Reporting and Analysis Plan

Study ID: 114971

Official Title of Study: Reporting and Analysis Plan for 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

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Title	:	Reporting and Analysis Plan for 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
Clinical Study Identifier	:	HZA114971
Effective Date	:	Refer to Document Date

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol HZA114971.
- This RAP is intended to describe the analyses of growth and other data required for the study.
- This RAP will be provided to the study team members to convey the content of the Statistical Analysis Complete (SAC) deliverable, and to the statistical programming team for use as a guide during programming development.

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol HZA114971:

Revision Chronology:		
2016N269987_00	28-JUN-2016	Original
2016N269987_01	04-NOV-2016	Amendment 1
2016N269987_02	06-MAR-2019	Amendment 2

Note that in line with the guidelines, this RAP will use the term "participant" (except Section 11.9: List of Data Displays), while all data displays (Tables, Figures & Listings) produced as part of the planned dry-run and the Statistical Analysis Complete (SAC), will use the term "subject" which reflects GSK Data Display Standards terminology.

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Changes from the originally planned statistical analysis specified in the protocol amendment 2 (Dated: 06/MAR/2019) are outlined in Table 1.

Table 1 Changes to Protocol Defined Analysis Plan

Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
Section 9.4.1.1: 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	**Section 7:** Additional supportive analyses will be provided: 1. Excluding participants who exhibit greater than or equal to Tanner Stage 2 characteristics at any point during the treatment period or follow-up period 2. Excluding questionable height measurements (definition of questionable measurements is provided in Section 11.6.3) 3. Excluding height measurements taken after participant receiving rescue systemic corticosteroids during the treatment period 4. Excluding height measurements taken after participant receiving rescue inhaled and/or intranasal and/or systemic corticosteroids during the treatment period	This is to clarify that the intention in the protocol was to exclude from the supportive analyses the individual height measurements from scenarios 2-5 and not the participants.

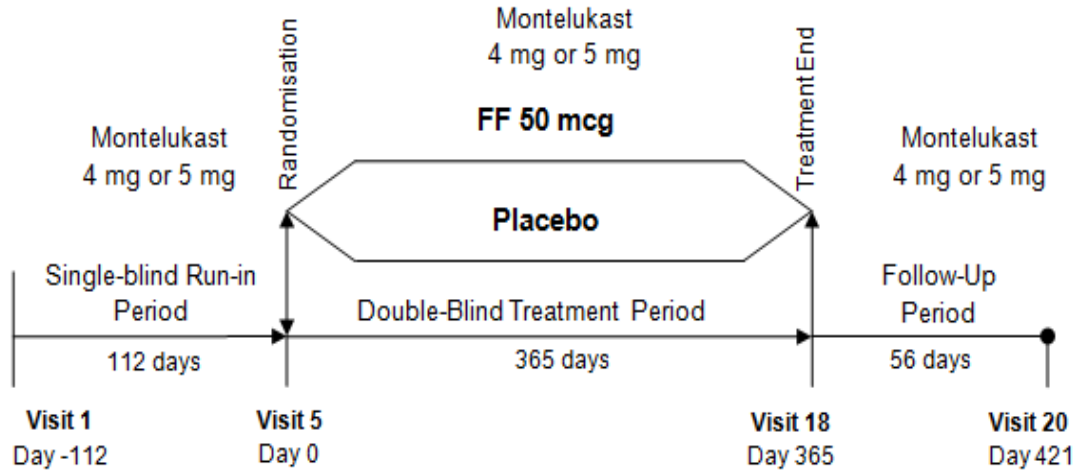
Protocol	Reporting & Analysis Plan	
Statistical Analysis Plan	**Statistical Analysis Plan**	**Rationale for Changes**
intranasal and/or systemic corticosteroids during the treatment period 5. Excluding subjects who have any of the above	5. Excluding height measurements for any of the above scenarios	
Section 9.4.2.2: 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.	**Section 8.1:** Adverse events (AEs) will be collected starting with the first administration of single-blind study treatment. 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 double-blind study treatment initiation and on or before the double-blind study treatment termination date. Adverse events during the post-treatment period include those with date of onset after the double-blind study treatment termination date.	The intention in the protocol was to summarise AEs relative to the treatment start date (i.e., pre-treatment, on-treatment and post-treatment), and not by study period (i.e., 16-week single-blind baseline period, 52-week double-blind treatment period, and 8-week follow-up period).
Section 9.4.2.3: 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.	**Section 8.3:** 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. Asthma exacerbations will not be recorded as an AE unless they meet the definition of an SAE. The incidence of exacerbations will be summarized by treatment group and listed.	The protocol indicates that exacerbations will also be summarised for the FU period. Instead, we will summarise by phase (on-treatment and post-treatment).

2.2. Study Objective(s) and Endpoint(s)

Objectives	Endpoints
Primary	**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	• Growth velocity (cm/yr) over the double-blind treatment period, as determined by stadiometry
	Secondary
	• Proportion of participants 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	**Secondary**
• To assess the safety of inhaled FF 50 mcg OD	• Incidence of adverse events
	• Incidence of asthma exacerbations
Other	**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 C-ACT score at the end of the double-blind treatment period

2.3. Study Design

Overview of Study Design and Key Features



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.

Design Features	• 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. Study randomisation will be stratified by country. • 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. Approximately 900 asthmatic prepubertal participants, aged 5 to <8 years (females) or 5 to <9 years (males) will be screened to achieve at least 450 randomised and 406 evaluable participants (approximately 203 evaluable participants per treatment group). Eligible participants will receive a single-blind placebo inhaler during the 16-week run-in period. After completing the run-in period, eligible participants will be randomly allocated to one of two treatment regimens: o Inhaled FF 50 mcg administered OD in the morning for 52 weeks or, o 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. • All participants will also receive open-label montelukast (4 mg for participants who are 5 years old and 5 mg for participants who are ≥6 years old). Participants 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: Participants who turn 6 years old during the study will subsequently receive 5 mg of open-label montelukast. • In addition, each participant will receive a short acting beta 2 agonist (SABA) (i.e., albuterol/salbutamol [inhalation aerosol or nebuliser]) to be used as needed

Overview of Study Design and Key Features	
	throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.
Dosing	• Run-in: Single-blind placebo, administered OD via the ELLIPTA™ inhaler each morning, and concurrently with open-label montelukast tablet (4 mg in 5-year-old participants, 5 mg in older participants), administered OD each evening. • Treatment Period: Double-blind fluticasone furoate (FF) 50 mcg or double-blind placebo, administered OD via the ELLIPTA™ inhaler each morning, and concurrently with open-label montelukast tablet (4 mg in 5-year-old participants, 5 mg in older participants), administered OD each evening. • Follow-up: Open-label montelukast tablet (4 mg in 5-year-old participants, 5 mg in older participants), administered OD each evening. • **Note**: Participants who turn 6 years old during the study will subsequently receive 5 mg of open-label montelukast.
Time & Events	• Refer to Appendix 2: Schedule of Activities
Treatment Assignment	• Approximately 900 asthmatic prepubertal participants will be screened to achieve at least 450 randomised and 406 evaluable participants (approximately 203 evaluable participants per treatment group). • Participants will be randomised in a 1:1 ratio to receive either inhaled FF 50 mcg or inhaled placebo. • Randomisation will be stratified by country. At the time of study start-up, those countries identified to participate included Argentina, Poland, Romania, Russia, South Africa, and the United States. • A blocked randomisation schedule will be generated by PAREXEL Informatics. An on-demand allocation of blocks to each of the strata will be used. • Treatments will be allocated via an Interactive Voice Recognition System (IVRS).
Interim Analysis	• No interim analyses are planned.

2.4. Statistical Hypotheses

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

No formal statistical hypotheses are to be tested.

3. PLANNED ANALYSES

3.1. Interim Analyses

No interim analyses are planned in this study.

3.2. Final Analyses

The final planned primary analyses will be performed after the completion of the following sequential steps:

1. All participants have completed the study as defined in the protocol.
2. All required database cleaning activities have been completed and final database release (DBR), source data lock (SDL) and database freeze (DBF) have been declared by Data Management.
3. All criteria for unblinding the randomisation codes have been met.
4. Randomisation codes have been distributed according to PAREXEL and PAREXEL Informatics Standard Operating procedures.

4. ANALYSIS POPULATIONS

Population	Definition / Criteria	Analyses Evaluated
Total	• Comprised of all participants screened and for whom a record exists on the study database.	• Study Population • Safety
Intent-to-Treat (ITT)	• Comprised of all randomised participants who receive at least one dose of study treatment. • This population will be based on the treatment to which the participant was randomised. • Any participant who receives a treatment randomisation number will be considered to have been randomised.	• Study Population • Safety (including Growth Analyses) • Efficacy
Growth	• Comprised of all ITT participants who have stadiometric height assessments from at least three post-randomisation, on-treatment clinic visits (i.e., including all available height measurements after Visit 5 up to and including Visit 18, without exclusion) during the double-blind treatment period. • Note: To be included in the Growth population, the 1st and 3rd height measurements need to be at least 7 weeks apart.	• Study Population • Safety (i.e., Growth Analyses)

Refer to Appendix 9: List of Data Displays which details the population used for each display.

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the Protocol Deviation Specifications.

- Data will be reviewed prior to unblinding and freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
- This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the electronic case report form (eCRF).

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

Treatment Group Description			
Randomisation Schedule (IVRS system)		Data Displays for Reporting	
Code	Description	Description	Order in TLF
A	PLACEB	Placebo	1
B	FLUTIC	FF 50	2

Note: Order of treatments presented in displays, as appropriate. Treatment comparisons will be displayed as follows using the descriptors as specified: FF 50 vs Placebo.

5.2. Baseline Definitions

In general, the baseline study period will be defined as an aggregate of measurements recorded during the period between screening and randomisation (Visits 1 – 5). Specific details follow below.

Baseline growth velocity

Each participant's baseline growth velocity (cm/yr) will be calculated based on the stadiometric height measurements recorded at Visits 1, 3, and 5. These data will be used to fit a simple linear regression line against time. The slope of the fitted regression line will be the participant's baseline growth velocity. Note that baseline growth velocity will be derived if there are baseline stadiometric height assessments from at least two clinic visits. Otherwise baseline will be missing.

Baseline height standard deviation score (SDS)

Each participant's Visit 5 height standard deviation score will serve as the baseline height SDS. Height standard deviation scores will be calculated as described in Section 11.6.3.

Baseline eDiary measures
Baseline PEF will be defined as the average of the measurements recorded on the morning of randomisation (Visit 5) and on the previous 6 days.

The average daily rescue medication used over the last 7 days prior to randomisation, including the rescue medication use recorded on the morning of randomisation, will be used as the baseline value.

The baseline percentage of rescue-free 24-hour periods will be defined as the percentage of 24-hour periods in the 6 days prior to randomisation and on the day of randomisation in which a participant used no rescue medication. Percentage rescue-free 24-hour periods will be calculated as described in Section 11.6.5.

The baseline percentage of symptom-free 24-hour periods will be defined as the percentage of 24-hour periods in the 6 days prior to randomisation and on the day of randomisation for which a participant's daytime asthma symptom score and night-time symptom score is 0. Percentage symptom-free 24-hour periods will be calculated as described in Section 11.6.5.

Baseline C-ACT score

Each participant's Visit 5 C-ACT score will serve as the baseline score.

Derivations and handling of missing baseline data

If the baseline for an endpoint is missing it will not be imputed using a different time point or derivation but will remain missing. For example, if there is no C-ACT value available at Visit 5, then baseline C-ACT will be missing.

5.3. Multicentre Studies

In this multicentre global study, enrolment will be presented by country and investigative site, unless otherwise specified.

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 participants. Consequently, wherever country is incorporated into a statistical analysis, all centres within the same country will be pooled. In addition, if there are any countries enrolling very small numbers of participants in total (<12 in the ITT population), these countries will be pooled with others within a similar geographical region. All amalgamations will be finalized and documented prior to unblinding the treatment codes.

5.4. Examination of Covariates, Other Strata and Subgroups

5.4.1. Covariates and Other Strata

The list of covariates and other strata to be used in all statistical analyses of growth velocity is as described in table below, unless otherwise specified in Section 7.

