inhaled long-acting beta2-agonists (e.g. salmeterol, formoterol) or combination products containing inhaled long–acting beta2-agonists (e.g. SERETIDE™, Symbicort, Dulera)
The following potent Cytochrome P450 3A4 (CYP3A4) inhibitors (Clarithromycin, atazanavir, indinavir, itraconazole, ketoconazole, nefazadone, nelfinavir; ritonavir; saquinavir; telithromycin, troleandomycin, voriconazole, mibefradil, cyclosporine)
Within 12 weeks prior to Visit 1 and at any time during the study
Systemic, oral, or depot corticosteroids **NOTE:** During the double-blind treatment period subjects who require limited courses of oral corticosteroids should remain on study treatment.
Anti-IgE (e.g. Xolair) and anti-IL 5
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 subject remains in the maintenance phase throughout the study)
General therapies not permitted prior to or during the study
Prior use of any medication or treatment that might affect growth including, but not limited to: amphetamines, anabolic steroids, anticonvulsants, biphosphonates, calcitonin, erythropoietin, estrogens, growth hormone, methylphenidate, phosphate binders, progestins, thyroid hormone, or testosterone.

In addition, albuterol/salbutamol (inhalation aerosol or nebuliser) use should be withheld for 4 hours prior to the FEV_1 measurement at screening.

7. STUDY ASSESSMENTS AND PROCEDURES

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

This section lists the procedures and parameters of each planned study assessment. The exact timing of each assessment is listed in the Time and Events Table Section 7.1.

7.1. Time and Events Table

	Screening/Baseline					**Double-blind Treatment**													**Follow Up**		**T/D**	**W/D**
Visit Number (*Child Visits)	1*	2	3*	4	5*	6*	7*	8*	9*	10	11	12*	13	14	15*	16	17	18*	19	20*	*	*
Week Number	-16	-12	-8	-4	0	4	8	12	16	20	24	28	32	36	40	44	48	52	+4	+ 8		
Day (All visits to occur within -5 to +2 days of specified day)	-112	-84	-56	-28	1	29	57	85	113	141	169	197	225	253	281	309	337	365	+28	+56		
Written Informed Consent[1] for Study and PGx Sample	X																					
Assign Subject Number	X																					
Subject Demography	X																					
Medical (Including Asthma) History	X																					
Therapy History	X																					
Physical Examination	X																					
Tanner Staging	X				X							X						X		X	X	X
Stadiometry[2]	X		X		X	X	X	X	X			X			X			X		X	X	X
Body Weight Measurement	X		X		X			X				X			X			X		X	X	X
BMI Measurement	X		X		X			X				X			X			X		X	X	X
Inclusion/Exclusion Criteria Verified	X																					
Completion of daily e-diary (PEF, asthma symptoms and compliance with study medication)[3]	X[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening/Baseline					**Double-blind Treatment**													**Follow Up**		**T/D**	**W/D**
Visit Number (*Child Visits)	1*	2	3*	4	5*	6*	7*	8*	9*	10	11	12*	13	14	15*	16	17	18*	19	20*	*	*
Week Number	-16	-12	-8	-4	0	4	8	12	16	20	24	28	32	36	40	44	48	52	+4	+ 8		
Day (All visits to occur within -5 to +2 days of specified day)	-112	-84	-56	-28	1	29	57	85	113	141	169	197	225	253	281	309	337	365	+28	+56		
Assess e-diary and compliance[3]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry-generated FEV_1	X																					
cACT	X				X													X			X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacogenetic Sample[5]							X (One Sample Only)															
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Oropharyngeal Exam	X		X		X	X	X	X	X			X			X			X		X	X	X
Hand/Wrist X-Ray Scheduled		←	—	→																		
Bone Age Result					X																	
Assess Randomisation Criteria					X																	
Assign Randomisation Number					X																	
Dispense Open-label Montelukast	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

	Screening/Baseline					**Double-blind Treatment**													**Follow Up**		**T/D**	**W/D**
Visit Number (*Child Visits)	1*	2	3*	4	5*	6*	7*	8*	9*	10	11	12*	13	14	15*	16	17	18*	19	20*	*	*
Week Number	-16	-12	-8	-4	0	4	8	12	16	20	24	28	32	36	40	44	48	52	+4	+ 8		
Day (All visits to occur within -5 to +2 days of specified day)	-112	-84	-56	-28	1	29	57	85	113	141	169	197	225	253	281	309	337	365	+28	+56		
Dispense Single-Blind Treatment	X	X	X	X																		
Dispense Double-Blind Treatment					X	X	X	X	X	X	X	X	X	X	X	X	X					
Dispense Rescue Med (PRN)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect All Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

1. If applicable, subject 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/IRB.
2. Subjects must attend the clinic for scheduled visits when stadiometry will be assessed. Subjects' parents/guardians will need to attend the clinic every month to collect/return diaries and study medication.
3. Subjects will be required to record compliance with study medication (single-blind run-in treatment, double-blind treatment and open label montelukast) each day in the e-diary. Daily salbutamol use, asthma symptom scores and PEF will be recorded in the e-diary each day and will be collected at each visit. Note: After the Early Treatment Discontinuation Visit subjects will no longer be required to complete the e-diary.
4. At Visit 1, e-diary will be dispensed only.
5. Saliva (2mL) is spit into the DNA self-collection kit. This should ideally be taken as soon after randomisation (Visit 5) as possible, but may be taken at any other visit after randomisation, if necessary. Genetics consent must be obtained prior to PGx sampling.

***= Child Visit – these visits are where the child (subject) must attend the clinic.**

NOTE: W/D = Early Withdrawal Visit and T/D= Early Treatment Discontinuation Visit

7.2. Screening and Critical Baseline Assessments

The following demographic parameters will be captured: month and year of birth, sex, race and ethnicity.

Medical/medication/family history will be assessed as related to the inclusion/exclusion criteria listed in Section 5.

A hand/wrist x-ray (left hand) will be performed in the period between Visit 2 and Visit 4 so that the results are available prior to the randomisation visit (Visit 5). If subjects are unable to use their left hand due to injury or deformity then the right hand can be used for the x-ray.

Spirometry-generated FEV_1 will be measured at screening only. All sites will use standardized spirometry equipment provided by an external vendor. At least two acceptable efforts (no more than 8) will be obtained, confirmed by central overread of spirometry results and the highest will be recorded in the eCRF. Subjects must withhold from using albuterol/salbutamol (inhalation aerosol or nebuliser) for 4 hours prior to FEV_1 measurements.

