15 December 2022
EMA/49502/2023
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Revinty Ellipta

fluticasone furoate / vilanterol

Procedure no: EMEA/H/C/002745/P46/009

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	17/10/2022	17/10/2022	☐
☐	CHMP Rapporteur Assessment Report	21/11/2022	25/11/2022	☐
☐	CHMP members comments	05/12/2022	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	08/12/2022	n/a	☐
☒	CHMP adoption of conclusions:	15/12/2022	15/12/2022	☐

Abbreviations

ACQ	Asthma control questionnaire
ACT	Asthma Control Test
AE	Adverse Event
AESI	AEs of special interest
AM	Ante meridiem (before noon)
ANCOVA	Analysis of covariance
BMI	Body Mass Index
cACT	Childhood Asthma Control Test
CDC	Centre for Disease Control
CFR	Code of Federal Regulations
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
COVID-19	Corona Virus Disease 2019
CRF	Case report form
CTD	Common Technical Document
CYP3A4	Cytochrome P450 3A4
DPI	Dry powder inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDiary	Electronic diary
EMA	European Medicines Agency
ER	Emergency room
ETD	Early treatment discontinuation
EW	Early withdrawal
FBG	Fasting blood glucose
FDA	Food and drug administration
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FP	Fluticasone propionate
FRP	Females of reproductive potential
GCSP	Global Clinical Safety and Pharmacovigilance

ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
ITT	Intent-to-Treat
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
L	Liter
LABA	long-acting beta-2 agonist
LS	Least square
LTRA	Leukotriene receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model repeated measures
NDPI	Novel dry powder inhaler
NIH	National Institutes of Health
PDCO	Paediatric Committee
PEF	Peak expiratory flow
PIP	Paediatric investigational plan
PM	Post meridiem (after noon)
PT	Preferred term
QTc	QT corrected interval
QTcF	QT corrected interval by Frederica's formula
SABA	Short-acting beta agonist
SAE	Serious Adverse Event
SAESI	Serious AESI
SAMA	Short-acting muscarinic antagonist
SAWP	Scientific Advice Working Party
SD	Standard deviation
SMQ	Standardised MedDRA queries
SoA	Schedule of assessments
SOC	System organ class
Std Err	Standard error
VI	Vilanterol (as trifenate)

Table of contents

1. Introduction

On 21st September 2022, the MAH submitted a completed paediatric study (Study No. HZA107116) for Relvar Ellipta and its duplicate Revinty Ellipta (fluticasone furoate/vilanterol [as trifenatate]), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

On 13th November 2013, Relvar Ellipta (Fluticasone furoate/Vilanterol [as trifenatate] Inhalation Powder [FF/VI]) was approved by the European Commission (EC) for "the regular treatment of asthma in adults and adolescents aged 12 years and older where use of a combination product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate", as well as for "the symptomatic treatment of adults with chronic obstructive pulmonary disease (COPD)".

Pursuant to Article 7 of Regulation (EC) No. 1901/2006, as amended, the application included an EMA Decision on the granting of a class waiver for the condition COPD (EMA/825560/2008) and an EMA Decision on the agreement of a paediatric investigation plan (PIP) for the condition asthma (EMEA-000431-PIP01-08-M04; P/0049/2012), which included a waiver in children under 5 years of age and a deferral in children aged 5-11 years. According to the last EMA Decision (P/0092/2021), the agreed PIP for FF/VI (EMEA-000431-PIP01-08-M12) is expected to be completed by October 2022.

In accordance with Article 46 of the regulation (EC) No. 1901/2006, Glaxo Group Ltd hereby submits to the EMA a final study report for study number HZA107116 which is part of the last PIP agreed to FF/VI (PIP Study 12).

The MAH stated that the study HZA107116 titled “A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids” is part of a clinical development program. The type II variation application consisting of the full relevant data package (i.e., containing several studies) is expected to be submitted by March 2023. A line listing of all the concerned studies has not been submitted by the applicant.

2.2. Information on the pharmaceutical formulation used in the study

Fluticasone furoate/Vilanterol (as trifenatate) Inhalation Powder (FF/VI) is authorised in the European Union (EU) as a pre-dispensed multi dose dry powder inhaler in strengths of 100/25 micrograms and 200/25 micrograms. Both strengths of this inhalation powder for oral inhalation are approved in the paediatric population (adolescents aged 12 years and older) for use as a once-daily (OD) treatment of asthma.

In the hereby submitted study, orally inhaled FF/VI (50/25 micrograms or 100/25 micrograms) or orally inhaled FF (50 micrograms or 100 micrograms) were administered OD in asthmatic children and

adolescents (aged 5 to <18 years) during its 24-week double-blind treatment period. Both FF/VI and FF treatments, were administered as dry inhalation powder by using the same inhaler device (ELLIPTA inhaler) as the Relvar/Revinty products approved in the EU.