Category	Details
Strata	Study randomisation will be stratified by country. Unless otherwise specified, country will be used as a covariate in statistical models and not the randomisation stratum.
Covariates	• Baseline Growth Velocity • Randomised Treatment • Age at Visit 1 • Gender • Country (or group of countries, if pooling defined before unblinding)

5.4.2. Examination of Subgroups

The list of subgroups to be used in descriptive summaries and/or statistical analyses are listed below.

- If the percentage of participants is small within a particular subgroup, then the subgroup categories may be refined prior to unblinding the trial.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup	Categories
Gender	Male, Female
Ethnicity	Hispanic/Latino, non-Hispanic-Latino
Region	US, non-US sites

5.5. Multiple Comparisons and Multiplicity

There will be no statistical adjustments made to account for multiplicity. The objective of this study is to estimate the treatment difference in growth velocity over 52 weeks, rather than to test any formal hypotheses of treatment differences; hence, no multiplicity adjustment is needed.

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
11.3	Appendix 3: Assessment Windows
11.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
11.5	Appendix 5: Data Display Standards & Handling Conventions
11.6	Appendix 6: Derived and Transformed Data
11.7	Appendix 7: Reporting Standards for Missing Data

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Intent-to-Treat (ITT) population (as defined in Section 4), unless otherwise specified.

If the number of participants in the Growth Population is <90% of the ITT population an additional set of study population analyses may be repeated based on the Growth population.

Study population analyses including analyses of participant's disposition, protocol deviations, demographic and baseline characteristics, prior and concomitant medications, and exposure and treatment compliance will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 9: List of Data Displays.

Section 11.6.2 includes details with regards to derivation of data for the study population analyses.

7. GROWTH ANALYSES

7.1. Primary Growth Analyses

7.1.1. Endpoint / Variable

The primary endpoint is the growth velocity (cm/yr) over the double-blind treatment period, as determined by stadiometry. Details regarding the calculation of growth velocity are provided in Section 11.6.3.

7.1.2. Summary Measure

The summary measure used for the treatment comparison will be an estimate of the mean treatment difference in growth velocity over the double-blind treatment period and a 95% confidence interval (CI).

7.1.3. Population of Interest

The primary growth analyses will be based on the Growth Population, as defined in Section 4, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomisation) Events

The primary treatment effect to be estimated is the treatment policy effect of initial randomised treatment. The list of intercurrent events/events leading to missing data that may occur during the study and may affect the estimation of the treatment effect are:

- **Discontinuation of Randomised Treatment**: Participants may prematurely discontinue double-blind treatment and continue in the study. This is considered an intercurrent event.
- **Participants Presenting Tanner Stage ≥2**: Participants must be pre-pubertal (Tanner Stage 1) at the time of randomisation but may present physical characteristics of Tanner Stage 2 or higher at any point during the study. This is considered an intercurrent event.
- **Use of Rescue Systemic Corticosteroids**: Participants may receive rescue systemic corticosteroids at any point during the study. This is considered an intercurrent event.
- **Use of Rescue Inhaled/Intranasal Corticosteroids:** Participants may receive rescue inhaled/ intranasal corticosteroids at any point during the study. This is considered an intercurrent event.
- **Early Withdrawal from Study**: Participants may prematurely withdraw from the study which results in missing endpoint data.
- **Week 52 Height Not Available (other reasons than early withdrawal)**: Height information at Week 52 may not be available for other reasons (not Early Withdrawal).

All available data up to the time of study withdrawal will be included in the primary analyses, regardless of discontinuation of randomised treatment, use of rescue corticosteroids, or Tanner Stage. To minimize study withdrawals, participants who

discontinue randomised treatment will be encouraged to stay in the study and complete all remaining protocol-specified visits and be followed-up as per the protocol until the completion of follow-up assessments. All non-missing data will be included in the primary analyses. Missing data will be assumed missing at random (MAR) in the primary analysis and will not be imputed. Missing data will be imputed in sensitivity analyses as described below in Section 7.1.6.

The strategies for handling these events for this endpoint are described in the below Table.

Event	Handling Strategy
Discontinuation of Randomised Treatment	Available height data will be used in the analysis, regardless of early discontinuation of randomised treatment.
Tanner Stage ≥2	Available height data will be used in the analysis, regardless of whether participants exhibited physical characteristics of Tanner Stage 2 or higher at any point during the double-blind treatment or follow-up period.
Use of Rescue Systemic Corticosteroids	Available height data will be used in the analysis, regardless of whether participants have received rescue systemic corticosteroids during the double-blind treatment period.
Use of Rescue Inhaled/ Intranasal Corticosteroids	Available height data will be used in the analysis, regardless of whether participants have received rescue inhaled/intranasal corticosteroids during the double-blind treatment period.
Missing height data due to EW or any other reason	Missing height data (for any reason) will be treated as missing (assuming MAR) and will not be imputed.

7.1.5. Statistical Analyses / Methods

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints/variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed. By-treatment summaries of growth velocity over the baseline, treatment, and follow-up periods will also be provided.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• Growth velocity (cm/yr) over the double-blind treatment period as determined by stadiometry. For details of growth velocity calculation see Section 11.6.3.
Model Specification
• The primary endpoint will be analysed using an analysis of covariance (ANCOVA) model adjusting for baseline growth velocity (continuous, see Section 5.2: Baseline Definitions), age at Visit 1 (continuous), gender (categorical), and country (categorical).

• The primary analysis will include all available height data, regardless of any intercurrent events (defined in Section 7.1.4) that occur during the study. • Missing data will be assumed to be missing at random (MAR) and will not be imputed. The mean difference in growth velocity over the treatment period between treatments and a 95% confidence interval will also be provided.
Model Checking & Diagnostics
• The Kenward and Roger method [Kenward, 1997] of approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance matrix of the fixed effects will be used in the diagnostic analyses of ANCOVA models. The Kenward-Roger method will be invoked by specifying the DDFM=KR option in the PROC MIXED model statement. • Appropriate graphs will be reviewed as part of the model-checking process in order to ensure that distributional assumptions hold. Additional analyses may be considered if these assumptions are not met. These graphs will include a normal probability plot of the residuals and a plot of the residuals versus the fitted values. If there are any departures from the distributional assumptions, alternative models will be explored using appropriate transformed data.
Model Results Presentation
• The point estimate of the mean treatment difference in growth velocity and corresponding 95% confidence interval will be presented for the comparison between treatment arms.

7.1.6. Supportive Analyses

Details of the planned displays are provided in Appendix 9: List of Data Displays and will be based on GSK data standards and statistical principles.

For each of the following analyses, the estimate of the mean treatment difference in growth velocity during the double-blind treatment period will be provided, using all the available height data provided while participants were on randomised double-blind treatment, unless otherwise specified. By-treatment summaries of growth velocity over the baseline, treatment, and follow-up periods will also be provided. The change from baseline will also be summarised by treatment group.

Supportive Estimand I for Primary Endpoint

- Given that participants who prematurely discontinue randomised treatment may be administered other medications that may affect growth, a supportive estimand (Supportive Estimand I) will be defined for the primary endpoint, as defined in Section 7.1.1.
- This estimand will be based on the Growth Population, as defined in Section 4: Analysis Populations.
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4, apart from the intercurrent event of *"Discontinuation of Randomised Treatment*" which will be handled as described below:

Event	Handling Strategy
Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.

Supportive Estimand II for Primary Endpoint

- Another supportive estimand defined for the primary endpoint (as defined in Section 7.1.1) will be Supportive Estimand II.
- This estimand will be based on the Growth Population (as defined in Section 4: Analysis Populations) and will exclude participants who presented Tanner Stage ≥2 at any time during the double-blind treatment period or follow up period.
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4, apart from the intercurrent event of "Discontinuation of Randomised Treatment" which will be handled as described below:

Event	Handling Strategy
Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.

Supportive Estimand III for Primary Endpoint

- Another supportive estimand defined for the primary endpoint (as defined in Section 7.1.1 but excluding questionable height data as defined in Section 11.6.3) will be Supportive Estimand III.
- This estimand will be based on the Growth Population (as defined in Section 4: Analysis Populations)
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4 for the primary analysis, apart from the intercurrent event of "Discontinuation of Randomised Treatment" which will be handled as described below:

Event	Handling Strategy
Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.

Supportive Estimand IV for Primary Endpoint

- Another supportive estimand defined for the primary endpoint (as defined in Section 7.1.1) will be Supportive Estimand IV.
- This estimand will be based on the Growth Population, as defined in Section 4: Analysis Populations.
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4, apart from the intercurrent event of *"Use of Rescue Systemic Corticosteroids*" and "*Discontinuation of Randomised Treatment*" which will be handled as described below:

Event	Handling Strategy
Use of Rescue Systemic Corticosteroids	Only available height data prior to receiving rescue systemic corticosteroids will be used in the analysis.

Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.

Supportive Estimand V for Primary Endpoint

- Another supportive estimand defined for the primary endpoint (as defined in Section 7.1.1) will be Supportive Estimand V.
- This estimand will be based on the Growth Population, as defined in Section 4: Analysis Populations.
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be the same as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4, apart from the intercurrent events of *"Use of Rescue Systemic Corticosteroids*", *"Use of Rescue Inhaled/Intranasal Corticosteroids*" and "*Discontinuation of Randomised Treatment*" which will be handled as described below:

Event	Handling Strategy
Use of Rescue Systemic Corticosteroids	Only available height data prior to receiving rescue systemic corticosteroids will be used in the analysis.
Use of Rescue Inhaled/Intranasal Corticosteroids	Only available height data prior to receiving rescue inhaled/intranasal corticosteroids will be used in the analysis.
Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.

Supportive Estimand VI for Primary Endpoint

- Another supportive estimand defined for the primary endpoint, as defined in Section 7.1.1, but also excluding questionable height data as defined in Section 11.6.3, will be Supportive Estimand VI.
- This estimand will be based on the Growth Population (as defined in Section 4: Analysis Populations) and will exclude participants who presented Tanner Stage ≥2 at any time during the double-blind treatment period or follow up period.
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be the same as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described below:

Event	Handling Strategy
Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.
Use of Rescue Systemic Corticosteroids	Only available height data prior to receiving rescue systemic corticosteroids will be used in the analysis.
Use of Rescue Inhaled/Intranasal Corticosteroids	Only available height data prior to receiving rescue inhaled/intranasal corticosteroids will be used in the analysis.

Missing height data due to EW or any other reason	Missing height data (for any reason) will be treated as missing (assuming MAR) and will not be imputed.

Supportive Estimand VII for Primary Endpoint

- Another supportive estimand defined for the primary endpoint (as defined in Section 7.1.1) will be Supportive Estimand VII.
- This estimand will be based on the Growth Population (as defined in Section 4: Analysis Populations) and will focus on growth velocity among participants who complete 1 year of treatment with double-blind study treatment. These participants must complete 1 year of treatment and have had a stadiometric height assessment at Visit 18 (Week 52), but do not necessarily have to have had stadiometric height assessments made at all visits during the double-blind treatment period.
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4, apart from the intercurrent event of *"Discontinuation of Randomised Treatment*" which will be handled as described below:

Event	Handling Strategy
Discontinuation of Randomised Treatment	Only available height data while the participant is on randomised double-blind treatment will be used in the analysis.

Supportive Estimand VIII for Primary Endpoint

- Another supportive estimand defined for the primary endpoint (as defined in Section 7.1.1) will be Supportive Estimand VIII.
- This estimand will be based on the ITT Population (as defined in Section 4: Analysis Populations).
- The summary measure will be as described in Section 7.1.2 for the primary analysis, and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events/events leading to missing data for this estimand will be as described in Section 7.1.4 for the primary analysis.