General procedures conducted as part of the subject's routine clinical management e.g. blood count and obtained prior to signing of informed consent may be utilised for screening or baseline purposes. If liver function tests are abnormal then the subject should be excluded from participating in the study.

7.3. Safety

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

7.3.1. Height (Stadiometry) Measurement

Height (stadiometry) measurements will be carried out as outlined in the Time and Events Table (Section 7.1). Stadiometers will be provided by GSK. Measurements will be conducted by site personnel who are trained in the study-specific stadiometry and calibration procedures. Every effort should be made to ensure that the same site personnel take all the height measurements in the study at a given centre, and should be blinded to the study phase.

Three reproducible height measurements will be taken using a stadiometer and will be recorded in the CRF. The measurements **must** be taken consistently at the same time of day (± 3 hours) for each subject at each visit. Measurements will be recorded to the nearest $1/10^{th}$ of a centimetre. If the stadiometer has not been calibrated in the last 4 hours before the subject's height is measured, it must be calibrated immediately before use. A calibration log must be kept. All subjects' heights will be measured without socks, shoes or hats in place.

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

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

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

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

- Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) or related to a GSK product will be recorded from the time a subject consents to participate in the study up to and including any follow-up contact.
- AEs will be collected from the start of Study Treatment until the follow-up contact (see Section 7.3.2.3), at the timepoints specified in the Time and Events Table (Section 7.1).
- Medical occurrences that begin prior to the start of study treatment but after obtaining informed consent may be recorded on the Medical History/Current Medical Conditions section of the CRF.
- All SAEs will be recorded and reported to GSK within 24 hours, as indicated in Appendix 4.
- Investigators are not obligated to actively seek AEs or SAEs in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably related to the study treatment or study participation, the investigator must promptly notify GSK.

NOTE: The method of recording, evaluating and assessing causality of AEs and SAEs plus procedures for completing and transmitting SAE reports to GSK are provided in Appendix 4.

7.3.2.2. Method of Detecting AEs and SAEs

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

- “How are you feeling?”
- “Have you had any (other) medical problems since your last visit/contact?”
- “Have you taken any new medicines, other than those provided in this study, since your last visit/contact?”
- “How does your child seem to feel?”
- “Has your child had any (other) medical problems or seem to act differently in any way since his/her last visit/contact?”
- “Has your child needed to take any medicines, other than those provided in this study, since his/her last visit/contact?”

7.3.2.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, and non-serious AEs of special interest (as defined in Section 4.6.1) will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up (as defined in Section 5.5.2). Further information on follow-up procedures is given in Appendix 4.

7.3.2.4. Regulatory Reporting Requirements for SAEs

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

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

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

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

7.3.3. Asthma Exacerbations

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 (ED) 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 AEs, unless they meet the definition of an SAE (Appendix 4). 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.

7.3.4. Physical Exams

- A complete physical examination will be done as indicated in the Time and Events Schedule. It will include, at a minimum, assessment of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems.
- Body weight (including BMI) will be measured and recorded as as outlined in the Time and Events Schedule (see Table in Section 7.1).
- Tanner staging will be assessed as outlined in the Time and Events Schedule (see Table in Section 7.1). Further details will be provided in the SRM.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

7.3.5. Oropharyngeal Examination

Oropharyngeal examination for visual evidence of oral candidiasis will be carried out at as outlined in the Time and Events Table. If the visual oropharyngeal examination is abnormal prior to randomisation they 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.

7.4. Efficacy (as a Measure of Compliance)

7.4.1. Daily Diaries

Subjects/parents/guardians will be issued an eDiary for daily use throughout the study and will be instructed on how to complete the eDiary. As well as recording compliance with study medication (single-blind treatment during the run-in period, double-blind treatment and open-label montelukast) in the eDiary, the following parameters will be recorded used as a measure of compliance to help identify non-adherence and/or poorly controlled asthma:

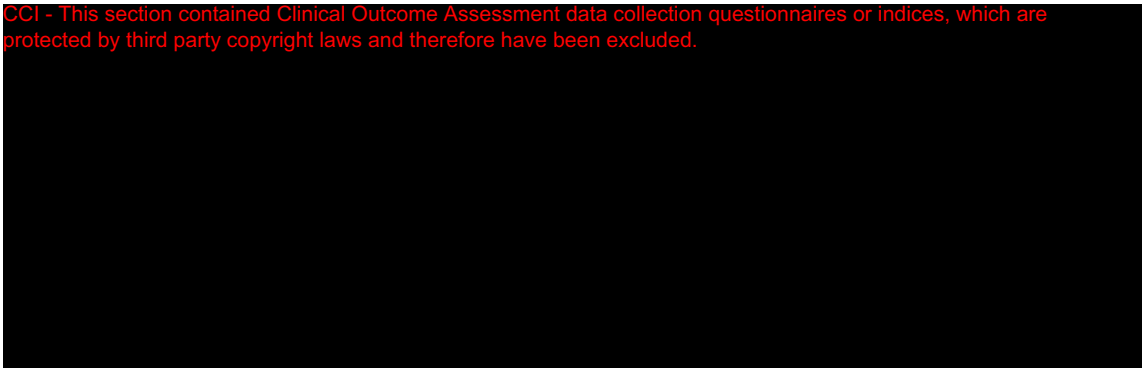
- Daily asthma symptom scores
- Daily PEF (measured in the morning only)
- Daily albuterol/salbutamol use. Number of inhalations of rescue albuterol/salbutamol inhalation aerosol used during the day and night.
  Note: Rescue medication taken as preventative treatment before exercise will be excluded from this count and should not be entered into the daily eDiary.

If a subject discontinues study treatment, the subject should be encouraged to remain in the study and continue to follow the regular visit schedule. However, the subject will no longer be required to complete the eDiary.