The doses of each of the components of FF/VI 50/25 micrograms administered in the 5 to less than 12 years age group were selected from the results of 2 Phase IIb dose ranging studies (HZA106853 for VI and HZA106855 for FF) in asthmatic participants aged 5 to 11 years of age (inclusive). The dose of FF/VI 100/25 micrograms was selected as the appropriate dose in this study for the 12 to less than 18 years age group based on the data generated from the FF and VI Phase 2b and FF/VI Phase 3 studies in participants aged 12 years and older. Moreover, FF/VI 100/25 micrograms is the approved starting dose in over 60 countries for the once daily treatment of asthma.

The formulations of FF alone used in the present study are not currently approved in the EU. However, as said above, the dose of FF 50 micrograms has been previously assessed in completed paediatric studies performed in asthmatic children and adolescents. FF 100 micrograms was selected for this study as this is the starting dose currently approved for FF in participants aged 12 years of age and older.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for the study number HZA107116 (EudraCT number: 2016-004086-87) titled "A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids".

2.3.2. Clinical study

Clinical study number HZA107116 (EudraCT number: 2016-004086-87) titled "A randomised, double-blind, parallel group, multicentre, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids".

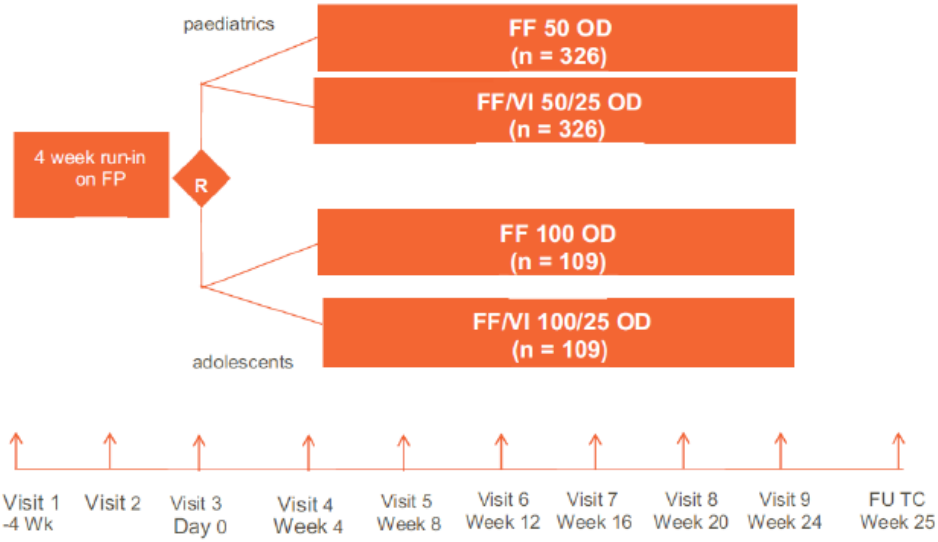
Description

HZA107116 was a phase 3, randomised, double-blind, stratified, parallel group, multicentre study to evaluate the efficacy and safety of once daily fluticasone furoate/vilanterol (as trifenatate) inhalation powder (FF/VI) compared to once daily fluticasone furoate inhalation powder (FF) in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Study randomisation was stratified by age as follows: participants from 5 to 11 years were randomly (1:1) allocated to receive FF/VI 50/25 micrograms or FF 50 micrograms whereas participants from 12 to 17 years were randomly (1:1) allocated to receive FF/VI 100/25 micrograms or FF 100 micrograms.

This study was conducted over a total duration of approximately 29 weeks: a 4-week open-label run-in period where all participants received fluticasone propionate (FP) 100 micrograms twice daily, a 24-week double-blind treatment period where participants received FF/VI or FF as described above, and a

1-week follow-up period. Participants received a short-acting beta agonist (SABA) (i.e., salbuterol/salbutamol) as needed throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms.

Figure 1. Study Schematic



Abbreviations: ETD = early treatment discontinuation; EW = early withdrawal; FF = fluticasone furoate; FF/VI = fluticasone furoate/vilanterol; FP = fluticasone propionate; FU = follow-up visit; OD = once daily; n= number of participants; R = randomisation; Wk = week

Note: Visits 1 and 3 were done in the clinic. Spirometry for V6 was done in the clinic. Visit 2 was for spirometry only and could have been done at home or clinic. Visits 5 and 7 could have been parent only visits or video-calls. If spirometry was done at Visit 5, it could have been done at home or clinic. Visits 4, 9, ETD and EW could be done in the home or clinic. Visit 8 could be a video-call, phone-call or clinic visit. The FU TC could be a phone-call or video-call.

The population of interest (required by the EMA) was the ITT (5 to 11 Years Old) Population and the primary endpoint was AM PEF over Weeks 1 to 12.