Supportive Analyses - Assessing Missing Data

- Two approaches have been defined to assess the effects of missing data. For these analyses the population of interest will be the Intent-to-Treat (ITT) population, as defined in Section 4: Analysis Populations.
- In cases where the final height measurement at week 52 is missing, these missing height data will be imputed using Multiple Imputation (described at length in Section 11.7.2) by applying to the last available height measurement the following sets of rules:
    1. Use the 'worst growth rate' (i.e., smallest growth velocity) from participants from the FF 50 treatment group who complete the double-blind treatment period as the central value for imputations of missing data in the FF treatment group, and the 'worst growth rate' from participants from the placebo group who complete the double-blind treatment period as the central value for imputations of missing data in the placebo treatment group.
    2. Use the 'worst growth rate' (i.e. smallest treatment velocity) from participants from the FF 50 treatment group who complete the double-blind treatment period as the central

value for imputations of missing data in the FF treatment group, and assume any data missing in the placebo treatment group are missing at random.

- The summary measure will be as described in Section 7.1.2 for the primary analysis and the statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation) will be as described in Section 7.1.5 for the primary analysis.
- The strategies for handling the intercurrent events will be as described in Section 7.1.4 for the primary analysis.
- Additionally, the proportion of missing stadiometric height measurements will be summarized by clinic visit and treatment group.

7.2. Secondary Growth Analyses

Secondary analyses pertinent to growth will be provided and are detailed. All secondary analyses described in the following sections will be based on the Growth Population, as defined in Section 4: Analysis Populations, unless otherwise specified.

7.2.1. Percentage of Participants with Growth Velocity Below the 3rd Percentile During the Double-Blind Treatment Period

The number and percentage of participants whose growth velocity during the double-blind treatment period is below the 3rd percentile will be summarized by treatment and listed. Details of the calculation of these percentiles can be found in Section 11.6.3. This characterization of growth velocity will be based on all available on- and off-treatment height data.

No formal statistical analysis is planned.

7.2.2. Change from Baseline in Growth Velocity Quartiles

Shifts from baseline to endpoint in growth velocity percentile based on quartiles will be summarized by treatment group. Baseline is defined as the baseline study period (see Section 5.2: Baseline Definitions); endpoint is defined as the last 12 weeks of the double-blind treatment period. Participants with a decrease in growth velocity quartile from baseline to endpoint will be listed. Details of the calculation of these quartiles can be found in Section 11.6.3. This characterization of growth velocity will be based on all available on- and off-treatment height data.

No formal statistical analysis is planned.

7.2.3. Analysis of Growth Velocity Over the First 12 Weeks of the Double-Blind Treatment Period

Growth velocity during the first 12 weeks (~10 to 13 weeks given visit windows, Appendix 2: Schedule of Activities) of the double-blind treatment period will be analysed (Supportive Estimand XI). Regarding the intercurrent event of "*Discontinuation of Randomised Treatment*", all available height data collected during the double-blind treatment period up to Visit 8 while the participant is on randomised double-blind

treatment will be considered. In order to be included in this analysis, a participant must have data from a Visit 8 (Week 12) stadiometric height assessment.

An analysis of covariance (ANCOVA) model, similar to the one defined for the primary analysis, will be used to estimate the mean treatment difference in growth velocities over the first 12 weeks of the double-blind treatment period. The summary measure, statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation), and strategies for handling all other intercurrent events/events leading to missing data will be as described in Section 7.1: Primary Growth Analyses. By-treatment summaries of growth velocity during the baseline period and the first 12 weeks of the double-blind treatment period will also be provided. The change from baseline in growth velocity will also be summarised.

7.2.4. Growth Velocity by Gender and Ethnicity

Growth velocity during each study period will be summarized by gender (male/female), and ethnicity (Hispanic or Latino/not Hispanic or Latino). All available on- and off-treatment height data will be used regardless of the occurrence of the intercurrent events defined in Section 7.1.4.

No formal statistical analysis is planned.

7.2.5. Growth Velocity by Region (US and non-US sites)

Analyses of growth velocity by region (i.e., US vs non-US sites) will be provided (Supportive Estimand XII).

The summary measure, statistical analyses/methods (i.e., model specification, model checking and diagnostics, and model results presentation), and strategies for handling the intercurrent events/events leading to missing data will be as described in Section 7.1: Primary Growth Analyses. Separate analysis of covariance (ANCOVA) models, similar to the one defined for the primary analysis (excluding country from list of covariates), will be used to estimate the mean treatment difference in growth velocities for all participants enrolled in US sites and non-US sites, respectively. By-treatment summaries of growth velocity for all study periods (baseline, treatment, and follow-up) will be provided. The change from baseline in growth velocity will also be summarised.

7.2.6. Height Standard Deviation Scores

Height standard deviation scores will be summarized by treatment at each study visit. A box-plot illustrating the height standard deviation scores at each visit for the two treatment groups will also be provided. Details of the calculation of the height standard deviation scores can be found in Section 11.6.3. All available on- and off-treatment height data will be used.

The change from baseline (Visit 5) to endpoint (Visit 18, Week 52) in height standard deviation scores will also be summarized by treatment group. The endpoint value will be selected from available on- and off-treatment height data at Visit 18. Change from baseline will be defined as the difference between the value of the measure at the

timepoint of interest and the baseline. If either baseline or endpoint values are missing, then the change from baseline in height SDS will not be calculated.

No formal statistical analysis is planned.

7.2.7. Random Effects Model Assessing Height

A sensitivity analysis (Supportive Estimand XIII) will be provided to support the primary analysis using height (cm, via stadiometry) as the dependent variable (endpoint).

Intercurrent events will be handled as described in Section 7.1.4 for the primary analysis i.e., all available on- and off- treatment height data collected during the double-blind treatment period will be considered regardless of the occurrence of an intercurrent event.

A mixed effects ANCOVA model with baseline height (i.e., Visit 1, continuous), age at Visit 1 (continuous), gender (categorical), double-blind treatment (categorical), time (days since treatment start, continuous), and the treatment-by-time interaction as explanatory variables will be used. The intercept and the slope for the regression of height over time are assumed to be random effects (i.e., each participant has their own linear growth over time). A 95% confidence interval will be constructed for the treatment difference in mean growth velocity over the double-blind treatment period, using the estimate for the treatment-by-time interaction in the mixed effects model. The model checking and diagnostics, and strategies for handling the intercurrent events/events leading to missing data will be as described in Section 7.1: Primary Growth Analyses.

8. SAFETY ANALYSES

The safety analyses will be based on the Intent-to-Treat (ITT) population (as defined in Section 4: Analysis Populations), unless otherwise specified.

8.1. Adverse Events Analyses

Adverse events analyses including the analysis of adverse events (AEs), Serious (SAEs) and other significant AEs will be based on GSK Core Data Standards. The details of the planned displays are provided in Appendix 9: List of Data Displays.

Adverse events (AEs) will be collected starting with the first administration of single-blind study treatment. 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 double-blind study treatment initiation and on or before the double-blind study treatment termination date. Adverse events during the post-treatment period include those with date of onset after the double-blind study treatment termination date.

The AE text recorded in the eCRF will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. The version of MedDRA used in reporting will be noted in a footnote of the AE overview table.

For the standard AE tables, the number and percentage of participants with all AEs (regardless of causality) will be summarized for each treatment group by System Organ Class (SOC) and Preferred Term (PT). Results will be displayed in the order of decreasing frequency, both across SOC and within SOC. A SOC will not be included if no AEs in that SOC are reported. If the total incidence for any two or more adverse events is equal, the events will be presented in alphabetical order.

Adverse events will also be listed.

8.2. Adverse Events of Special Interest Analyses

A comprehensive list of MedDRA terms based on clinical review will be used to identify AEs of special interest to FF. Changes to the MedDRA dictionary may occur between the start of the study and the time of reporting and/or emerging data from on-going studies may highlight additional adverse events of special interest, therefore the list of terms to be used for each event of interest and the specific events of interest will be based on the safety review team (SRT) agreements in place at the time of reporting. The details of the planned displays are provided in Appendix 9: List of Data Displays.

The number and percentage of participants with AEs of special interest will be summarized for each treatment group by special interest term, subgroup and PT. The ordering of the special interest terms, the subgroups and the PTs within them will all be in descending order of total incidence. If the total incidence for any two or more AEs is equal, the events will be presented in alphabetical order.

8.3. 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.

Asthma exacerbations will not be recorded as an AE unless they meet the definition of an SAE.

The incidence of exacerbations will be summarized by treatment group and listed.

8.4. Oropharyngeal Examination

Oropharyngeal examinations will be conducted according to the Protocol Defined Schedule of Events (see Section 11.2.1). Any adverse finding will be recorded as an AE or SAE and included in summaries and listings of AEs/SAEs.

8.5. Other Safety Measures

All investigational product (IP) inhaler malfunction data for participants reporting at least one IP inhaler malfunction will be listed. Pneumonia data (on- and post-treatment) will be summarised. All pneumonia data collected on the pneumonia eCRF page will be listed. For any deaths, cardiovascular events or liver events reported during the study, Integrated Data Standards Library (IDSL) standards for reporting will be followed for all data collected in the eCRF.

A summary of risks plot will be produced summarizing the following AE information:

- SAE (any)
- Withdrawal due to AE (including events leading to permanent discontinuation of study drug and/or withdrawal from the study)
- AESI (any)

Individual AESI will also be summarized:

- Pneumonia
- Hypersensitivity
- Local steroid effects
- Ocular effects
- Effects on glucose
- Adrenal suppression

The frequencies, relative risk and corresponding 95% CI for FF 50 vs. Placebo will be displayed for the ITT population (as defined in Section 4: Analysis Populations). Calculations of the relative risks and 95% CIs are described in Section 11.6.4.

9. EFFICACY ANALYSES

The efficacy analyses will be based on the Intent-to-Treat (ITT) population (as defined in Section 4: Analysis Populations), unless otherwise specified.

The following parameters will be 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
- C-ACT score at Visit 1 (Screening), Visit 5 (Randomisation), and Visit 18

Each morning, a parent or caregiver will assess the daytime symptoms from the previous day and the night-time symptoms from the night just ended. Each 24-hour period will incorporate the morning symptom assessment with the evening symptom assessment recorded on that date but, will refer to the day immediately before. Therefore, the symptom scores recorded on the date of randomisation (i.e., Day 1) will in fact reflect the 24 hours prior to randomisation (Day -1), and the first day of symptoms on treatment will be associated with the date following the day of randomisation (Day 2).

The baseline morning PEF will be defined in a similar manner. Since PEF assessments are recorded before morning study treatment is administered, the same rules as described above will also apply to PEF. In other words, the first day of on-treatment PEF will be associated with the date following the day of randomisation (Day 2).

9.1. Change from Baseline in the Percentage of Rescue/Symptom Free 24-Hour Periods Over the Double-Blind Treatment Period

The change from baseline in the percentage of rescue-free and symptom-free days over the double-blind treatment period will be summarised by treatment. The baseline percentage of rescue-free and symptom free 24-hour periods will be as defined in Section 5.2: Baseline Definitions. Change from baseline will be defined as the difference between the average over the double-blind treatment period and the baseline value.

The efficacy endpoints relating to daily diary assessments will be calculated from all available data over the period of interest. No imputation will be considered with respect to missing daily diary data. See also Section 11.6.5.

No formal statistical analysis is planned

9.2. Change from Baseline in Morning Peak Expiratory Flow Over the Double-Blind Treatment Period

The change from baseline in the morning Peak Expiratory Flow (PEF) over the double-blind treatment period will be summarised by treatment group. Baseline is as defined in Section 5.2: Baseline Definitions. Change from baseline will be defined as the difference between the average over the double-blind treatment period and the baseline value.

The efficacy endpoints relating to daily diary assessments will be calculated from all available data over the period of interest. No imputation will be considered with respect to missing daily diary data.

No formal statistical analysis is planned.

9.3. C-ACT Score

C-ACT scores will be summarized by treatment at each planned visit (Visit 1, Visit 5 and Visit 18), and will include summaries of the number of participants at each visit whose asthma is considered controlled (i.e., who have a C-ACT score at that visit of 20 or more). In addition, the change from baseline (Visit 5) C-ACT score at endpoint (Visit 18) will be summarized by treatment. Change from baseline will be defined as the difference between the value of the measure at Visit 18 and the baseline value. If Visit 5 or Visit 18 data is not available, change from baseline will not be calculated.

No formal statistical analysis is planned.