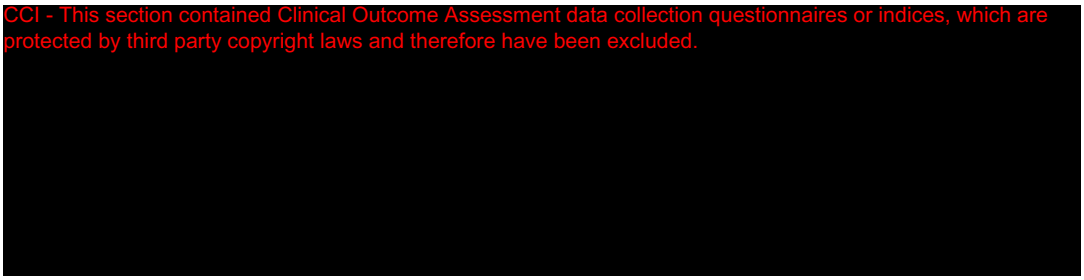
7.4.1.1. Daily Asthma Symptom Scores

The following asthma symptom scores will be recorded once daily in the morning in the eDiary before taking any study treatment, before using any rescue medication, and before the daily PEF measurement:

Day-time Symptom Score for previous day:



Night-time Symptom Score:



7.4.1.2. Daily PEF

PEF will be measured daily in the morning using an electronic Peak Flow Meter that will be issued to subjects at Visit 1. The best of three attempts will be recorded by the subjects in the eDiary.

PEF will be measured and recorded daily throughout the study. PEF measurements must be done:

- Each morning prior to taking any study treatment and before using any rescue medication.

For all randomised subjects, a PEF Stability Limit will be calculated as follows:

- Mean PEF from the available 7 consecutive days preceding Visit 2 (during run-in period) x 60%.

- The PEF from the morning of Visit 2 will be included in the calculation of the PEF stability limit.

Subjects will be alerted if their PEF has fallen below the PEF Stability Limit.

7.4.2. Childhood Asthma Control Test

The Childhood Asthma Control Test (C-ACT) will be assessed at scheduled visits outlined in the Time and Events Table.

The C-ACT is a 7-item questionnaire which has been developed as a measure of paediatric subjects' (4-11 years old) asthma control [Liu, 2007], and which can be quickly and easily completed in clinical practice. It is designed for completion by the subject and by the subject's parent/legal guardian. The subject (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 patient not to skip questions on the C-ACT or take breaks during the completion of the paper questionnaire. Responses to questions should not be changed or modified after collection. Upon completion of the C-ACT, the investigator or designated site personnel will collect the questionnaire and calculate the total score. The C-ACT responses will be administered and recorded in the CRF by the investigator or delegate.

7.5. Genetics

Information regarding genetic research is included in Appendix 3.

8. DATA MANAGEMENT

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

9. STATISTICAL CONSIDERATIONS AND DATA ANALYSES

9.1. Hypotheses

The primary objective of this study is to characterise the estimated difference in prepubescent growth velocities between subjects treated for one year with inhaled FF 50 mcg once daily (OD) (plus montelukast 4mg or 5mg open-label) and inhaled placebo (plus montelukast 4mg or 5mg open-label).

No formal statistical hypotheses are to be tested.

9.2. Sample Size Considerations

9.2.1. Sample Size Assumptions

The proposed sample size for this study is based on FDA guidance [Guidance for Industry Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children, March 2007].

The study is not powered to detect any treatment differences. The study is designed to provide the estimated mean treatment difference between inhaled FF 50 mcg once daily (OD) (plus montelukast open-label) and inhaled placebo (plus montelukast open-label) in prepubescent growth velocities, with a certain degree of precision on the 95% confidence interval. The primary population for growth analyses will be the Growth Population (defined in Section 9.3.1). An analysis of covariance (ANCOVA) model will be used to estimate the mean treatment difference in growth velocities over the double-blind treatment period, adjusting for baseline growth velocity, age at Visit 1, gender, and country. A 95% confidence interval will also be provided for the estimated mean treatment difference in growth velocity over the double-blind treatment period (Section 9.4.1).

Eligible subjects will be stratified by country and randomised in a 1:1 ratio to inhaled FF 50 mcg OD (plus montelukast open-label) or inhaled placebo (plus montelukast open-label). At least 450 subjects will be randomised (approximately 225 per treatment arm). Assuming a withdrawal rate from study medication of up to 10% within the first 12 weeks, this would still ensure at least 406 eligible subjects (approximately 203 per treatment arm) for inclusion in the Growth Population (Section 9.3.1) analyses. Assuming a standard deviation for the growth velocities of 1.2 cm/year (based on study FFR101782), a sample size of 203 eligible subjects per treatment arm ensures the width of the confidence interval for the mean treatment difference is no greater than 0.5cm/year (Section 9.2.2).

9.2.2. Sample Size Sensitivity

To demonstrate the sensitivity of the sample size calculation for this study, the following table presents the precision of the two-sided 95% confidence interval for the estimated mean treatment difference on growth velocities under different circumstances in terms of standard deviation and the number of subjects per treatment group for the growth analyses.

	Distance from mean to limit (½ of the width of 95% confidence interval)								
Common standard deviation	n=250	n=240	n=230	n=220	n=210	n=200	n=190	n=180	n=170
1.7	0.298	0.304	0.311	0.318	0.325	0.333	0.342	0.351	0.361
1.6	0.280	0.286	0.292	0.299	0.306	0.314	0.322	0.331	0.340
1.5	0.263	0.268	0.274	0.280	0.287	0.294	0.302	0.310	0.319
1.4	0.245	0.250	0.256	0.262	0.268	0.274	0.282	0.289	0.298
1.3	0.228	0.233	0.238	0.243	0.249	0.255	0.261	0.269	0.276
1.2	0.210	0.215	0.219	0.224	0.230	0.235	0.241	0.248	0.255
1.1	0.193	0.197	0.201	0.206	0.210	0.216	0.221	0.227	0.234
1.0	0.175	0.179	0.183	0.187	0.191	0.196	0.201	0.207	0.213

The shaded area represents the number of subjects per treatment group and the standard deviation that correspond to a 95% confidence interval with a width no greater than 0.5cm/year, as recommended in the FDA guidance.

9.2.3. Sample Size Re-estimation or Adjustment

Sample size re-estimation or adjustment is not planned.

9.3. Data Analysis Considerations

9.3.1. Analysis Populations

Three subject populations will be defined:

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

Intent-to-Treat (ITT) Population: The ITT Population is defined as all randomised subjects who receive at least one dose of study drug. All safety and efficacy (compliance assessments) data analyses will use the Intent-to-Treat (ITT) population.

Growth Population: The Growth Population is defined as all ITT subjects with height assessments via stadiometry from at least three post-randomisation, on-treatment clinic visits during the double-blind treatment period. This will be the primary population for analyses of growth data (Section 9.4.1).

9.3.2. Interim Analysis

No interim analyses are planned during this study.

9.4. Key Elements of Analysis Plan

It is anticipated that approximately 70 sites from multiple countries in North America, South America, South Africa and Europe will participate in the study. Therefore it is likely that many centres will enrol very small numbers of subjects. Consequently, all centres 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 country is incorporated into the analysis.