Methods

Study participants

Inclusion/Exclusion Criteria at the Screening Visit

A participant was only eligible for inclusion in this study at the Screening visit (Visit 1) if all of the following criteria applied:

- Prepubertal (Tanner Stage 1),
- Male or female,
- Aged 5 to <9 years for boys and 5 to <8 years for girls,
- Height centile between 3% and 97% (US CDC charts),
- Body weight and body mass index (BMI) between the 3rd and 97th centile (US CDC charts),

- Written consent had to be provided from at least one parent/care giver and accompanying assent from the participant (where the participant was able to provide assent) prior to study admission,
- Documented history of symptoms consistent with a diagnosis of asthma for at least 6 months prior to Visit 1,
- Pre-bronchodilatory FEV1 at Visit 1 of ≥60%,
- Able to replace their current SABA treatment with study supplied rescue albuterol/salbutamol provided at Visit 1 for use as needed for the duration of the study,
- cACT score of >19,
- Needed at least one course of corticosteroid for their asthma (inhaled or oral) in the previous year,
- Using either a SABA inhaler alone (e.g., salbutamol) on an as needed basis and/or regular non-ICS controller medications for asthma (e.g., cromones or leukotriene receptor antagonists) prior to entry into the study.

A participant was not eligible for inclusion in this study if they had:

- A history of asthma exacerbation requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or had used a depot corticosteroid injection within 3 months,
- Required hospitalisation for asthma (within 6 months) prior to Visit 1,
- A culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus, or middle ear that was not resolved within 4 weeks of Visit 1 and led to a change in asthma management,
- A clinical visual evidence of candidiasis at Visit 1,
- Any significant abnormalities or medical condition identified at Visit 1,
- Any previous or current condition that affected growth, including sleep disorders, endocrine disorders, skeletal dysplasia,
- Turner and Noonan syndromes,
- Marfan, Beckwith-Wiedeman, and Sotos syndromes,
- Klinefelter's syndrome,
- Coeliac disease,
- Inflammatory bowel diseases,
- Renal failure,
- Any significant abnormality or medical condition that was identified at Visit 1 (including serious psychological disorder) that was likely to interfere with the conduct of the study,
- Premature adrenarche,
- Unable to stand, or who found standing difficult due to illness or physical disabilities,
- Prior use of any medication or treatment that might have affected growth including, but not limited to: amphetamines, anticonvulsants, biphosphonates, calcitonin, erythropoietin, oestrogens, growth hormone, methylphenidate, phosphate binders, progestins, antithyroid drugs (e.g., methimazole) thyroid hormone or testosterone,
- Known hypersensitivity to corticosteroids, leukotrienes, or any excipients in the ELLIPTA inhaler and study tablets, or history of severe milk protein allergy.
- Any of the prohibited medications listed below, according to the timeframes indicated, unless they were deemed necessary to treat an asthma exacerbation or another condition appropriately:

    1. From screening visit (Visit 1) to Visit 9:

LTRAs, ketotifen, nedocromil sodium, orally inhaled sodium cromoglycate, SABA/SAMA combinations, and inhaled corticosteroids (except for FP which was given during the run-in).

2. Within 4 weeks of Visit 1:
Participants who had changed their asthma medication.

3. Within 4 weeks of Visit 1, or any time between Visit 1 to 9:
Theophyllines, oral long-acting beta 2-agonists (e.g., bambuterol), inhaled long-acting beta 2-agonists (e.g., salmeterol, formoterol), combination products containing inhaled long-acting beta 2 agonists and inhaled long-acting anticholinergics (e.g., tiotropium). Potent CYP3A4 inhibitors (e.g., clarithromycin).

Prescription or over-the-counter medication that could significantly affect the course of asthma or change in asthma medication, or interact with study drug including (but not limited to): anticonvulsants (barbiturates, hydantoins, carbamazepine); polycyclic anti-depressants; oral, systemic or transdermal beta-adrenergic blocking agents; phenothiazines and monoamine oxidase inhibitors.

4. Within 6 weeks of Visit 1 or any time between Visit 1 to 9:
Oral corticosteroids.

Note: During the double-blind treatment period, participants who required limited courses of oral corticosteroids could have remained on study intervention.

5. Within 12 weeks of Visit 1 or any time between Visit 1 to 9:
Systemic or depot corticosteroids, anti-IgE, anti-IL5, immunosuppressive medications (immunotherapy for the treatment of allergies was allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the participant remained in the maintenance phase throughout the study).

6. Other:
A participant should not have used any inhaled SABA within 4 hours of Visit 1.

Screening and Run-in Failures

Screen failures were defined as participants who consented to participate in the clinical study but were not subsequently randomised in the study whereas Run-in failures are withdrawals after Visit 1 (Screening) and prior to randomisation.

Participants who failed any of the screening or run-in criteria could be rescreened once after a period of at least 1 month from the date of screen failure or run-in failure.

Any rescreened participant had to satisfy all of the protocol-specified inclusion/exclusion requirements at the time of the rescreening visit. Rescreened participants were to be assigned a new participant number at the time of rescreening.

Inclusion/Exclusion Criteria for Randomisation to Treatment

Participants had to meet the following criteria to be eligible for randomisation:

1. Growth

a. Prepubertal: Tanner Stage 1.

b. Body weight and BMI: Between the 3rd and 97th percentile based on the US CDC standard statistics or any local standards outside the US.