10. REFERENCES

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11. APPENDICES

11.1. Appendix 1: Exclusions from Per Protocol Population

Instream and final analysis population reviews as per SOP 130050 are not planned for this study because it does not include a Per-Protocol population.

11.2. Appendix 2: Schedule of Activities

11.2.1. Protocol Defined Schedule of Events

	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																					

	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		
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
Assess e-diary and compliance	X	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																	

	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		
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			
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-dilary 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

11.3. Appendix 3: Assessment Windows

11.3.1. Definitions of Assessment Windows for Analyses

Clinic visits are scheduled to take place as specified in Appendix 2: Schedule of Activities. Note that all visits should occur within -5 to +2 days of the specified visit day. Individual measurements will be reported based on the visits they are assigned to in the study database without adjustment.

11.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

11.4.1. Study Phases

11.4.1.1. Study Phases for Assessments

Assessments will be classified according to time of occurrence relative to the start and/or stop date of the double-blind study treatment. The earliest and latest exposure double-blind treatment start and stop dates will be used to determine whether an assessment was pre-treatment, on-treatment or post-treatment. If it is not possible to tell whether an assessment or event was on-treatment or not it will be considered as on-treatment.

Study Phase	Definition
Pre-Treatment	Assessment Date ≤ Start Date of Double-Blind Treatment - 1
On-Treatment	Start Date of Double-Blind Treatment ≤ Assessment Date ≤ Stop Date of Double-Blind Treatment + 1
Post-Treatment	Assessment Date ≥ Stop Date of Double-Blind Treatment + 2

Note: For the analyses of growth velocity defined in Section 7: Growth Analyses, "off-treatment" refers to height data collected during the double-blind treatment period (i.e., after Visit 5 up to and including Visit 18/EW/TD) while participants were not receiving randomised double-blind treatment.

11.4.1.2. Study Phases for Concomitant Medication

A medication will be summarized in every study period (pre-, on-, or post-treatment) in which it was taken, so a medication that was started during the run-in period and stopped during the double-blind treatment period will appear in both the pre-treatment and the on-treatment summaries.

Pre-treatment will be considered prior to and until the day of double-blind treatment start. On-treatment will be considered to be from the day after the double-blind treatment start date until the double-blind treatment stop date.

11.4.1.3. Study Phases for Asthma Exacerbations

Asthma exacerbations will be classified according to the time of occurrence relative to start and/or stop date of the double-blind study treatment.

Study Phase	Definition
Pre-Treatment	Exacerbation Onset Date ≤ Start Date of Double-Blind Treatment - 1
On-Treatment	Start Date of Double-Blind Treatment ≤ Exacerbation Onset Date ≤ Stop Date of Double-Blind Treatment + 1
Post-Treatment	Exacerbation Onset Date ≥ Stop Date of Double-Blind Treatment + 2

11.4.1.4. Study Phases for eDiary

Diary measurements will be classified according to the time of occurrence relative to start and/or stop date of the double-blind study treatment. Note that rescue medication use, daytime symptoms, and overnight symptoms are recorded daily for the previous day.

Study Phase	Definition
Pre-Treatment	Date of Measurement ≤ Start Date of Double-Blind Treatment
On-Treatment	Start Date of Double-Blind Treatment < Date of Measurement ≤ Stop Date of Double-Blind Treatment + 1
Post-Treatment	Date of Measurement ≥ Stop Date of Double-Blind Treatment + 2

11.4.2. Treatment Emergent Flag for Adverse Events

Adverse Events will be classified according to the time of occurrence relative to start and/or stop date of the double-blind study treatment.

Treatment state	Definition
Pre-Treatment	AE Start Date ≤ Start Date of Double-Blind Treatment - 1
On-Treatment	Start Date of Double-Blind Treatment ≤ AE Start Date ≤ Stop Date of Double-Blind Treatment + 1
Post-Treatment	AE Start Date ≥ Stop Date of Double-Blind Treatment + 2
Onset Time Since 1st Dose (Days)	Time Since 1st Dose will be derived as follows: If Start Date of Double-Blind Treatment > AE Onset Date, then => AE Onset Date – Start Date of Double-Blind Treatment If Start Date of Double-Blind Treatment ≤ AE Onset Date, then => AE Onset Date – Start Date of Double-Blind Treatment + 1 If Double-Blind Treatment Start Date or AE Onset Date are missing, then => missing
Duration (Days)	AE resolution date – AE onset date + 1
Drug-Related	If relationship is marked 'YES' OR value is missing.

NOTE: If the study treatment stop date is missing then the AE will be considered to be on-treatment.

11.5. Appendix 5: Data Display Standards & Handling Conventions

11.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: /arenv/arprod/gw685698/hza114971
Analysis Datasets	
• Analysis datasets will be created according to current CDISC standards (Study Data Tabulation Model (SDTM) Implementation Guide Version 3.2 or higher & Analysis Data Model (AdaM) Implementation Guide Version 1.3 or higher). • The same version of dictionary datasets will be implemented for conversion from SI to SDTM in the creation of ADaM datasets (ADCM/ADAE).	
Generation of RTF Files	
• RTF files will be generated for Table displays to support the Clinical Study Report (CSR) development.	

11.5.2. Reporting Standards

General

• The current GSK Statistical Display Standards in the GSK Standards Library (IDSL) will be applied for reporting, unless otherwise stated (Library Location): https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings
• Note: All data displays (Tables, Figures & Listings) produced as part of the Statistical Analysis Complete (SAC), will use the term “Subject” which reflects GSK Data Display Standards terminology.

Formats
• Unless otherwise stated, all results will be reported according to the treatment to which the participant was randomised. • GSK Statistical Display Principles (5.03 & 6.06.3) for decimal places (DP’s) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF or recorded in the raw dataset if from non-eCRF sources. • The reported precision from non eCRF sources will follow the GSK Standard Statistical Display Principles but may be adjusted to a clinically interpretable number of DP’s. • Summary and analysis data displays will include the following degrees of precision:

Specification of Number of Decimal Places for Descriptive Statistics		
Label	**Description**	**No. of decimal places more than raw data**
N	Number of participants in the treatment group	0
n	Number of participants with non-missing values	0
Mean	Arithmetic mean	1
SD	Standard deviation	2
Median	Median	1
Min.	Minimum	0
Max.	Maximum	0
Specification of Number of Decimal Places for Statistical Analyses		
Label	**Description**	**No. of decimal places more than raw data**
LS Mean	Least squares adjusted mean for the treatment group	1
Std Err	Standard error	2
Difference	Treatment difference	1
95% CI	95% Confidence interval around treatment difference/ratio	Same as difference or ratio

Planned and Actual Time

- Reporting for tables, figures and formal statistical analyses:
  - Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
- The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
- Reporting for Data Listings:
  - Planned and actual time relative to study drug dosing will be shown in listings (Refer to GSK Standard Statistical Display Principle 5.05.1).
  - Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits

- Height data collected at unscheduled visits will be included in summary tables, analyses and/or figures, unless otherwise specified.
- Unscheduled visits will be clearly labelled as unscheduled and slotted based on date of visit.
- All unscheduled visits will be included in listings.

Descriptive Summary Statistics	
Continuous Data	Refer to GSK Standard Statistical Display Principle 6.06.1
Categorical Data	N, n, frequency, %

Graphical Displays

- Refer to GSK Standard Statistical Display Principals 7.01 to 7.13.
- The programs for statistical analysis tables will create SAS datasets with the unrounded numbers from the statistical models to be used in any graphs. These datasets will include all LS means, standard errors, treatment differences or ratios, and CIs. These analysis datasets will be created for all analysis tables regardless of whether or not a figure is planned as part of SAC.

- The programs for all graphical displays will also create a CSV file with the final data that is used in the graph in order to allow the graph to be redrawn for any potential publication requirement in the future.

11.6. Appendix 6: Derived and Transformed Data

11.6.1. General

Multiple Measurements at One Analysis Time Point
• If a circumstance should arise where multiple measurements have been collected and recorded against the same time point, then the first valid value will be used for that time point. If the value that was recorded first cannot be determined based on the available information, then the average will be taken.
Study Day

• Calculated as the number of days from Randomisation Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < Randomisation Date → Study Day = Ref Date – Randomisation Date
  • Ref Data ≥ Randomisation Date → Study Day = Ref Date – (Randomisation Date) + 1

Time Since First Dose

• Calculated as the number of days from First Dose Date of Double-Blind Treatment:
  • Ref Date = Missing → Time Since First Dose = Missing
  • Ref Date < First Dose Date → Time Since First Dose = Ref Date – First Dose Date
  • Ref Date ≥ First Dose Date → Time Since First Dose = Ref Date – (First Dose Date) + 1

Double-Blind Treatment Start/Stop Date
• Participants who permanently discontinue double-blind study treatment are encouraged to continue in the study, attend the remaining visits and complete the scheduled assessments. • Data displays will state if on-treatment, off-treatment (as defined in Section 11.4.1), or both on-treatment and off-treatment data are included in the summary or analysis, when applicable. • Double-Blind Treatment Start Date will be defined as the earliest treatment start date of double-blind treatment and Double-Blind Treatment Stop Date will be defined as the latest treatment stop date of double-blind treatment (from the study treatment compliance eCRF log and treatment discontinuation eCRF page). These dates will be used to determine whether a measurement is on-treatment or off-treatment (See Section 11.4.1).

11.6.2. Study Population

Demographics

Age

- Age is being calculated in the Interactive Voice Recognition System (IVRS) and will be imported from the IVRS into the clinical database.
- The IVRS will use GSK standard IDSL algorithms to calculate age. In accordance with GSK policy, only month and year are collected in the IVRS. A complete birthdate will be imputed by using the month and year recorded by the IVRS and assigning a day value of '15.' Any participant with a missing month will have day and month imputed as '30 June'.
- Birth date will be presented in listings as 'YYYY'.
- Completely missing dates of birth will remain as missing, with no imputation applied. Consequently, the age of the participant will not be calculated and will remain missing.
- Age, in whole years, will be calculated with respect to the date of screening (Visit 1).

Body Mass Index (BMI)

- Calculated as weight (kg) / height $(m)^2$.

Race

The high-level Food and Drug Administration (FDA) race categories and designated Asian subcategories are:

1. American Indian or Alaska Native
2. Asian
    a. Central/South Asian Heritage
    b. Japanese Heritage/East Asian Heritage/South East Asian Heritage
    c. Mixed Asian Heritage (only required if data exist)
3. Black or African Heritage
4. Native Hawaiian or other Pacific Islander
5. White

These will be summarized along with all combinations of high-level categories which exist in the data. All high-level race categories and the Asian subcategories must appear on the display even if there are no participants in a particular category, but combinations that do not exist in the data do not need to be represented. Combinations will be represented as the concatenation of the high-level category terms, e.g., "White & Asian". The designated Asian subcategories will not be summarized as combinations with other categories.

In addition, the standard race categories collected per IDSL will be summarized along with categories for mixed race. The categories are:

- American Indian or Alaska Native
- Asian - Central/South Asian Heritage
- Asian – East Asian Heritage
- Asian – Japanese Heritage
- Asian – South East Asian Heritage

- Native Hawaiian or other Pacific Islander
- White – Arabic/North African Heritage
- White – White/Caucasian/European Heritage
- Mixed White Race
- Mixed Asian Race
- Multiple

"Mixed Asian Race" is only used if more than one Asian category is selected, but no non-Asian races. Similarly, "Mixed White Race" is only used if both of the White categories are selected, and no non-White races. If multiple races of different types are selected, then the overall "Mixed Race" category is used. If multiple races of different types are selected, then the overall "Multiple" category is used.

A participant will only be represented in a single category. A participant who selects a combination of races will be counted as "Mixed Asian Race," "Mixed White Race," or "Multiple" but not in each of the constituent terms. Therefore, the counts will add up to the total number of participants with a response, and the percentages will add to 100%.

Treatment Compliance

Compliance with the study medication will be assessed throughout the study.