The detailed statistical methodology for the data analyses will be provided in the Reporting and Analysis Plan (RAP).

9.4.1. Primary Safety Analyses

9.4.1.1. Growth Velocity

Height assessments will be conducted at the following clinic visits: Visits 1, 3, and 5 during the 16-week baseline period; Visits 6-9, 12, 15 and 18 during the 52-week double-blind treatment period; and Visit 20 during the 8-week follow-up period. For each height assessment at a given clinic visit, triplicate stadiometry measurements will be collected for each subject. For the purposes of these analyses, each set of triplicate measurements will be averaged to derive one estimated height per subject per visit.

For each study period (baseline, double-blind treatment, and follow-up), growth velocity (cm/yr) will be calculated for each subject based on stadiometry data by fitting a regression line to all height measurements recorded for that subject during the period and determined by the slope of the fitted regression line. These will be calculated for the Growth population and for the ITT population and details of the calculations will be provided in the RAP. Baseline, double-blind treatment and follow-up growth velocities will be summarised by treatment while statistical analysis will only be performed for the double-blind treatment period.

The primary population for the primary growth analysis will be the Growth population (Section 9.3.1). The primary analysis will evaluate the primary de facto estimand: the mean difference in growth velocities between treatment groups over the double-blind treatment period, regardless of whether or not the subject remained on-treatment after their third post-randomization visit. For subjects in the Growth population who discontinue study treatment early after their third post-randomization clinic visit, all available on- and off- study treatment height assessments available during the treatment period will be included in the primary analysis. An ANCOVA model will be used to estimate the mean treatment difference in growth velocity over the double-blind treatment period, adjusting for baseline growth velocity, age at Visit 1, gender, and

country. A 95% confidence interval will also be provided for the mean treatment difference in growth velocity over the double-blind treatment period.

Given subjects who discontinue study treatment may be administered other medications that may affect growth, a supportive analysis will be performed to evaluate the following de jure estimand: the mean difference in growth velocities between treatment groups over the double-blind treatment period, based on data measured while subjects are taking study treatment. This will be estimated using the Growth Population (Section 9.3.1) and using all on-treatment height measurements obtained up to the point of study treatment discontinuation.

Additional supportive analyses will be provided for the following subsets of the Growth Population:

1. Excluding subjects who exhibit greater than or equal to Tanner Stage 2 characteristics at any point during the treatment period or follow-up period

2. Excluding subjects who have questionable height measurements (definition of questionable measurements will be provided in the RAP)

3. Excluding subjects who have height measurements taken after receiving *rescue* systemic corticosteroids during the treatment period

4. Excluding subjects who have height measurements taken after receiving *rescue* inhaled and/or intranasal and/or systemic corticosteroids during the treatment period

5. Excluding subjects who have any of the above

A supportive completers' analysis of growth velocity over the 1-year double-blind treatment period, based on subjects in the Growth Population who completed the double-blind treatment period and remained on study treatment during that period, will also be performed.

Additional supportive analyses evaluating the primary de facto estimand, including all subjects (using the ITT Population, Section 9.3.1) will be performed. Further details will be provided in the RAP.

9.4.2. Secondary Safety Analyses

9.4.2.1. Growth

Secondary analyses pertinent to growth will also include the following:

1. Summary of the proportion of children who are below the 3rd percentile of growth velocity

2. Summary of change (shift) in growth velocity quartile for each child from baseline to endpoint (definition of baseline and endpoint will be provided in the RAP)

3. Analysis of the first 12 weeks (~10 to 13 weeks given visit windows, Section 7.1) of data

4. Summary of growth velocities during the baseline and follow-up periods

5. Analysis of growth velocities for the following region subgroups: USA and Non-USA

6. Descriptive comparison of the growth velocities based on gender and ethnicity

7. Summary by visit and by treatment group of standard deviation scores and summary of change in height standard deviation scores from baseline to endpoint (definition of standard deviation scores, baseline and endpoint will be provided in the RAP)

8. Analysis of random coefficients

9.4.2.2. Adverse Events

Regarding the safety assessment of inhaled FF 50 mcg, adverse events (incidence, type, severity) will be assessed throughout the study.

Adverse events (AEs) will be summarised for each study period (16-week single-blind baseline period, 52-week double-blind treatment period, and 8-week follow-up period) and displayed by treatment group. The onset date of the adverse events relative to the clinic visit dates will be used to determine in which period an adverse event occurs. Adverse events during the pre-treatment period include those with date of onset prior to study treatment initiation (first dose date). Adverse events during the on-treatment period include those with date of onset on or after the date of study treatment initiation and on or before the study treatment termination date. Adverse events during the post-treatment period include those with date of onset after the study treatment termination date.

The CRF text for AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be reported using the primary System Organ Class (SOC) and Prederred Term (PT). The number of subjects with one or more events of any type will be calculated. Results will be displayed in the order of decreasing frequency, both across SOC and within SOC. A SOC will not be presented when the overall incidence for any adverse event within the particular system is 0. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order.
Adverse events during each study period (baseline, treatment and follow-up) will also be listed, with SOC, event (preferred term), treatment group, number of subjects with the event, and specific subject numbers. Demographic details (e.g. age, gender and race), as well as details of the individual adverse events, will be included in these listings. Listings will be sorted within subject by the date of onset of the AE.

Similar summaries and listings will be provided for drug-related adverse events, and adverse events leading to withdrawal from study treatment.

Any deaths, pregnancies and serious adverse events (SAEs) reported during the study period will also be listed.

9.4.2.3. Asthma Exacerbations

The number and percentage of subjects experiencing an exacerbation over the double-blind treatment period and the follow-up period will be summarised for each treatment group alongside the primary causes of the exacerbation.

9.4.3. Other Analyses

The reporting of other endpoints pertaining to efficacy as a measure of compliance as specified in the protocol will be described in the RAP.

10. STUDY GOVERNANCE CONSIDERATIONS

10.1. Posting of Information on Publicly Available Clinical Trial Registers

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

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

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

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

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

- IRB/IEC review and favorable opinion/approval of the study protocol and amendments as applicable
- Obtaining signed informed consent
- Investigator reporting requirements (e.g. reporting of AEs/SAEs/protocol deviations to IRB/IEC)
- GSK will provide full details of the above procedures, either verbally, in writing, or both.