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

d. Bone age: Within 2 years of participant's chronological age as determined by hand/wrist x-ray using the Greulich and Pyle method during the baseline period.

2. Disease Changes

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

3. Medications

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

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

4. Study Compliance:

a. Responsibility: Participant/parent/guardian had to demonstrate the ability to comply with all study procedures during the run-in study period, including proper study treatment administration during the randomisation visit.

b. Single-blind treatment: Complied with single-blind placebo treatment as recorded in the daily e-diary and based on the dose counter. Participants did not take their inhaler at least 80% of the time during the last 30 days of the run-in period were not eligible for randomisation.

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

A participant was not eligible for randomisation in this study if they had:

1. Changes in asthma medication that occur after screening.

2. Occurrence of a culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear during the run-in period that led to a change in asthma management or, in the opinion of the investigator, was expected to affect the participant's asthma status or the participant's ability to participate in the study.

3. Evidence of an exacerbation, defined as:

• a deterioration of asthma requiring the use of oral corticosteroids for at least 3 days, or

• a depot corticosteroid injection, or

• an in-patient hospitalisation due to asthma that required systemic corticosteroids between screening and randomisation.

4. Clinical visual evidence of oropharyngeal candidiasis at the Randomisation Visit.

5. Unable to use the ELLIPTA inhaler correctly.

Withdrawal Criteria

Participants could be discontinued from study intervention at any time by the investigator if the study intervention was considered to be detrimental for them to continue on study intervention. Specifically, a participant was discontinued from study intervention if he/she met any of the following criteria outlined below:

• A participant became pregnant.
• Female participants who reached menarche after Visit 1 and who did not agree to follow 1 of the options listed in the modified list of highly effective methods for avoiding pregnancy in females of reproductive potential (which included abstinence) as outlined in the clinical study protocol.

- A participant met the liver stopping criteria.
- A participant met the QTc stopping criteria.

A participant could discontinue study intervention at any time at his/her own request. An early treatment discontinuation visit was conducted within approximately 24 hours of the participant stopping study medication. In the event a participant discontinued study intervention at or during a scheduled visit, an early treatment discontinuation visit was not required; however, all study procedures scheduled at an early treatment discontinuation visit were to be performed at this visit instead and reasons for treatment discontinuation must have been collected. These participants were not allowed to restart study intervention; however, participants were asked to continue to follow the regular visit schedule, including the completion of the daily electronic patient diary (until Visit 6), and attending the clinic at Visit 6 to obtain serial FEV1 measurements. The investigator was to prescribe appropriate asthma medication to participants who discontinued study intervention and elected to continue in the study. After treatment discontinuation, the prohibited medications listed in the clinical study protocol were no longer applicable. Every effort was made to contact participants who did not attend the end of treatment visit to collect information on any AEs, SAEs and exacerbations, and to collect the e-diary.

A participant could withdraw from the study at any time at his/her own request (or at the request of his/her legal guardians). In this case, all study-related medications and other study-related materials were to be returned to the site by the participant. An early withdrawal visit was to be scheduled within approximately 24 hours of the participant withdrawing from the study. In the event a participant withdrew at or during a scheduled visit, an early withdrawal visit was not required; however, all study procedures scheduled at an early withdrawal visit were to be performed at this visit instead. The primary reason for withdrawal from the study was recorded in the e-CRF, and any data collected up until the point of withdrawal was used in the analyses.

Participants Lost to Follow-up

The following actions were to be taken for participants who failed to attend the clinic for a required study visit:

• The site was to attempt to contact the parent/participant and reschedule the missed visit as soon as possible and counsel the parent/participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wished to and/or should continue in the study.

• In cases where the participant was deemed 'lost to follow-up', the investigator or designee was to make every effort to regain contact with the parent/participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts were to be documented in the participant's medical record.

• If the parent/participant continued to be unreachable, only then was the participant considered to have withdrawn from the study, with a primary reason of "Lost to Follow-up".

Liver Chemistry Stopping Criteria

Clinical laboratory tests to check liver function were not planned at screening or during study conduct.

QTc Stopping Criteria

QT corrected interval by QTcF was used for each individual participant to determine eligibility for and discontinuation from the study.

• The QTc must have been based on single or averaged QTc values of triplicate ECGs obtained over a brief (e.g., 5 to 10 minutes) recording period.

A participant who met the bulleted criteria based on the average of triplicate ECG readings was withdrawn from study intervention:

• QTcF >500 ms OR Uncorrected QT >600 ms

• Change from baseline of QTcF >60 ms.

For participants with underlying bundle branch block, the discontinuation criteria listed in the clinical study protocol were to be followed.

Treatments

Different treatments were planned to be administered during the different periods of the study: a 4-week open-label run-in period, a 24-week double-blind treatment period, and a 1-week follow-up period.

Study interventions

Study interventions that were administered in this study are detailed in Table 1.