- Compliance with open-label montelukast will be assessed based on the daily eDiary data during both the run-in and double-blind treatment periods. The percentage of times the parent answered "Yes" to the question "Did your child take their daily Study Asthma Tablet yesterday evening?" will be summarized for each study period.
- Compliance with the single-blind/double-blind study inhaler will be assessed during the run-in/ double-blind treatment periods based on the daily eDiary data. The percentage of times the parent answered "Yes" to the question "Did your child take their daily Study Medication Inhaler yesterday morning?" will be summarized for each study period.
- In addition, compliance with the single-blind/double-blind study inhaler during the run-in/double-blind treatment period will also be calculated based on the dose counter of the inhalers, which are re-supplied during the study. The number of doses of study inhaler taken by each participant will be calculated from the dose counter start and stop counts for each inhaler dispensed during the study. If a dose counter start count is missing, then it will be assumed to be 30. If dose counter stop count is non-missing, then the percentage compliance will be calculated as:

$$Compliance = \left(\frac{Total \quad Number \quad of \quad Inhalations \quad Taken}{Expected \quad Inhalations \times (Stop \quad Date - Start \quad Date + 1)} \right)$$

where *Total Number of Inhalations Taken* is the total number of doses taken from all inhalers, *Expected Inhalations* is equal to 1 and *Start Date* and *Stop Date* are the earliest treatment start date and the latest treatment stop date recorded for all of the inhalers used in the calculation.
Participants who are either under- (<80%) or over- (>120%) compliant over the run-in and double-blind treatment periods according to both the diary card and the inhaler dose counter, will be identified. The numbers of these participants, as well as the number of participants whose compliance is unknown, will be summarized by treatment.

Extent of Exposure

- Duration of exposure (days) to double-blind study treatment will be calculated as:
  - Double-Blind Treatment Stop Date – Double-Blind Treatment Start Date + 1
- Participants who were randomised but did not report a double-blind treatment start/stop date, will have missing exposure.
- Duration of post-treatment time (days) spent in the study will be calculated as:
  - Study Conclusion Date – Double-Blind Treatment Stop Date
- Duration of total time (days) spent in the study since first dose will be calculated as:
  - Study Conclusion Date – Double-Blind Treatment Start Date + 1
- Double-blind treatment start and stop dates used will be the earliest (start) and latest (stop) of all dates recorded for the participant. Study conclusion is defined as completion or withdrawal, as applicable.

Concomitant Medications

- Concomitant medications will be coded using the GSK Drug coding dictionary. Summaries of the number and percentage of participants taking concomitant medications will be displayed by ingredient without regard to Anatomical Therapeutical Chemical (ATC) classifications. These summaries will include single-ingredient medications and will present multi-ingredient medications according to the combination of the component ingredients. Summaries will be split into asthma and non-asthma concomitant medications, as well as into those taken pre-, on-, and post-treatment (as described in Section 11.4.1).

Screening Failures, Run-in Failures, Treatment Discontinuation, and Study Withdrawal

- A participant who completes the screening visit and is dispensed single-blind study medication and electronic/paper diaries is considered to have entered the run-in period. Participants who enter the run-in period but are not randomised are considered run-in failures.
- Participants who complete the run-in period but fail to meet all randomisation criteria are also considered to be run-in failures.
- Participants who discontinue study treatment will not be automatically 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 participant stopping study medication (or in the event a participant discontinues study treatment at or during a scheduled visit, all study procedures scheduled at an Early Treatment Discontinuation visit will be performed at this visit instead). These participants will not be allowed to restart study treatment; however, participants will be asked to continue to follow the regular visit schedule.
- A participant will be considered discontinued from study treatment (i.e. double-blind treatment) if the participant was randomised, and has completed all visits including the follow-up visits, but prematurely discontinued from double-blind treatment during the treatment period.
- The date of study treatment discontinuation refers to the date that a participant's study medication is intentionally and permanently stopped (as recorded in the eCRF).

Time to Study Withdrawal / Treatment Discontinuation

For Kaplan-Meier plots of study withdrawal over time and premature discontinuation from double-blind treatment over time, censoring will be performed as follows:

- For study withdrawal, participants are represented from the date of start of double-blind treatment to the date of early withdrawal from the study (or date of death). Participants that completed the study are censored at the earliest of the date of completion or Day 423.
- For premature discontinuation from study treatment, participants are represented from the date of start of double-blind treatment to the date of discontinuation from double-blind treatment (or date of death). Participants that complete study randomised treatment are censored at the earliest of their double-blind treatment stop date or Day 367.

11.6.3. Growth Data

Triplicate stadiometric height measurements, as well as the average of each set of triplicate measurements, will be collected at each planned visit according to the Protocol Defined Schedule of Events (see Section 11.2.1). The average will serve as the participant's height at that clinic visit.

Growth Data
Growth Velocity Calculation
• Growth velocity will be calculated for each participant over each study period (i.e., baseline, double-blind treatment, and follow-up) by fitting a regression line to the height measurements recorded for that participant during the period. The slope of this regression line will be the participant's growth velocity for that study period. • Stadiometric height measurements obtained at Visits 1, 3, and 5 will be used to determine the baseline period growth velocity, which will be calculated based on data from at least two of these visits. • Stadiometric height measurements obtained at Baseline (Visit 5) and during the double-blind treatment period (Visit 6 up to and including Visit 18) will be used to determine the double-blind treatment period growth velocity. Separate estimands for growth velocity during the double-blind treatment period will be considered in the Growth and ITT populations (as defined in Section 7.1: Primary Growth Analyses). • Stadiometric height measurements obtained at Visits 18 and during the follow-up period will be used to determine the follow-up period growth velocity. • Stadiometry measurements obtained during the Early Withdrawal/Early Treatment Discontinuation Visit will be included in the calculation of the growth velocity over the double-blind treatment period.
Growth Velocity Below the 3rd Percentile
• Using Table VIIA and Table VIIB in *Standards from Birth to Maturity for Height, Weight, Height Velocity, and Weight Velocity: British Children, 1965 Part II* (Tanner, 1966) data values for the 3rd percentile for growth velocity will be input into an Excel spreadsheet and then imported into the SAS programming environment. • Each participant's double-blind treatment period growth velocity, calculated based on all on- and off-treatment height data, will be programmatically compared to these imported data using the 3rd percentile value of the age closest to the participant's age at the end of the endpoint (i.e., either the end of the participant's double-blind treatment period [Visit 18] or withdrawal from study [Early Withdrawal Visit]).
Change from Baseline in Growth Velocity Quartiles
• Growth velocity quartile (defined as 1Q = 1st – 25th percentile, 2Q = 26th – 50th percentile, 3Q = 51st – 75th percentile, 4Q = 76th – 100th percentile) will be determined for each participant at both baseline and endpoint. • Baseline growth velocity will be calculated as the slope from a simple linear regression of the average stadiometric height measurements recorded at Visits 1, 3, and 5. • Endpoint growth velocity will be defined as the slope of a simple linear regression of the average stadiometric height measurements recorded at Visit 12 up to and including Visit 18 and will include both on- and off-treatment measurements. • Using Table I in Special Article: *Clinical longitudinal standards for height and height velocity for North American children (Tanner, 1985)* and Table VIIA and Table VIIB in *Standards from Birth to Maturity for Height, Weight, Height Velocity, and Weight Velocity: British Children, 1965 Part II (Tanner, 1966*), data values for the 25th, 50th, and 75th growth velocity percentiles will be input into an Excel spreadsheet and then imported into the SAS programming environment.

- Each participant's baseline period growth velocity will be programmatically compared to these imported data using the participant's estimated age at Visit 5 and age in the imported data that is closest to the actual age of the participant to determine the participant's baseline growth velocity quartile.
- Each participant's endpoint growth velocity will be programmatically compared to the imported data using the participant's age at endpoint (age at the last Visit included in the endpoint) and age in the imported data that is closest to the actual age of the participant to determine the participant's endpoint growth velocity quartile.
- Shifts from baseline will be determined as follows:

Analysis category	**Change from baseline**
Increase	1Q to 2Q, 3Q or 4Q; 2Q to 3Q or 4Q; 3Q to 4Q
Decrease	4Q to 3Q, 2Q or 1Q; 3Q to 2Q or 1Q; 2Q to 1Q
No change	Same quartile at both baseline and endpoint

- Shifts from quartile to quartile, both increases and decreases, will be summarized by treatment group in terms of frequency and percentage of the treatment group.

Questionable Height Measurements

- Questionable height measurements will be defined as either of the following:
    1. Any measurement obtained at a visit that is at least 0.05 cm less than the smallest measurement obtained at the previous visit; or
    2. Any measurement obtained at a visit that is at least 0.20 cm larger than the largest measurement obtained at the previous visit with the following caveat: if a subsequent visit was conducted and the mean of that visit is ≥ the mean of the visit in question, then the measurement is acceptable; if a subsequent visit was not conducted then the measurement will be considered questionable. A hypothetical example appears below:

Visit	**Height Measurement 1**	**Height Measurement 2**	**Height Measurement 3**
6	100.0 cm	100.0 cm	101.0 cm
7	160.0 cm	101.0 cm	102.0 cm
8	101.0 cm	101.0 cm	101.0 cm

According to the rules outlined above, measurement 1 at Visit 7 (160.0 cm) would be flagged as questionable, as it is more than 0.20 cm larger than the largest measurement recorded at Visit 6 (101.0 cm). Additionally, because the mean of the subsequent Visit 8 measurements, 101.0 cm, is not greater than the mean of the Visit 7 measurements (121.0 cm) the measurement of 160.0 cm is still flagged as questionable.

Height Standard Deviation Scores (SDS)
• Each participant's standard deviation score for each of the three required stadiometric height measurements is calculated as: [observed height measurement – standard median height for age at Visit 1] / [(standard 95th height percentile for age at the visit – standard 5th height percentile for age at the visit) /(2 x 1.645)]. • The standard median, 95th percentile, and 5th percentile values will be obtained from standard tables available on the website of the Centers for Disease Control and Prevention (CDC) [Guidance for Industry Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children, 2007]. • The standard deviation scores for each height stadiometric measurement at each visit will be calculated using the CDC percentiles and will then be averaged for each participant before being summarized by treatment group.

11.6.4. Safety

Adverse Events
General
Adverse events will be coded using the current MedDRA coding dictionary at the time of reporting providing a Preferred Term (PT) and a System Organ Class (SOC) for analysis and reporting.
AEs of Special Interest
• The AEs of special interest are defined as AEs which have specified areas of interest for FF. • The adverse events of special interest groups, their subgroups and the PTs which will be counted towards each of them (groups and subgroups) will be based on the current version of MedDRA at the time of reporting and will be finalized prior to unblinding the study. • These AEs of special interest terms will be agreed prior to unblinding of the study and provided in a reference dataset for use in the specific summary tables. All special interest terms from the reference datasets will be listed.
Risks Plot
• Relative risks and corresponding 95% CIs will be calculated as follows (Altman, 2005): • Relative risk = (A/(A+C))/(B/(B+D)) where A = number of participants with event of interest in the FF treatment group B = number of participants with event of interest in the placebo treatment group C = number of participants without event of interest in the FF treatment group D = number of participants without event of interest in the placebo treatment group. • Standard Error(log relative risk) (SElogR) =square root of ((1/A)-(1/(A+C))+(1/B)-(1/(B+D))) • 95% CI lower limit = exponential of (log(relative risk) - (probit(0.975)*SElogR)) • 95% CI upper limit = exponential of (log(relative risk) + (probit(0.975)*SElogR)) • Relative risks and 95% CIs will not be calculated if either or both treatment groups have no events of interest.