- Signed informed consent must be obtained for each subject prior to participation in the study.
- Signed assent will be obtained where considered appropriate according to the subject's age and comprehension, as determined by the Investigator.
- The IEC/IRB, and where applicable the regulatory authority, approve the clinical protocol and all optional assessments, including genetic research.
- Optional assessments (including those in a separate protocol and/or under separate informed consent) and the clinical protocol should be concurrently submitted for approval unless regulation requires separate submission.
- Approval of the optional assessments may occur after approval is granted for the clinical protocol where required by regulatory authorities. In this situation, written approval of the clinical protocol should state that approval of optional assessments is being deferred and the study, with the exception of the optional assessments, can be initiated.

10.3. Quality Control (Study Monitoring)

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

GSK will monitor the study and site activity to verify that the:

- Data are authentic, accurate, and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

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

10.4. Quality Assurance

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

10.5. Study and Site Closure

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

10.6. Records Retention

- Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records (except for those required by local regulations to be maintained elsewhere), in a safe and secure location.
- The records must be maintained to allow easy and timely retrieval, when needed (e.g., for a GSK audit or regulatory inspection) and must be available for review in conjunction with assessment of the facility, supporting systems, and relevant site staff.
- Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken.
- The investigator must ensure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back-up of these reproductions and that an acceptable quality control process exists for making these reproductions.

- GSK will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, GSK standards/procedures, and/or institutional requirements.
- The investigator must notify GSK of any changes in the archival arrangements, including, but not limited to, archival at an off-site facility or transfer of ownership of the records in the event the investigator is no longer associated with the site.

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

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

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

GSK will provide the investigator with the 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.

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12. APPENDICES

12.1. Appendix 1 – Abbreviations and Trademarks

Abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ANCOVA	Analysis of Covariance
BMI	Body mass index
cACT	Childhood Asthma Control Test
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic Obstructive Pulmonary Disease
CS	Corticosteriod
CRF	Case Record Form
CYP3A4	Cytochrome P450 3A4
DPI	Dry Powder Inhaler
EU-RMP	European Union-Risk Management Plan
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Flow in 1 second
FF	Fluticasone furoate
FF/VI	Fluticasone furoate/vilanterol
FP	Fluticasone propionate
GCs	Glucocorticosteriods
GCSP	Global Clinical Safety and Pharmacovigilence
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GSK	GlaxoSmithKline
GSK Drug	GlaxoSmithKline Validated Medication Dictionary
IB	Investigator Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroid
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor-1
IgE	Immunoglobulin E
IL	Interleukin
IP	Investigational Product
IRB	Institutional Review Board
ITT	Intention to Treat
LABA	Long Acting Beta Agonist
mcg	Microgram
MD	Mean difference

MedDRA	Medical Dictionary for Regulatory Activities
MSDS	Material Safety Data Sheet
NDPI	Novel dry powder inhaler
OD	Once Daily
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
prn	As required
PT	Preferred Term
SABA	Short Acting Beta 2 Agonist
SAE	Serious Adverse Event
SOC	System organ class
SRM	Study Reference Manual
WHO	World Health Organisation
US	United States
US CDC	United States Centers for Disease Control and Prevention
VI	Vilanterol trifenatate

Trademark Information

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Xolair

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

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

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

Liver Chemistry Stopping Criteria - Liver Stopping Event	
ALT-absolute	ALT ≥ 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 following ANY Liver Stopping Event	
Actions	**Follow Up Assessments**
• Immediately discontinue study treatment • Report the event to GSK **within 24 hours** • Complete the liver event CRF and complete an SAE data collection tool if the event also meets the criteria for an SAE[2] • Perform liver event follow up assessments • Monitor the subject until liver chemistries resolve , stabilize, or return to within baseline (see **MONITORING** below) • **Do not restart/rechallenge** subject with study treatment unless allowed per protocol and GSK Medical Governance approval **is**	• Viral hepatitis serology[4] • 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]. • Blood sample for pharmacokinetic (PK) analysis, obtained within 1-5days after last dose[6] • Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH). • Fractionate bilirubin, if total

granted • If restart/rechallenge is **not allowed or not granted**, permanently discontinue study treatment and may continue subject 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 subjects 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 subjects weekly until liver chemistries resolve, stabilize or return to within baseline	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 **<u>For bilirubin or INR criteria:</u>** • Anti-nuclear antibody, anti-smooth muscle antibody, Type 1 anti-liver kidney microsomal antibodies, and quantitative total immunoglobulin G (IgG or gamma globulins). • Serum acetaminophen adduct HPLC assay (quantifies potential acetaminophen contribution to liver injury in subjects 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 subject 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 subjects receiving anticoagulants
3. New or worsening symptoms believed to be related to liver injury (such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, or jaundice) or believed to be related to hypersensitivity (such as fever, rash or eosinophilia)
4. Includes: Hepatitis A IgM antibody; Hepatitis B surface antigen and Hepatitis B Core Antibody (IgM); Hepatitis C RNA; Cytomegalovirus IgM antibody; Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing); Hepatitis E IgM antibody

5. If hepatitis delta antibody assay cannot be performed,, it can be replaced with a PCR of hepatitis D RNA virus (where needed) [Le Gal, 2005].
6. PK sample may not be required for subjects known to be receiving placebo or non-GSK comparator treatments. Record the date/time of the PK blood sample draw and the date/time of the last dose of study treatment prior to blood sample draw on the CRF. If the date or time of the last dose is unclear, provide the subject's best approximation. If the date/time of the last dose cannot be approximated OR a PK sample cannot be collected in the time period indicated above, do not obtain a PK sample. Instructions for sample handling and shipping are in the SRM.

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

Liver Chemistry Increased Monitoring Criteria – Liver Monitoring Event	
Criteria	**Actions**
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 subject safety. • Subject can continue study treatment • Subject must return weekly for repeat liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) until they resolve, stabilise or return to within baseline • If at any time subject meets the liver chemistry stopping criteria, proceed as described above • If ALT decreases from ALT ≥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 subjects twice monthly until liver chemistries normalize or return to within baseline.

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12.3. Appendix 3- Genetic Research

Genetics – Background

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

Genetic Research Objectives and Analyses

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

- Response to medicine, including any treatment regimens under investigation in this study or any concomitant medicines;
- Asthma susceptibility, severity, and progression and related conditions

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

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

Study Population

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

Study Assessments and Procedures

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

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

The genetic sample is labelled (or "coded") with the same study specific number used to label other samples and data in the study. This number can be traced or linked back to the subject by the investigator or site staff. Coded samples do not carry personal identifiers (such as name or social security number).