Orally inhaled fluticasone propionate (FP) 100 micrograms was administered twice daily as dry powder inhaler during the 4-week open-label run-in period.

During the 24-week double-blind treatment period, a fixed-dose combination of FF and VI (50/25 micrograms for children aged 5 to 11 years and 100/25 micrograms for adolescents aged 12 to 17 years of age) administered OD as dry powder was evaluated compared to a dose of FF alone (50 micrograms for children aged 5 to 11 years and 100 micrograms for adolescents aged 12 to 17 years of age).

Table 1 Study interventions

Study intervention Name:	Fluticasone Furoate / Vilanterol 50/25 µg dry powder inhaler*	Fluticasone Furoate / Vilanterol 100/25 µg dry powder inhaler*	Fluticasone Furoate 50 µg dry powder inhaler**	Fluticasone Furoate 100 µg dry powder inhaler**	Fluticasone Propionate 100 µg dry powder inhaler
Dosage formulation:	Dry powder inhaler	Dry powder inhaler	Dry powder inhaler	Dry powder inhaler	Dry powder inhaler
Unit dose strength(s)/Dosage level(s):	FF 50 µg and VI 25 µg per actuation	FF 100 µg and VI 25 µg per actuation	FF 50 µg per actuation	FF 100 µg per actuation	100 µg per actuation
Route of Administration:	Inhaled	Inhaled	Inhaled	Inhaled	Inhaled
Dosing instructions:	Inhale once in the morning	Inhale once in the morning	Inhale once in the morning	Inhale once in the morning	Twice daily
Device:	Ellipta	Ellipta	Ellipta	Ellipta	Diskus
Method of individualising dosage:	Inhalation (oral)	Inhalation (oral)	Inhalation (oral)	Inhalation (oral)	Inhalation (oral)

Rescue medication for symptomatic relief of asthma symptoms

Each participant received a SABA (i.e., salbuterol/salbutamol [inhalation aerosol or nebuliser]) as needed throughout the entire study period. as rescue medication for symptomatic relief of asthma symptoms.

Other Concomitant Medications

Any medication that was not prohibited in inclusion/exclusion criteria section (see sub-section "Study participants") was allowed during the study, as long as the dose remained constant wherever possible and their use was not expected to affect the outcome of the study assessments.

Objectives

Primary Objective

Common to both 5 to 11 years and 5 to 17 years population

- To compare the efficacy of once daily FF/VI with once daily FF in participants with asthma.

  The primary estimand was that of treatment policy (effectiveness-type estimand). The secondary efficacy-type estimand was defined for the primary and powered secondary endpoints.

Secondary Objective

Common to both 5 to 11 years and 5 to 17 years population

- To assess the safety of FF/VI in participants with asthma.

Outcomes/endpoints

Primary Endpoint

Primary endpoint for 5 to 11 years population (required by the EMA)

- Change from baseline, averaged over Weeks 1 to 12 of the treatment period, in pre-dose (i.e., trough) morning peak expiratory flow (AM PEF), captured daily via electronic patient diary.

  This was a secondary endpoint for the 5 to17 years population.

Primary endpoint for 5 to 17 years population (required by the Food and Drug Administration [FDA])

- Weighted mean FEV1 (0 to 4 hours) at Week 12.

  This was a secondary endpoint for the 5 to 11 years population.

Secondary Endpoint(s)

Secondary endpoints common to both 5 to 11- and 5 to 17 years population

- Change from baseline in the percentage of rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period (powered secondary endpoint for 5 to 11 years population) captured daily via electronic patient diary.

- Change from baseline in the percentage of symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period, captured daily via electronic patient diary.
- Change from baseline in AM FEV1 in participants who can perform the manoeuvre at Week 12.
- Change from baseline in ACQ-5 at Week 24.
- Incidence of exacerbations over the 24-week treatment period.

Secondary endpoints common to both 5 to 11- and 5 to 17 years population

- Incidence of AEs.
- Evaluation of fasting blood glucose pre- and post-treatment.
- Evaluation of ECG at screening and end of treatment.

Other endpoints

Other endpoints common to both 5 to 11- and 5 to 17 years old population

- Change from baseline, averaged over Weeks 1 to 12 of the treatment period in PM PEF, captured daily via electronic patient diary.

Sample size

Approximately 2900 participants were to be screened to achieve a total of 870 participants to be randomised in a ratio of 1:1 giving 435 randomised participants per arm in the 5 to 17 years old population. There were to be 652 randomised participants who were 11 years old or less at screening (and at least 163/652 [25%] were to be aged 5 to less than 8 years), giving 326 randomised participants per arm in the 5 to 11 years old population, and 218 participants in the 12 to 17 years old population. A 70% screening failure rate was expected.

Assumptions for 5 to 17 Years Old Population

The sample size calculation for the 5 to 17 years old population was based on the primary efficacy endpoint of weighted mean FEV1 (0 to 4 hours). The sample size allowed for up to 20% of participants to not contribute to the primary endpoint giving a total of 348 evaluable participants per arm.