11.6.5. Efficacy

eDiary
Rescue-Free 24-Hour Periods
• Rescue medication use over the previous 24 hours is recorded in the eDiary each morning. Therefore, rescue medication use recorded on study day *n* refers to actual use on study day *(n – 1)*. • A given 24-hour period will only be set to "rescue free" if responses to the daily assessment of rescue medication use is 0. Any >0 values will require that the 24-hour period be marked as not rescue-free. • If the assessment of rescue medication use in a given 24-hour period is missing, then the "rescue-free" indicator will also be set to missing. • Percentages of rescue-free 24-hour periods are calculated as the number of 24-hour periods on which a participant recorded no use of albuterol/salbutamol divided by the length of the time period being assessed (with non-missing values of rescue medication recorded) x 100. • See Section 11.7.2 for determination of rescue-free 24-hour periods and handling of missing data.
Symptom-Free 24-Hour Periods
• Daytime symptoms, reflective of the participant's state during the previous day, are collected in the morning. Similarly, overnight symptoms are recorded the following morning. Therefore, daytime and nighttime symptoms recorded on study day *n* refer to the participant's symptoms on study day *(n – 1)*. • A given 24-hour period will only be set to "symptom free" for a given 24-hour period if responses to both the morning and evening asthma symptom scores are 0. Any >0 values in either the morning or evening assessment will require that the 24-hour period be marked as not symptom-free. • If either the morning or evening assessment asthma symptom score in a given 24-hour period is missing, then the "symptom-free" indicator will also be set to missing. • Percentages of symptom-free 24-hour periods are calculated as the number of 24-hour periods on which a participant recorded no symptoms divided by the length of the time period being assessed (with non-missing values of symptoms recorded) x 100. • See Section 11.7.2 for determination of symptom-free 24-hour periods and handling of missing data.
Peak Expiratory Flow (PEF)
Peak expiratory flow (PEF) is recorded in the morning, thus a PEF measurement recorded on study day *n* is associated with study day *n*.

11.7. Appendix 7: Reporting Standards for Missing Data

11.7.1. Premature Withdrawals

Element	Reporting Detail
General	• A completed participant is one who has completed all phases of the study (as specified in the protocol) including the follow-up visits. • Participants who withdrew prematurely either from study treatment or from the study itself will not be replaced. • All available data from participants who were withdrawn from study treatment (i.e., double-blind treatment) or from the study will be listed and where possible any available data from withdrawn participants will be included in summaries or analyses, unless otherwise specified.

11.7.2. Handling of Missing Data

Element	Reporting Detail
General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument: ○ These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table. ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.
Growth Analyses	Missing height data for the primary and supportive analyses of growth velocity described in Section 7: Growth Analyses, will not be imputed and will be treated as missing (assuming MAR). For the supportive analysis defined in Section 7.1.6, two approaches have been defined to assess the effect of missing data. For these analyses, the population of interest will be the Intent-to-Treat (ITT) population, as defined in Section 4: Analysis Populations. The final Week 52 (Visit 18) height measurement is scheduled for day 365 with a visit window of -5/+2 days. In cases where the final height measurement at week 52 is missing, (i.e. there is not a scheduled or unscheduled height measurement available for any of days 360 to 367 inclusive) the missing height measurement will be imputed at day 365 using Multiple Imputation based on two different approaches: **Approach 1:** Use the 'worst growth rate' (i.e., smallest growth velocity) from participants from the FF 50 treatment group who complete the double-blind treatment period as the central value for imputations of missing data in the FF treatment group, and the 'worst growth rate' from participants from the placebo group who complete the double-blind treatment period as the central value for imputations of missing data in the placebo treatment group (Supportive Estimand IX). **Implementation of Approach 1:** The steps are the same in both treatment arms, so the method for one arm will be described below: Let y_{it} be the value of the height measurement of participant i at day $t = 0, \ldots, 365$. Assume there are n participants in this treatment arm and of those: n_{obs} have a week

Element	Reporting Detail
	52 height observed (i.e. at least one height measurement observed between days 360 and 367 inclusive, $y_{i,365}$) and n_{miss} have it missing. The steps to follow will be: **A.** For every participant $i = 1, \dots, n_{obs}$ with observed week 52 height value (i.e.,$y_{i,365}$), fit a regression model $y_{it} = \alpha_i + \beta_i t$, using all available height data. The estimated value $\hat{\beta}_i$ (i.e., slope) is the growth rate of that participant i and is the outcome that will be included in the planned statistical analysis. Let $\hat{\beta}_W$ be the worst estimated growth rate, i.e. $\hat{\beta}_W = \min\{\hat{\beta}_1, \dots, \hat{\beta}_{n_{obs}}\}$. **B.** Let M be the number of imputations. For each imputation $m = 1, .., M$: • **Step 1:** For every participant j= $1, \dots, n_{miss}$ with missing week 52 height, the missing week 52 height value $y_{j,365}^{(\mathrm{m})}$ will be imputed at day 365 by drawing a random value from a Normal distribution $N(\mu_{j,365}, \sigma^2)$, where: ○ $\mu_{j,365} = y_{\tilde{t}_j} + \hat{\beta}_W \cdot (365 - \tilde{t}_j)$, where $\tilde{t}_j$ is the last day with an observed height for participant j. Note that $\mu_{j,365}$ represents the expected height at day 365 assuming the participant would grow at the 'worst' observed growth rate between the last day their height was measured and day 365. ○ The variance σ^2 is the estimated variance of heights at day 365, which is estimated by fitting a regression model to all heights from all n_{obs} subjects and extract the residual variance as σ^2. Note that the imputed height value $y_{j,365}^{(\mathrm{m})}$ must be equal or larger than the last observed height value $y_{j\tilde{t}_j}$ which means that a value from a truncated Normal should be drawn. • **Step 2:** For every participant j= $1, \dots, n_{miss}$, fit a regression model $y_{jt} = \alpha_j + \beta_j t$ using all the observed and imputed height data $y_{j0}, \dots, y_{j\tilde{t}}, y_{j,365}^{(\mathrm{m})}$ of participant j to obtain the estimated value of the growth rate $\hat{\beta}_j^{(m)}$ for participant j. This value will be the 'imputed' growth rate for participant j in the m^{th} imputed dataset. After completing steps A and B, each imputed dataset $m = 1, \dots, M$ will have observed growth rates $\hat{\beta}_i, i = 1, \dots, n_{obs}$ and imputed growth rates $\hat{\beta}_j^{(m)}, j = 1, \dots, n_{miss}$. These $\hat{\beta}$'s will be the endpoint of growth velocity to be analysed. The same ANCOVA model as the one used for the primary analysis (Section 7.1.5) will be used. The M results (i.e., mean treatment difference in growth velocities between the two arms, and associated CI) will be combined using Rubin's rules as implemented in Proc MIANALYZE. **Approach 2:** Use the 'worst growth rate' (i.e. smallest treatment velocity) from participants from the FF 50 treatment group who complete the double-blind treatment period as the central value for imputations of missing data in the FF treatment group, and assume any data missing in the placebo treatment group are missing at random (Supportive Estimand X).

<table>
<tr><th>Element</th><th>Reporting Detail</th></tr>
<tr><td></td><td>Implementation of Approach 2: For the FF 50 arm proceed as in approach 1. For the placebo arm the process simplifies to fitting a regression model $y_{it} = \alpha_i + \beta_i t$ for each of the n participants in the arm using their available height data (i.e. no distinction between participants who have and do not have the week 52 height observed). The estimated value $\hat{\beta}_i$ is the growth rate of participant i and is the endpoint of growth velocity to be analysed. The same ANCOVA model as the one used for the primary analysis (Section 7.1.5) will be used. The M results (i.e., mean treatment difference in growth velocities between the two arms, and associated CI) will be combined using Rubin's rules as implemented in Proc MIANALYZE.</td></tr>
<tr><td>eDiary Data & 24-hour periods</td><td>• Efficacy endpoints relating to daily diary assessments will be calculated from all available data over the time period of interest. No imputations will be performed on missing daily diary data. The Table below shows how missing data will be considered with respect to symptom- and rescue-free 24-hour periods.
<table>
<tr><th colspan="2">Symptom Scores</th><th rowspan="2">24-hour Period</th></tr>
<tr><th>AM</th><th>PM</th></tr>
<tr><td>>0</td><td>0</td><td>Not symptom-free</td></tr>
<tr><td>0</td><td>>0</td><td>Not symptom-free</td></tr>
<tr><td>0</td><td>0</td><td>Symptom-free</td></tr>
<tr><td>0</td><td>Missing</td><td>Missing</td></tr>
<tr><td>Missing</td><td>0</td><td>Missing</td></tr>
<tr><td>>0</td><td>Missing</td><td>Not symptom-free</td></tr>
<tr><td>Missing</td><td>>0</td><td>Not symptom-free</td></tr>
<tr><td>Missing</td><td>Missing</td><td>Missing</td></tr>
<tr><td colspan="2">Rescue medication use (puffs)</td><td></td></tr>
<tr><td colspan="2">0</td><td>Rescue-free</td></tr>
<tr><td colspan="2">>0</td><td>Not rescue-free</td></tr>
<tr><td colspan="2">Missing</td><td>Missing</td></tr>
</table></td></tr>
</table>

11.7.2.1. Handling of Missing and Partial Dates

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays. • Where necessary, display macros may impute dates as temporary variables for sorting data in listings only. In addition, partial dates may be imputed for 'slotting' data to study phases (see Section 11.4.1) or for specific analysis purposes as outlined below. • Imputed partial dates will not be used to derive study day, time to onset or duration (e.g., time to onset or duration of adverse events), or elapsed time variables (e.g., time since diagnosis).

Element	Reporting Detail

Adverse Events and Asthma Exacerbations	• The eCRF does allows partial dates to be captured for asthma exacerbations. Partial dates for any asthma exacerbation recorded in the eCRF will be imputed using the following conventions:
	  ○ If the partial date is an onset date, 1 will be used for missing days and 'Jan' will be used for the month. However, if these substitutions result in an onset date prior to Day 1 and, based on available information, the event could possibly have occurred during treatment, then the Day 1 date will be assumed to be the onset date. The event will then be considered to have started on treatment.
	  ○ If the partial date is a resolution date, either 28, 29, 30, or 31 (depending on the month and year) will be used for missing days and 'Dec' will be used for missing months.
	• The eCRF does not allow for partial dates to be recorded for adverse events. Should any partial dates appear for adverse events the missing date part will be raised to data management. If the full date cannot be ascertained, imputation may be used only for sorting data in listings and "slotting" data to study phases.
	• Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time-to-onset and duration of such events will also be missing.

Concomitant Medications	• The eCRF allows partial dates to be captured for concomitant medications.
	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention:
	  ○ If the partial date is a start date, a 1 will be used for the day and 'Jan' will be used for the month.
	  ○ If the partial date is a stop date, either 28, 29, 30, or 31 (depending on the month and year) will be used for the missing days and 'Dec' will be used for the missing months.
	• The answers to the questions "Taken Prior to Study?" and "Ongoing?" which are recorded in the eCRF will also be taken into consideration to determine if the medication was started pre-treatment or continued post-treatment. In each case, should the answers suggest a different classification than the dates, the medication will be summarized in all possible classifications (pre-/during/post-treatment) in which it could conceivably have been taken.

11.8. Appendix 8: Abbreviations & Trade Marks

11.8.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AM	*Ante meridian* (morning)
ANCOVA	Analysis of Covariance
C-ACT	Childhood Asthma Control Test
CDC	Centers for Disease Control and Prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
cm	Centimeter
CSR	Clinical Study Report
eCRF	Electronic Case Report Form
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Flow in 1 second
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FF	Fluticasone Furoate
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IDSL	Integrated Data Standards Library
IP	Investigational Product
ITT	Intent-to-Treat
IVRS	Interactive Voice Recognition System
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Microgram
mg	Milligram
MI	Multiple Imputation
OD	Once Daily
PEF	Peak Expiratory Flow
PRN	*Pro re nata* (as needed)
QC	Quality Control
RAP	Reporting & Analysis Plan
SABA	Short-Acting β_2 Agonist
SAC	Statistical Analysis Complete
SD	Standard Deviation
SDS	Standard Deviation Score
SDTM	Study Data Tabulation Model
SOC	System Organ Class
US	United States
yr	Year

11.8.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
ELLIPTA

Trademarks not owned by the GlaxoSmithKline Group of Companies
EXCEL
SAS

11.9. Appendix 9: List of Data Displays

11.9.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Safety	2.1 to 2.n	2.1 to 2.n
Efficacy	3.1 to 3.n	n/a
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

11.9.2. Mock Example Shell Referencing

Nonstandard specifications will be referenced as indicated and if required example mock-up displays provided in

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Efficacy	n/a	EFF_Tn	n/a
Safety	SAF_Fn	SAF_Tn	SAF_Ln

NOTES:

- Non-Standard displays are indicated in the 'GSK Statistical Display Standard / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

11.9.3. Deliverables

Delivery	Description
HL	Headline results
SAC	Final Statistical Analysis Complete

NOTE: Headline results will be specified by the study team at an appropriate time prior to database lock and will be documented in the Study Dissemination Plan.