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

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

Informed Consent

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

Subject Withdrawal from Study

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

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

If a subject withdraws consent for genetic research or requests sample destruction for any reason, the investigator must complete the appropriate documentation to request sample destruction within the timeframe specified by GSK and maintain the documentation in the site study records.

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

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

Screen and Baseline Failures

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

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

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

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

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

12.4.1. Definition of Adverse Events

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

Events <u>meeting</u> AE definition include:
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, vital signs measurements), including those that worsen from baseline, and felt to be clinically significant in the medical and scientific judgement of the investigator. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study treatment administration even though it may have been present prior to the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication (overdose per se will not be reported as an AE/SAE unless this is an intentional overdose taken with possible suicidal/self-harming intent. This should be reported regardless of sequelae). • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. However, the signs and symptoms and/or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or SAE.

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

12.4.2. Definition of Serious Adverse Events

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

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

from baseline is not considered an AE.

d. Results in disability/incapacity

NOTE:

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

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.
- Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse

g. Is associated with liver injury <u>and</u> impaired liver function defined as:

- ALT ≥ 3xULN and total bilirubin* ≥ 2xULN (>35% direct), **or**
- ALT ≥ 3xULN and INR** > 1.5.

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

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

12.4.3. Recording of AEs and SAEs

AEs and SAE Recording:

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event.
- The investigator will then record all relevant information regarding an AE/SAE in

the CRF

- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to GSK in lieu of completion of the GSK, AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by GSK. In this instance, all subject identifiers, with the exception of the subject number, will be blinded on the copies of the medical records prior to submission of to GSK.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis will be documented as the AE/SAE and not the individual signs/symptoms.

12.4.4. Evaluating AEs and SAEs

Assessment of Intensity

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

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities
- Severe: An event that prevents normal everyday activities. - an AE that is assessed as severe will not be confused with an SAE. Severity is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least one of the pre-defined outcomes as described in the definition of an SAE.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and the occurrence of each AE/SAE.
- A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study treatment will be considered and investigated.

- The investigator will also consult the Investigator Brochure (IB) and/or Product Information, for marketed products, in the determination of his/her assessment.
- For each AE/SAE the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report to GSK. However, **it is very important that the investigator always make an assessment of causality for every event prior to the initial transmission of the SAE data to GSK.**
- The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE data collection tool accordingly.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

12.4.5. Reporting of SAEs to GSK

SAE reporting to GSK via electronic data collection tool

- Primary mechanism for reporting SAEs to GSK will be the electronic data collection tool
- If the electronic system is unavailable for greater than 24 hours, the site will use the paper SAE data collection tool and fax it to the SAE coordinator
- Site will enter the serious adverse event data into the electronic system as soon as it becomes available.
- The investigator will be required to confirm review of the SAE causality by ticking the ‘reviewed’ box at the bottom of the eCRF page within 72 hours of submission of

the SAE.

- After the study is completed at a given site, the electronic data collection tool (e.g., InForm system) will be taken off-line to prevent the entry of new data or changes to existing data
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, the site can report this information on a paper SAE form or to the Medical Monitor or the SAE coordinator by telephone.
- Contacts for SAE receipt can be found at the beginning of this protocol on the Sponsor/Medical Monitor Contact Information page.

12.5. Appendix 5- Country Specific Requirements

No country-specific requirements exist.

12.6. Appendix 6 – Protocol Changes

Protocol Amendment 01

This amendment applies to all study centers participating in HZA114971.

Description

This amendment was implemented in order to make the following changes:

- Remove the term local growth charts and replace with US CDC charts for inclusion criteria 4 and 5.
- Amend the text for inclusion criterion 7 to provide clarity on the time window used for re-scheduling the spirometry assessment at screening (Visit 1).
- Remove the term WHO growth charts and replace with North America Longitudinal Standard Growth Velocity Charts for randomization criterion 1c.
- Amended typographical error in Section 5.5.4 and to clarify that the subject will be withdrawn from study treatment (for consistency with Section 5.5.1).
- Amend the text and provide clarity on the procedure around oropharyngeal exams in Section 7.3.5.
- Amend the time and events table to show an 'x' for body weight at Visit 3 as this was missing.
- Remove word "continuously" in Section 9.1.
- Add a supportive completers' analysis of growth velocity over the 1-year double-blind treatment period, based on subjects who completed the double-blind treatment period while remaining on study treatment, in Section 9.4.1.1.
- Add a summary of change in height standard deviation scores (SDS) from baseline to endpoint in Section 9.4.2.1.

Method of Amendment

Original and amended text is presented below with the original text preceding the revised text contained in this Amendment No. 01 in the order of occurrence within the protocol.

Amendment Details

<u>Section 5.1- Inclusion Criteria – Inclusion Criterion 4 (Height Centiles)</u>

This edit applies to inclusion criterion 4.

Original Text:

Inclusion Criterion 4: Height centile between 3% and 97% based on local growth charts.

Revised Text:

Inclusion Criterion 4: Height centile between 3% and 97% based on US CDC charts.

Section 5.1- Inclusion Criteria – Inclusion Criterion 5 (Body Weight and Body Mass Index)

This edit applies to inclusion criterion 5.

Original Text:

Inclusion Criterion 5: Subjects with body weight and body mass index that is between 3rd and 97th centile based on the US CDC standard statistics or any local standards outside the US. The US CDC standards are provided in the Study Reference Manual (SRM).

Revised Text:

Inclusion Criterion 5: Subjects with body weight and body mass index that is between 3rd and 97th centile based on the US CDC charts (provided in the Study Reference Manual [SRM]).

Section 5.1- Inclusion Criteria – Inclusion Criterion 7 (Pre-bronchodilatory FEV_1 at screening (Visit 1))

This edit applies to inclusion criterion 7.

Original Text:

Inclusion Criterion 7: A pre-bronchodilatory FEV_1 at Visit 1 (Screening) of between ≥60% to ≤95% predicted. There should be no SABA use within 4 hours of this measurement. **NOTE:** Only subjects who are unable to perform the FEV_1 manoeuvre at their Visit 1 can, at the discretion of the investigator, attend the clinic to perform the manoeuvre **once more** on another day (within the time window specified in the Time and Events Table). This repeat FEV_1 manoeuvre **must** be acceptable (as defined in the SRM) and **must** meet the FEV_1 inclusion limits to be eligible for the study.