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

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

Assumptions for 5 to 11 Years Old Population

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

For the primary endpoint of AM PEF, a standard deviation of 30 L/min was assumed, based on previous studies. The sample size had 91% power, based on a true population difference of 8 L/min and significance declared at the two-sided 5% significance level.

The smallest observed effect predicted to result in a statistically significant difference between treatment groups was 4.7 L/min.

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

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

Sample Size Re-estimation

No sample size re-estimation was performed.

Randomisation and blinding (masking)

Treatment Assignment

Participants meeting the criteria for randomisation were randomised to 1 of 2 treatment arms using Interactive Voice Response System (IVRS)/Interactive Web Response System (IWRS). Before the study was initiated, the telephone number and call-in directions for the IVRS and/or the log in information and directions for the IWRS were provided to each site.

Study intervention was dispensed (according to treatment assigned using IVRS at the study visits summarised in the Schedule of Assessments (SoA). Returned study intervention must not have been re-dispensed to the participants.

Blinding

This was a double-blind study and the following applied:

- The IVRS/IWRS were programmed with blind-breaking instructions. The blind might have been broken if, in the opinion of the investigator, it was in the participant's best interest for the investigator to know the study intervention assignment. GSK had to be notified before the blind was broken unless identification of the study intervention was required for a medical emergency in which the knowledge of the specific blinded study intervention affected the immediate management of the participant's condition (e.g., an antidote was available). In this case, GSK was to be notified within 24 hours after breaking the blind. The date and reason that the blind was broken was to be recorded in the source documentation and CRF, as applicable.

- The date and reason for the unblinding was to be fully documented in the CRF and source documentation.

- A participant might have continued in the study if that participant's treatment assignment was unblinded by GSK GCSP personnel. The primary reason for discontinuation (the event or Condition which led to the unblinding) was to be recorded in the CRF.

• GSK's GCSP staff might unblind the treatment assignment for any participant with an SAE. If the SAE required that an expedited regulatory report was to be sent to 1 or more regulatory agencies, a copy of the report, identifying the participant's treatment assignment, might have been sent to investigators in accordance with local regulations and/or GSK policy.

Treatment codes could be unblinded by the investigator or treating physician only in the case of a medical emergency or in the event of a serious medical condition, when knowledge of the study intervention was essential for the clinical management or welfare of the participant. GSK Global Safetystaff could unblind treatment codes in the event of a SAE.

Statistical Methods

Analysis Sets

For purposes of analysis, the following populations were defined:

- *Total Population*

The Total Population comprised all participants screened and for whom a record existed on the study database and was used for the tabulation and listings of reasons for withdrawal before randomisation.

- *Intent-to-Treat (ITT) (5 to 17 Years Old) Population*

The ITT (5 to 17 Years Old) Population comprised all participants randomised to treatment and who received at least 1 dose of study medication. Randomised participants were assumed to have received study medication unless definitive evidence to the contrary existed. Outcomes were reported according to the randomised treatment allocation. This constituted one of the 2 primary populations for all efficacy measures and safety measures.

- *The ITT (5 to 11 Years Old) Population*

The ITT (5 to 11 Years Old) Population is a subset of the ITT (5 to 17 Years Old) Population for participants aged 11 years old or younger at screening. Outcomes were reported according to the randomised treatment allocation. This constituted one of the 2 primary populations for all efficacy measures and safety measures.

Interim Analyses

No interim analysis was planned for this study.

Final Analyses

- *Hypotheses*

The primary efficacy endpoint for the 5 to 17 years old population was weighted mean FEV1 (0 to 4 hours). For the 5 to 11 years old population the primary efficacy endpoint was the change from baseline in AM PEF and the nominated powered secondary endpoint was the change from baseline in rescue-free 24-hour periods. For each of these endpoints there was a single inequality comparison of FF/VI versus FF. Demonstration of efficacy for each of these inequality comparisons was based on a hypothesis testing approach, whereby the null hypothesis was that there was no difference between treatment groups for the endpoint of interest and the alternative hypothesis was that there was a difference between treatment groups. A 2-sided 5% risk associated with incorrectly rejecting any of the null hypotheses (significance level) was considered acceptable for this study. As the comparisons on the 5 to 17 years old population and the 5 to 11 years old population were being made for different purposes, they each had distinct multiple testing strategies which were assessed separately. For each

of the 2 populations, in order to account for multiplicity across the key endpoints, a step-down closed-testing procedure was applied to the inequality comparison of FF/VI versus FF whereby this comparison was required to be significant at the 0.05 level for the primary endpoint in order to infer on the secondary endpoints and inference for a test in the pre-defined hierarchy of secondary endpoints was dependent upon statistical significance having been achieved for the previous comparison in the hierarchy of secondary endpoints. If a given statistical test failed to reject the null hypothesis of no treatment difference at the significance level of 0.05, then all tests lower down in the hierarchy were to be interpreted as descriptive only.