11.9.4. Study Population Tables

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Total	SP1	Summary of Study Populations	Only treatment arms and Total column to be presented.	SAC
1.2.	Total	ES6	Summary of Screening Status and Reasons for Screen Failure		SAC
1.3.	Total	IE1	Summary of Inclusion/Exclusion Criteria Deviations for Screen Failures		SAC
1.4.	Total	ES6	Summary of Randomisation Status and Reasons for Run-In Failure	This should present both randomised subjects and subjects classified as run-in failures.	SAC
1.5.	Total	IE1	Summary of Inclusion/Exclusion Criteria Deviations for Run-in Failures	This will include all run-in failures, including randomisation failures	SAC
1.6.	Total	NS1	Summary of Number of Subjects Enrolled by Country and Site ID -Total Population	EudraCT/Clinical Operations	SAC
1.7.	ITT	NS1	Summary of Number of Subjects Enrolled by Country and Site ID – Intent-to-Treat	EudraCT/Clinical Operations	SAC
1.8.	Total	Non-Standard POP_T1	Summary of Subjects Screened by Age		SAC
1.9.	ITT	ES1	Summary of Subject Status and Reason for Study Withdrawal	ICH E3, FDAAA, EudraCT	SAC

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.10.	ITT	SD1	Summary of Study Treatment Status and Reason for Discontinuation of Study Treatment	ICH E3	SAC
1.11.	ITT	SD1	Summary of Treatment Status and Reasons for Discontinuation of Study Treatment by Relationship to COVID-19 Pandemic	Repeat of the existing table (that is based on SD1) but summarized by both “Related to COVID-19” and “Not-related to COVID-19”	SAC
1.12.	ITT	ES1	Summary of Subject Status and Study Disposition by Relationship to COVID-19 Pandemic	Repeat of the existing table (that is based on ES1) but summarized by both “Related to COVID-19” and “Not-related to COVID-19”	SAC
1.13.	ITT	Non-Standard POP_T2	Summary of Attendance at Each Visit		SAC
Protocol Deviation					
1.14.	ITT	Non-Standard POP_T3	Summary of Inclusion/Exclusion and Randomisation Criteria Deviations		SAC
1.15.	ITT	DV1	Summary of Important Protocol Deviations		SAC
1.16.	ITT	DV1	Summary of Important Protocol Deviations by Relationship to COVID-19 Pandemic	Repeat of the existing table (that is based on DV1) but summarized by both “Important Related to COVID-19” and “Important Not-related to COVID-19”	SAC
Demographic and Baseline Characteristics					
1.17.	ITT	DM1	Summary of Demographic Characteristics – Intent-to-Treat	ICH E3, FDAAA, EudraCT	SAC
1.18.	Growth	DM1	Summary of Demographic Characteristics – Growth Population	ICH E3, FDAAA, EudraCT	SAC

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.19.	Total	DM11	Summary of Age Ranges	EudraCT	SAC
1.20.	ITT	DM5	Summary of Race and Racial Combinations	ICH E3, FDA, FDAAA, EudraCT	SAC
1.21.	ITT	DM6	Summary of Race and Racial Combination Details		SAC
1.22.	ITT	Non-Standard POP_T5	Summary of Asthma History		SAC
1.23.	ITT	Non-Standard POP_T6	Summary of Lung Function at Screening		SAC
1.24.	ITT	MH4	Summary of Current Medical Conditions	ICH E3	SAC
1.25.	ITT	MH4	Summary of Past Medical Conditions	ICH E3	SAC
Prior and Concomitant Medications					
1.26.	ITT	CM8	Summary of Pre-Treatment Concomitant Asthma Medications		SAC
1.27.	ITT	CM8	Summary of On-Treatment Concomitant Asthma Medications		SAC
1.28.	ITT	CM8	Summary of Post-Treatment Concomitant Asthma Medications		SAC
1.29.	ITT	CM8	Summary of Pre-Treatment Concomitant Non-Asthma Medications		SAC
1.30.	ITT	CM8	Summary of On-Treatment Concomitant Non-Asthma Medications		SAC
1.31.	ITT	CM8	Summary of Post-Treatment Concomitant Non-Asthma Medications		SAC

Study Population Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Exposure and Treatment Compliance					
1.32.	ITT	Non-Standard POP_T7	Summary of Exposure to Study Treatment and Study Duration		SAC
1.33.	ITT	Non-Standard POP_T8	Summary of Treatment Compliance based on eDiary	Run-in and double-blind treatment periods; include montelukast and single-blind/double-blind treatment; include frequencies of over- (>120%), under- (<80%), and missing compliance.	SAC
1.34.	ITT	Non-Standard POP_T8	Summary of Treatment Compliance based on Dose Counter	Run-in and double-blind treatment periods; include frequencies of over- (>120%), under- (<80%), and missing compliance.	SAC
Intercurrent Events					
1.35.	ITT	Non-Standard POP_T9	Summary of Intercurrent Events – Intent-to-Treat		SAC
1.36.	Growth	Non-Standard POP_T9	Summary of Intercurrent Events – Growth Population		SAC

11.9.5. Study Population Figures

Study Population Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	ITT	Non-Standard POP_F1	Kaplan-Meier Plot of Time to Premature Discontinuation of Study Treatment		SAC
1.2.	ITT	Non-Standard POP_F2	Kaplan-Meier Plot of Time to Study Withdrawal		SAC

11.9.6. Safety Tables

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
General – Growth Analyses					
2.1.	Growth	Non-Standard POP_T4	Summary of Height Assessed by Stadiometry at Each Visit		SAC
Primary Growth Analyses					
2.2.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Using On- and Off-Treatment Height Data	Including Summary of Change from Baseline.	SAC
2.3.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Using On- and Off-Treatment Height Data (Primary Estimand)	See Section 7 for handling of intercurrent events in the analysis.	SAC
Supportive Growth Analyses					
2.4.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Using On-Treatment Height Data	Including Summary of Change from Baseline.	SAC
2.5.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Using On-Treatment Height Data (Supportive Estimand I)	See Section 7 for handling of intercurrent events in the analysis.	SAC
2.6.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Excluding Subjects with Tanner Stage ≥ 2	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC
2.7.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Excluding Subjects with Tanner Stage ≥ 2 (Supportive Estimand II)	Using all available on-treatment height data. See Section 7 for handling of intercurrent events in the analysis.	SAC

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.8.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Excluding Questionable Height Measurements	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC
2.9.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Excluding Questionable Height Measurements (Supportive Estimand III)	Using all available on-treatment height data. See Section 7 for handling of intercurrent events in the analysis.	SAC
2.10.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Excluding Height Measurements Taken after Receiving Rescue Systemic Corticosteroids	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC
2.11.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Excluding Height Measurements Taken after Receiving Rescue Systemic Corticosteroids (Supportive Estimand IV)	Using all available on-treatment height data. See Section 7 for handling of intercurrent events in the analysis.	SAC
2.12.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Excluding Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC
2.13.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Excluding Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids (Supportive Estimand V)	Using all available on-treatment height data. See Section 7 for handling of intercurrent events in the analysis.	SAC
2.14.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Excluding Subjects with Tanner Stage ≥ 2 and/or Questionable Height Measurements and/or Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.15.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Excluding Subjects with Tanner Stage ≥ 2 and/or Questionable Height Measurements and/or Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids (Supportive Estimand VI)	Using all available on-treatment height data. See Section 7 for handling of intercurrent events in the analysis.	SAC
2.16.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) in Completers of One Year of Double-Blind Study Treatment	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC
2.17.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) in Completers of One Year of Double-Blind Study Treatment (Supportive Estimand VII)	Using all available on-treatment height data. See Section 7 for handling of intercurrent events in the analysis.	SAC
2.18.	ITT	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Using On- and Off-Treatment Height Data	Including Summary of Change from Baseline.	SAC
2.19.	ITT	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/year) Using On- and Off-Treatment Height Data (Supportive Estimand VIII)	See Section 7 for handling of intercurrent events in the analysis.	SAC
2.20.	ITT	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Using On- and Off-Treatment Height Data – Imputation of Missing Week 52 Height Measurements - Approach I	Including Summary of Change from Baseline.	SAC
2.21.	ITT	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Using On- and Off-Treatment Height Data – Imputation of Missing Week 52 Height Measurements - Approach I (Supportive Estimand IX)	See Section 7 for handling of intercurrent events in the analysis.	SAC
2.22.	ITT	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Using On- and Off-Treatment Height Data – Imputation of Missing Week 52 Height Measurements - Approach II	Including Summary of Change from Baseline.	SAC

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.23.	ITT	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/year) Using On- and Off-Treatment Height Data – Imputation of Missing Week 52 Height Measurements - Approach II (Supportive Estimand X)	See Section 7 for handling of intercurrent events in the analysis.	SAC
2.24.	ITT	Non-Standard GRO_T3	Summary of Missing Stadiometric Height Measurements by Visit – Intent-to-Treat	Base on POP_T4.	SAC
2.25.	Growth	Non-Standard GRO_T3	Summary of Missing Stadiometric Height Measurements by Visit – Growth Population	Base on POP_T4.	SAC
Secondary Growth Analyses					
2.26.	Growth	Non-Standard GRO_T4	Summary of the Proportion of Subjects Below the 3rd Percentile of Growth Velocity During the Double-Blind Treatment Period	Using all available on- and off-treatment height data; *cf* FFR101782 Table 6.11.	SAC
2.27.	Growth	Non-Standard GRO_T5	Summary of Shifts from Baseline to Endpoint in Growth Velocity Quartile	Using all available on-and-off-treatment height data.	SAC
2.28.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) Over the First 12 Weeks of the Double-Blind Treatment Period	Using all available on-treatment height data and including Summary of Change from Baseline.	SAC
2.29.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) Over the First 12 Weeks of the Double-Blind Treatment Period	Using all available on- treatment height data.	SAC
2.30.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) by Region	Using all available on- and off-treatment height data. (US and non-US sites)	SAC
2.31.	Growth	Non-Standard GRO_T2	Analysis of Growth Velocity (cm/yr) by Region	Using all available on- and off-treatment height data. (US and non-US sites)	SAC

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.32.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) by Gender	Using all available on- and off-treatment height data and including Summary of Change from Baseline.	SAC
2.33.	Growth	Non-Standard GRO_T1	Summary of Growth Velocity (cm/yr) by Ethnicity	Using all available on- and off-treatment height data and including Summary of Change from Baseline.	SAC
2.34.	Growth	Non-Standard GRO_T6	Summary of Height Standard Deviation Scores	Using all available on- and off-treatment height data.	SAC
2.35.	Growth	Non-Standard GRO_T7	Summary of Change in Height Standard Deviation Scores from Baseline to Endpoint	Similar to summary of C-ACT scores.	SAC
2.36.	Growth	Non-Standard GRO_T8	Analysis of Growth Velocity (cm/yr) using Random Coefficients	Using all available on- and off-treatment height data.	SAC
Adverse Events (AEs)					
2.37.	ITT	AE13	Adverse Events Overview	By epoch: pre-treatment, on-treatment, and post-treatment.	SAC
2.38.	ITT	AE1	Summary of Pre-Treatment Adverse Events		SAC
2.39.	ITT	AE1	Summary of On-Treatment Adverse Events		SAC
2.40.	ITT	PAN10	Summary of On-Treatment Adverse Events Over the Time Course of the Trial (Pre, During, and Post Pandemic)	Use IDSL PAN10 shell	SAC
2.41.	ITT	AE1	Summary of Post-Treatment Adverse Events		SAC