Revised Text:

Inclusion Criterion 7: A pre-bronchodilatory FEV_1 at Visit 1 (Screening) of between ≥60% to ≤95% predicted. There should be no SABA use within 4 hours of this measurement. **NOTE:** Only subjects who are unable to perform the FEV_1 manoeuvre at their Visit 1 can, at the discretion of the investigator, attend the clinic to perform the manoeuvre **once more** on another day before Visit 2. This repeat FEV_1 manoeuvre **must** be acceptable (as defined in the SRM) and **must** meet the FEV_1 inclusion limits to be eligible for the study.

Section 5.4- Randomisation Criteria – Randomisation Criterion 1c (Baseline Growth Velocity)

This edit applies to randomisation criterion 1c.

Original Text:

Baseline growth velocity: Between the 3rd and 97th percentile based on World Health Organisation (WHO) charts.

Revised Text:

Baseline growth velocity: Between the 3rd and 97th percentile based on North America Longitudinal Standard Growth Velocity charts.

Section 5.5.4 QTc Stopping Criteria

This edit applies to amend the typographical errors in the sentence before the bullet and to clarify that the subject will be withdrawn from study treatment (for consistency with Section 5.5.1)

Original Text:

A subject who meets either of the bulleted criteria below will be withdrawn from the study:

- QTc > 500 msec OR Uncorrected QT > 600 msec

Revised Text:

A subject who meets the bulleted criteria below will be withdrawn from study treatment:

- QTc > 500 msec OR Uncorrected QT > 600 msec

Section 7 Study Assessments and Procedures –Time and Events Table

This edit applies to addition of an 'X' at Visit 3 for body weight (Visit 3 only) on the Time and Events Table.

Original Text:

There was no 'X' at Visit 3 for body weight on the Time and Events Table. This was missing in error.

Revised Text:

An 'X' was added at Visit 3 for body weight on the Time and Events Table.

Section 7.3 Safety – Sub-Section 7.3.5 Oropharyngeal Exams

This edit applies to Section 7.3.5 second sentence of the first paragraph.

Original Text:

If the visual oropharyngeal examination is abnormal at Visits 1 and 3 (screening and run-in period), the subject must be excluded from entering the randomisation period. If the visual oropharyngeal examination is abnormal at Visit 5 (randomisation), the subject must not be randomised.

Revised Text:

If the visual oropharyngeal examination is abnormal prior to randomisation they must not be randomised.

Section 9.1. Hypotheses

This edit applies to Section 9.1.

Original Text:

The primary objective of this study is to characterise the estimated difference in prepubescent growth velocities between subjects continuously treated for one year with inhaled FF 50 mcg once daily (OD) (plus montelukast 4mg or 5mg open-label) and inhaled placebo (plus montelukast 4mg or 5mg open-label).

Revised Text:

The primary objective of this study is to characterise the estimated difference in prepubescent growth velocities between subjects treated for one year with inhaled FF 50 mcg once daily (OD) (plus montelukast 4mg or 5mg open-label) and inhaled placebo (plus montelukast 4mg or 5mg open-label).

Section 9.4.1 Primary Safety Analysis – Sub-Section 9.4.1.1 Growth Velocity

This edit applies to the end of Section 9.4.1.1:

Original Text:

Additional supportive analyses evaluating the primary de facto estimand, including all subjects (using the ITT Population, Section 9.3.1) will be performed. Further details will be provided in the RAP.

Revised Text:

A supportive completers' analysis of growth velocity over the 1-year double-blind treatment period, based on subjects in the Growth Population who completed the double-

blind treatment period and remained on study treatment during that period, will also be performed.

Additional supportive analyses evaluating the primary de facto estimand, including all subjects (using the ITT Population, Section 9.3.1) will be performed. Further details will be provided in the RAP.

Section 9.4.2 Secondary Safety Analysis – Sub-Section 9.4.1.2 Growth

This edit applies to Section 9.4.1.2:

Original Text:

Secondary analyses pertinent to growth will also include the following:

1. Summary of the proportion of children who are below the 3rd percentile of growth velocity

2. Summary of change (shift) in growth velocity quartile for each child from baseline to endpoint (definition of baseline and endpoint will be provided in the RAP)

3. Analysis of the first 12 weeks (~10 to 13 weeks given visit windows, Section 7.1) of data

4. Summary of growth velocities during the baseline and follow-up periods

5. Analysis of growth velocities for the following region subgroups: USA and Non-USA

6. Descriptive comparison of the growth velocities based on gender and ethnicity

7. Summary by visit and by treatment group of standard deviation scores (definition of standard deviation scores will be provided in the RAP)

8. Analysis of random coefficients

Revised Text:

Secondary analyses pertinent to growth will also include the following:

1. Summary of the proportion of children who are below the 3rd percentile of growth velocity

2. Summary of change (shift) in growth velocity quartile for each child from baseline to endpoint (definition of baseline and endpoint will be provided in the RAP)

3. Analysis of the first 12 weeks (~10 to 13 weeks given visit windows, Section 7.1) of data

4. Summary of growth velocities during the baseline and follow-up periods

5. Analysis of growth velocities for the following region subgroups: USA and Non-USA

6. Descriptive comparison of the growth velocities based on gender and ethnicity

7. Summary by visit and by treatment group of standard deviation scores and summary of change in height standard deviation scores from baseline to endpoint (definition of standard deviation scores, baseline and endpoint will be provided in the RAP)

8. Analysis of random coefficients

Protocol Amendment 02

This amendment applies to all study centers participating in Study HZA114971.

Description

This amendment was implemented in order to make the following changes:

- Removal of the upper limit of the FEV_1 from inclusion criterion 7 (Section 5.1).
- Removal of calcitriol from exclusion criterion 3 (Section 5.2) and from the prohibited medications Table 3 (Section 6.10.2).
- Update of text in Section 5.3 Screening/Baseline/Run-in Failures to allow re-screening of screen failures.

Method of Amendment

Original and amended text is presented below with the original text preceding the revised text contained in this Amendment No. 01 in the order of occurrence within the protocol.

Amendment Details

Section 5.1- Inclusion Criteria – Inclusion Criterion 7 (Pre-bronchodilatory FEV_1)

This edit applies to inclusion criterion 7.

Original Text:

Inclusion Criterion 7: A pre-bronchodilatory FEV_1 at Visit 1 (Screening) of between ≥60% to ≤95% predicted. There should be no SABA use within 4 hours of this measurement.