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

Testing of each endpoint is dependent on significance at the 0.05 level having been achieved on the previous endpoint in the hierarchy.	
Primary Efficacy Endpoint	
1) Weighted mean FEV1 (0 to 4 hours):	FF/VI vs. FF
Secondary Efficacy Endpoints	
2) Rescue-free 24-hour periods:	FF/VI vs. FF
3) Symptom-free 24-hour periods:	FF/VI vs. FF
4) AM FEV1:	FF/VI vs. FF
5) AM PEF:	FF/VI vs. FF
6) ACQ:	FF/VI vs. FF

Abbreviations: ACQ = asthma control questionnaire; AM = ante meridiem (before noon); FF = fluticasone furoate; VI = Vilanterol; FEV1 = Forced expiratory volume in 1 second; PEF = peak expiratory flow.

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

Testing of each endpoint is dependent on significance at the 0.05 level having been achieved on the previous endpoint in the hierarchy.	
Primary Efficacy Endpoint	
1) AM PEF:	FF/VI vs. FF
Secondary Efficacy Endpoints	
2) Rescue-free 24-hour periods:	FF/VI vs. FF
3) Symptom-free 24-hour periods:	FF/VI vs. FF
4) AM FEV1:	FF/VI vs. FF
5) ACQ:	FF/VI vs. FF
6) Weighted mean FEV1 (0 to 4 hours):	FF/VI vs. FF

Abbreviations: ACQ = asthma control questionnaire; AM = ante meridiem (before noon); FF = fluticasone furoate; VI = Vilanterol; FEV1 = Forced expiratory volume in 1 second; PEF = peak expiratory flow.

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

In each population, if significance was achieved for the FF/VI versus FF treatment comparison on the primary efficacy endpoint, then the secondary endpoints were tested in a closed-testing manner using the hierarchy of comparisons. If significance was also achieved for each of the secondary efficacy

endpoints, then all other efficacy endpoints were tested for the FF/VI versus FF treatment comparison without further multiplicity adjustment.

- *Treatment Comparisons*
  - Primary Comparison of Interest

The primary treatment comparison for the 5 to 17 years old population was F.F/VI versus FF for the primary efficacy endpoint of weighted mean FEV1 (0 to 4 hours) at Week 12.

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

Please, note that the population of interest for the EMA was the ITT (5 to 11 Years Old) Population whereas the population of interest For the FDA was the ITT (5 to 17 years old).

  - Other Comparisons of Interest

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

- *Key Elements of Analysis Plan*

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

The main analysis for all efficacy endpoints evaluated the primary *de facto* estimand of treatment policy (effectiveness-type estimand): the mean difference between treatment groups for the time point of interest regardless of whether the participant remained on-treatment. This means that for any given endpoint, all available data for a participant were used including any data that had been collected after the participant discontinued study medication. Specific details for inclusion were detailed in the reporting and analysis plan, but in general the minimum data required was a baseline evaluation and at least one postbaseline evaluation. For the powered endpoints only, a secondary de jure efficacy-type estimand was evaluated by using only on-treatment data.

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

For the derivation of the percentage of symptom-free 24-hour periods, a given 24-hour period was considered as missing if both the day-time and night-time data were missing or if one was symptom-free but the other was missing. However, if either the daytime or the night-time has symptoms then the 24-hour period were considered not symptom-free.

The same principals were applied to the derivation of the percentage of rescue-free 24-hour periods. Any tests for interactions were 2-sided at the 10% level of significance. In all cases, if any assumptions of the proposed method of analyses were not met, alternative methods of analyses were to be used.

It was anticipated that a large number of centres participated in the study. Therefore, it was likely that many centres enrolled very small number of participants. Consequently, all centres within the same country were pooled. In addition, if there were any countries enrolling very small numbers in total

(<12 in either of the ITT 5 to 17 or 5 to 11 years old populations), these countries were pooled with another country within a similar geographical region. All amalgamations were finalised and documented prior to unblinding the treatment codes. These amalgamations were used wherever region was incorporated into the analysis.

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

- Primary Efficacy Analyses

Primary Efficacy Analyses for 5 to 17 Years Old Population

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5 to 17 Years Old) population included data from all participants regardless of whether or not they were on-treatment at the time of their Week 12 serial FEV1 measurements.

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

The primary endpoint of weighted mean FEV1 (0 to 4 hours) at Week 12 was derived using the post-dose assessments (after 30 minutes and 1, 2, 3, 4 hours) with their actual times and using the pre-dose assessment as the 0-hour measurement. The weighted mean was calculated as the average area under the curve using the trapezoidal rule, and dividing by the relevant time interval (i.e., the time between the actual time of dose and the actual time of the last FEV1 measurement being used).

The weighted mean was analysed using an analysis of covariance (ANCOVA) model with effects due to baseline pre-dose FEV1, region, sex, age and treatment group. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison were presented together with 95% confidence intervals (CI) for the difference and a p-value for the treatment comparison.