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.42.	ITT	AE1	Summary of Drug-Related Adverse Events		SAC
2.43.	ITT	AE1	Summary of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
2.44.	ITT	AE3	Summary of Common (>=3%) On-Treatment Adverse Events by Overall Frequency		SAC
2.45.	ITT	AE15	Summary of Common (>=3%) On-Treatment Non-serious Adverse Events (Number of Subjects and Occurrences)	FDAAA, EudraCT	SAC
2.46.	ITT	AE3	Summary of Non-Serious Drug-Related Adverse Events by Overall Frequency	Plain Language Summary requirements.	SAC
Serious and Other Significant Adverse Events					
2.47.	ITT	AE1	Summary of Pre-Treatment Serious Adverse Events		SAC
2.48.	ITT	AE1	Summary of On-Treatment Serious Adverse Events		SAC
2.49.	ITT	AE1	Summary of Post-Treatment Serious Adverse Events		SAC
2.50.	ITT	AE1	Summary of Drug-Related Serious Adverse Events		SAC
2.51.	ITT	AE16	Summary of Serious Adverse Events (Number of Subjects and Occurrences)	FDAAA, EudraCT By epoch: pre-treatment, on-treatment, and post-treatment.	SAC

Safety Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.52.	ITT	Non-Standard SAF_T1	Summary of On-Treatment and Post-Treatment Adverse Events of Special Interest	AEs of special interest. Reference HZA107116 shell.	SAC
2.53.	ITT	Non-Standard SAF_T1	Summary of On-Treatment and Post-Treatment Serious Adverse Events of Special Interest	SAEs of special interest.	SAC
2.54.	Total	AE2	Relationship of AE System Organ Class, Preferred Term and Verbatim Text		SAC
2.55.	Total	Non-Standard SAF_T2	Record of All Preferred Terms That Could Have Mapped to Special Interest Terms	Reference HZA107116 shell	SAC
Asthma exacerbations					
2.56.	ITT	Non-Standard SAF_T3	Summary of Asthma Exacerbations Over the Double-Blind Treatment Period Using On- and Post-Treatment Data	On treatment and post-treatment in separate summaries. Reference HZA107116 shell	SAC
Pneumonia					
2.57.	ITT	Non-Standard SAF_T4	Summary of Pneumonia	By epoch: on-treatment, post-treatment. Include all reported terms that share preferred term of "pneumonia." Reference HZA107116 shell	SAC

11.9.7. Safety Figures

Safety: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.1.	Growth	Non-Standard GRO_F1	Height Standard Deviation Scores	Boxplot of Standard Deviation Scores using all available on- and off- treatment height data.	SAC
2.2.	Growth	Non-Standard GRO_F2	Growth Velocity (cm/yr) Over the Double-Blind Treatment Period	Histograms by treatment.	SAC
2.3.	Growth	Non-Standard GRO_F3	Distribution of Double-Blind Treatment vs Baseline Growth Velocity Using On- and Off-Treatment Height Measurements – Growth Population	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using all available on- and off-treatment data.	SAC
2.4.	ITT	Non-Standard GRO_F3	Distribution of Double-Blind Treatment vs Baseline Growth Velocity Using On- and Off-Treatment Height Measurements – Intent-to-Treat	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using all available on- and off-treatment data.	SAC
2.5.	Growth	Non-Standard GRO_F3	Distribution of Double-Blind Treatment vs Baseline Growth Velocity Using On-Treatment Height Measurements – Growth Population	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using only available on-treatment data.	SAC

Safety: Figures					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.6.	Growth	Non-Standard GRO_F3	Distribution of Double-Blind Treatment vs Baseline Growth Velocity Excluding Subjects with Tanner Stage ≥ 2	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using only available on-treatment data.	SAC
2.7.	Growth	Non-Standard GRO_F3	Distribution of Double Blind Treatment vs Baseline Growth Velocity Excluding Questionable Height Measurements	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using only available on-treatment data.	SAC
2.8.	Growth	Non-Standard GRO_F3	Distribution of Double Blind Treatment vs Baseline Growth Velocity Excluding Height Measurements Taken after Receiving Rescue Systemic Corticosteroids	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using only available on-treatment data.	SAC
2.9.	Growth	Non-Standard GRO_F3	Distribution of Double Blind Treatment vs Baseline Growth Velocity Excluding Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using only available on-treatment data.	SAC
2.10.	Growth	Non-Standard GRO_F3	Distribution of Double Blind Treatment vs Baseline Growth Velocity Excluding Subjects with Tanner Stage ≥ 2 and/or Questionable Height Measurements and/or Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids	Scatter plot of baseline growth velocity vs growth velocity during double-blind treatment period using only available on-treatment data.	SAC
Adverse Events (AEs)					
2.11.	ITT	Non-Standard SAF_F1	Summary of Risks for FF vs. Placebo	See Section 11.6.4 for details.	SAC

11.9.8. Efficacy Tables

Efficacy: Tables					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
eDiary Measures					
3.1.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in Percentage of Rescue-Free 24-Hour Periods Over the Double-Blind Treatment Period	Change from baseline is based on entire double-blind treatment period. Double-blind treatment period is defined from Visit 5 up to the last available visit (i.e., Visit 18/EW/TD visit).	SAC
3.2.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in Percentage of Symptom-Free 24-Hour Periods Over the Double-Blind Treatment Period	Change from baseline is based on entire double-blind treatment period. Double-blind treatment period is defined from Visit 5 up to the last available visit (i.e., Visit 18/EW/TD visit).	SAC
3.3.	ITT	Non-Standard EFF_T1	Summary of Change from Baseline in Morning Peak Expiratory Flow (L/min) Over the Double-Blind Treatment Period	Change from baseline is based on entire double-blind treatment period. Double-blind treatment period is defined from Visit 5 up to the last available visit (i.e., Visit 18/EW/TD visit).	SAC
Childhood Asthma Control Test					
3.4.	ITT	Non-Standard EFF_T2	Summary of Change from Baseline in Childhood Asthma Control Test (C-ACT) Scores at the End of the Double-Blind Treatment Period	Change from baseline is based on Visit 18 (Week 52).	SAC

11.9.9. ICH Listings

ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Total	ES7	Listing of Reasons for Screen or Run-in Failure		SAC
2.	ITT	SD2	Listing of Reasons for Study Treatment Discontinuation		SAC
3.	ITT	ES2	Listing of Reasons for Study Withdrawal		SAC
4.	ITT	BL1	Listing of Subjects for Whom the Treatment Blind was Broken		SAC
5.	ITT	TA1	Listing of Randomised and Actual Treatments		SAC
Protocol Deviations					
6.	ITT	DV2	Listing of Important Protocol Deviations		SAC
7.	Total	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations for Screen Failures and Run-in Failures	Include a flag for subjects with a screen/run-in failure.	SAC
8.	ITT	IE3	Listing of Subjects with Inclusion/Exclusion or Randomisation Criteria Deviations		SAC
9.	ITT	DV2	Listing of All Non-Important COVID-19 Related Protocol Deviations	Repeat of the existing listing (that is based on DV2) but for non-important COVID-19 related deviations.	SAC
Demographic and Baseline Characteristics					
10.	ITT	DM2	Listing of Demographic Characteristics		SAC

ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
11.	ITT	DM9	Listing of Race		SAC
Prior and Concomitant Medications					
12.	ITT	CM3	Listing of Concomitant Medications	ICH E3 1. Present by randomised treatment. 2. Include column "Study Periods Taken in" listing the study periods (i.e., Pre-treatment, On-treatment, Post-treatment) in which the medication was taken.	SAC
Exposure and Treatment Compliance					
13.	ITT	Non-Standard POP_L1	Listing of Exposure and Compliance Data	Reference HZA107116 shell	SAC
Adverse Events					
14.	ITT	AE8	Listing of All Adverse Events	1. Present by randomised treatment. 2. Include column "Study Phase at AE Onset", listing the study phase (i.e., Pre-treatment, On-treatment, Post-treatment) in which the AE onset date was recorded.	SAC
15.	Not in ITT	AE8	Listing of Adverse Events for Subjects Not in the Intent-to-Treat Population		SAC
16.	ITT	AE7	Listing of Subject Numbers for Individual Adverse Events	ICH E3	SAC

ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
17.	ITT	PAN12	Listing of COVID-19 Assessments and Symptom Assessments for Subjects with COVID-19 Adverse Events	Use IDSL PAN12 shell	SAC
Serious and Other Significant Adverse Events					
18.	ITT	AE8	Listing of Fatal Serious Adverse Events	1. Present by randomised treatment. 2. Include column "Study Phase at AE Onset", listing the study phase (i.e., Pre-treatment, On-treatment, Post-treatment) the in which the AE onset date was recorded.	SAC
19.	ITT	AE8	Listing of Non-Fatal Serious Adverse Events	1. Present by randomised treatment. 2. Include column "Study Phase at AE Onset", listing the study phase (i.e., Pre-treatment, On-treatment, Post-treatment) the in which the AE onset date was recorded.	SAC
20.	ITT	AE8	Listing of Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study		SAC
21.	ITT	AE14	Listing of Reasons for Considering as a Serious Adverse Event		SAC
Pneumonia					
22.	ITT	Non-Standard SAF_L2	Listing of Pneumonia Data	ICH E3	SAC

11.9.10. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Study Population					
23.	ITT	Non-Standard POP_L2	Listing of Study Treatment Misallocations		SAC
24.	ITT	Non-Standard POP_L3	Listing of Height Assessed by Stadiometry	Include all visits, including early withdrawal from study and treatment discontinuation visits.	SAC
25.	ITT	Non-Standard POP_L4	Listing of Asthma History at Screening		SAC
26.	ITT	MH2	Listing of Medical Conditions	Includes both current and past medical conditions.	SAC
27.	Growth	Non-Standard POP_L5	Listing of Subjects Presenting Tanner Stage 2 or Higher		SAC
28.	ITT	CM6	Relationship between ATC Level 1, Ingredient and Verbatim Text for Non-Respiratory Medications		SAC

Non-ICH: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Safety (Growth)					
29.	Growth	GRO_L1	Listing of Growth Velocity (cm/yr)	Include flags for: o Subjects presenting Tanner Stage ≥ 2 o Subjects with Questionable Height Measurements o Subjects with height measurements taken after receiving rescue systemic corticosteroids Subjects with height measurements taken after receiving rescue inhaled and/or intranasal On-treatment and on- and off-treatment growth velocity will be displayed separately.	SAC
30.	Growth	Non-Standard GRO_L1	Listing of Subjects Below the 3rd Percentile of Growth Velocity During the Double-Blind Treatment Period	Using all the available on-and-off-treatment height data.	SAC
31.	Growth	Non-Standard GRO_L1	Listing of Subjects with Decrease from Baseline to Endpoint in Growth Velocity Quartile	Using all the available on-and-off-treatment height data.	SAC
Safety (AEs)					
32.	ITT	Non-Standard SAF_L1	Listing of Asthma Exacerbations		SAC
33.	ITT	SAF_L3	Listing of Study Treatment Inhaler Malfunctions	If any events reported.	SAC

11.9.11. Patient Profiles Listings

Patient Profile: Listings					
No.	**Population**	**GSK Standard / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
34.	ITT	ARR1	Listing of Arrhythmias	If any events reported.	SAC
35.	ITT	CHF1	Listing of Congestive Heart Failure	If any events reported.	SAC
36.	ITT	CVATIA1	Listing of Cerebrovascular Events/ Stroke/ Transient Ischemic Attack	If any events reported.	SAC
37.	ITT	DVT1	Listing of Deep Vein Thrombosis / Pulmonary Embolism	If any events reported.	SAC
38.	ITT	MI1	Listing of Myocardial Infarction / Unstable Angina	If any events reported.	SAC
39.	ITT	PATE1	Listing of Peripheral Arterial Thromboembolism	If any events reported.	SAC
40.	ITT	PUL1	Listing of Pulmonary Hypertension	If any events reported.	SAC
41.	ITT	REV1	Listing of Revascularization	If any events reported.	SAC
42.	ITT	VAL1	Listing of Valvulopathy	If any events reported.	SAC

11.10. Appendix 10: Example Mock Shells for Data Displays

The data display shells are contained in separate documents and are available upon request.

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Reason for signing: Approved	Name: PPD Role: Approver Date of signature: 20-May-2021 21:15:30 GMT+0000

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