NOTE: Only subjects who are unable to perform the FEV_1 manoeuvre at their Visit 1 can, at the discretion of the investigator, attend the clinic to perform the manoeuvre **once more** on another day before Visit 2. This repeat FEV_1 manoeuvre **must** be acceptable (as defined in the SRM) and **must** meet the FEV_1 inclusion limits to be eligible for the study.

Revised Text:

Inclusion Criterion 7: A pre-bronchodilatory FEV_1 at Visit 1 (Screening) of ≥60%. There should be no SABA use within 4 hours of this measurement.
NOTE: Only subjects who are unable to perform the FEV_1 manoeuvre at their Visit 1 can, at the discretion of the investigator, attend the clinic to perform the manoeuvre **once more** on another day before Visit 2. This repeat FEV_1 manoeuvre **must** be acceptable (as defined in the SRM) and **must** meet the FEV_1 inclusion limits to be eligible for the study.

Section 5.2- Exclusion Criterion 3 a (Concomitant Medications - General)

This edit applies to inclusion criterion 3 (a).

Original Text:

Exclusion Criterion 3 (as): Prior use of any medication or treatment that might affect growth including, but not limited to: amphetamines, anticonvulsants, biphosphonates, calcitonin, calcitriol, erythropoietin, growth hormone, methylphenidate, phosphate binders, antithyroid drugs (e.g., Methimazole) or thyroid hormone.

Revised Text:

Exclusion Criterion 3 (as): Prior use of any medication or treatment that might affect growth including, but not limited to: amphetamines, anticonvulsants, biphosphonates, calcitonin, erythropoietin, growth hormone, methylphenidate, phosphate binders, antithyroid drugs (e.g., Methimazole) or thyroid hormone.

Section 6.10.2 – Prohibited Medications and Non-drug Therapies (Table 3 Row Related to General)

This edit applies to the last row in Table 3 within Section 6.10.2.

Original Table:

Table 3 Prohibited Medications

Within 2 weeks prior to Visit 1 and at any time during the study
Theophyllines
Administration of prescription or over-the-counter medication that would significantly affect the course of asthma, or interact with study drug.
Within 6 weeks prior to Visit 1 and at any time during the study
Intranasal, inhaled and high potency topical (dermatological) corticosteroids

NOTE: During the double-blind treatment period subjects who require limited courses of inhaled and/or intranasal corticosteroids should remain on study treatment.
Oral long-acting beta2-agonists (e.g. bambuterol) and inhaled long-acting beta2-agonists (e.g. salmeterol, formoterol) or combination products containing inhaled long–acting beta2-agonists (e.g. SERETIDE™, Symbicort, Dulera)
The following potent Cytochrome P450 3A4 (CYP3A4) inhibitors (Clarithromycin, atazanavir, indinavir, itraconazole, ketoconazole, nefazadone, nelfinavir; ritonavir; saquinavir; telithromycin, troleandomycin, voriconazole, mibefradil, cyclosporine)
Within 12 weeks prior to Visit 1 and at any time during the study
Systemic, oral, or depot corticosteroids **NOTE:** During the double-blind treatment period subjects who require limited courses of oral corticosteroids should remain on study treatment.
Anti-IgE (e.g. Xolair) and anti-IL 5
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 subject remains in the maintenance phase throughout the study)
General therapies not permitted prior to or during the study
Prior use of any medication or treatment that might affect growth including, but not limited to: amphetamines, anabolic steroids, anticonvulsants, biphosphonates, calcitonin, calcitriol erythropoietin, estrogens, growth hormone, methylphenidate, phosphate binders, progestins, thyroid hormone, or testosterone.

Revised Table:

Table 3 Prohibited Medications

Within 2 weeks prior to Visit 1 and at any time during the study
Theophyllines
Administration of prescription or over-the-counter medication that would significantly affect the course of asthma, or interact with study drug.
Within 6 weeks prior to Visit 1 and at any time during the study
Intranasal, inhaled and high potency topical (dermatological) corticosteroids **NOTE:** During the double-blind treatment period subjects who require limited courses of inhaled and/or intranasal corticosteroids should remain on study treatment.
Oral long-acting beta2-agonists (e.g. bambuterol) and inhaled long-acting beta2-

agonists (e.g. salmeterol, formoterol) or combination products containing inhaled long–acting beta2-agonists (e.g. SERETIDE™, Symbicort, Dulera)
The following potent Cytochrome P450 3A4 (CYP3A4) inhibitors (Clarithromycin, atazanavir, indinavir, itraconazole, ketoconazole, nefazadone, nelfinavir; ritonavir; saquinavir; telithromycin, troleandomycin, voriconazole, mibefradil, cyclosporine)
Within 12 weeks prior to Visit 1 and at any time during the study
Systemic, oral, or depot corticosteroids **NOTE:** During the double-blind treatment period subjects who require limited courses of oral corticosteroids should remain on study treatment.
Anti-IgE (e.g. Xolair) and anti-IL 5
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 subject remains in the maintenance phase throughout the study)
General therapies not permitted prior to or during the study
Prior use of any medication or treatment that might affect growth including, but not limited to: amphetamines, anabolic steroids, anticonvulsants, biphosphonates, calcitonin, erythropoietin, estrogens, growth hormone, methylphenidate, phosphate binders, progestins, thyroid hormone, or testosterone.

Section 5.3. Screening/Baseline/Run-in Failures

This edit applies to the screening failure text:

Original Text:

Screen failures are defined as subjects who consent to participate in the clinical trial, are assigned a subject number, and complete at least one study procedure but are not subsequently randomised. Subjects who enter the run-in period but are not randomised are considered run-in failures. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required which may include Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events relating to study participation.

Re-screening of screen failures and run-in failures is not permitted.

Revised Text:

Screen failures are defined as subjects who consent to participate in the clinical trial, are assigned a subject number, and complete at least one study procedure but are not subsequently entered into the run-in period. Subjects who enter the run-in period but are

not randomised are considered run-in failures. In order to ensure transparent reporting of screen failure subjects, meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements, and respond to queries from Regulatory authorities, a minimal set of screen failure information is required which may include Demography, Screen Failure details, Eligibility Criteria, and any Serious Adverse Events relating to study participation.

Re-screening of screen failures is permitted. Individuals who do not meet the criteria for participation in this study (i.e., are a screen failure) may be re-screened up to one additional time if the investigator judges the subject can meet the eligibility criteria. Any re-screened subject must satisfy all of the protocol specified inclusion/exclusion requirements at the re-screening visit. Re-screened subject should be assigned a new subject number at the time of re-screening.

Re-screening of run-in failures **is not** permitted.