Primary Efficacy Analyses for 5 to 11 Years Old Population

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5 to11 years old) population included all available AM PEF data from Weeks 1 to 12, regardless of whether the participant had been still on-treatment at the time of the measurement.

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

The primary endpoint of change from baseline in AM PEF averaged over Weeks 1 to 12 was calculated for each participant using only data that were from the first 84 calendar days after randomisation.

The primary analysis as performed using an analysis of covariance (ANCOVA) model with effects due to baseline AM PEF, region, sex, age and treatment group. The adjusted means for each treatment and the estimated treatment differences for the treatment comparison were presented together with 95% CIs for the difference and a p-value for the treatment comparison.

A sensitivity analysis for the primary effectiveness-type estimand was performed including all data from Weeks 1 to 12 (regardless of treatment state). For this analysis, the Weeks 1 to 12 time period was split into 6 separate time periods: Weeks 1 to 2, Weeks 3 to 4, Weeks 5 to 6, Weeks 7 to 8, Weeks 9 to 10 and Weeks 11 to 12. The data was then analysed using a mixed model repeated measures (MMRM) model, which allowed for effects due to baseline AM PEF, region, sex, age, time period and treatment group. This model also contained a time period-by-baseline interaction term and a time period-by-treatment interaction term. Missing data were not implicitly imputed in this analysis.

However, all non-missing data for a participant was used within the analysis to estimate the average treatment effect over Weeks 1 to 12.

- Secondary Efficacy Analyses

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

To address the primary effectiveness-type estimand, the primary analysis on the ITT (5 to 11 Years Old) population included all available data from Weeks 1 to 12, regardless of whether the participant had been still on-treatment at the time of the question.

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

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

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

A sensitivity analysis for the primary effectiveness-type estimand was performed including all data from Weeks 1 to 12 (regardless of treatment state). For this analysis, the Weeks 1 to 12 time period was split into 6 separate time periods: Weeks 1 to 2, Weeks 3 to 4, Weeks 5 to 6, Weeks 7 to 8, Weeks 9 to 10 and Weeks 11 to 12. The data were then analysed using a MMRM model, which allowed for effects due to baseline, region, sex, age, time period and treatment group. This model also contained a time period-by-baseline interaction term and a time period-by-treatment interaction term. Missing data were not implicitly imputed in this analysis.

However, all non-missing data for a participant were used within the analysis to estimate the average treatment effect over Weeks 1 to 12.

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

The change from baseline in the percentage of rescue-free 24-hour periods over Weeks 1 to 12 was a secondary endpoint for the 5 to 17 years old population and was calculated for each participant using only data that were from the first 84 calendar days after randomisation. The primary analysis was performed using an ANCOVA model with effects due to baseline, region, sex, age and treatment group.

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

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

Change from Baseline in AM FEV1

Change from baseline in AM FEV1 at Week 12 was defined using the pre-dose FEV1 assessment at the Week 12 clinic visit. Analysis was performed using an MMRM model, which allowed for effects due to baseline FEV1, region, sex, age, visit and treatment group. This model also contained a visit-by-baseline interaction term and a visit-by-treatment interaction term. Missing data were not implicitly imputed in this analysis. However, all non-missing pre-dose data for a participant taken at scheduled Visits 3, 4 and 5 (Weeks 4, 8 and 12) were used within the analysis to estimate the Week 12 treatment effects.

Change from Baseline in ACQ-5

Change from baseline in ACQ-5 at Week 24 was analysed using an MMRM model, which will allow for effects due to baseline, region, sex, age, visit and treatment group.

This model also contained a visit-by-baseline interaction term and a visit-by-treatment interaction term. Missing data were not implicitly imputed in this analysis. However, all non-missing data for a participant taken at scheduled Visits 5 and 8 (Weeks 12 and 24) were used within the analysis to estimate the Week 24 treatment effects.

Weighted Mean FEV1 (0 to 4 hours) for 5 to 11 Years Old Population

Weighted mean FEV1 (0 to 4 hours) at Week 12 was a secondary endpoint for the 5 to 11 years old population. It was analysed using an ANCOVA model with effects due to baseline FEV1, region, sex, age and treatment group.

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

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

Change from Baseline in PM PEF

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

Results

Participant flow

A total of 2402 participants were screened, of whom 1187/2402 (49%) participants failed screening (Table 2) and 1215 participants entered the run-in period.

Table 2 Summary of Reasons for Screen Failure

	Total (N=2402)
Screen Failures	1187 (49%)
Primary Reason for Screen Failure	
Did not meet inclusion/exclusion criteria	1154 (48%)
Serious adverse event	0
Investigator discretion	3 (<1%)
Withdrew consent	29 (1%)
Other	1 (<1%)

Source: Table: 1.2
Note: Screen failures are subjects who failed screening and withdrew at Visit 1 (Screening).

In the run-in period, additional 309/2402 (13%) participants failed the eligibility check; the reasons for run-in failure are shown in Table 3.

Table 3 Summary of Reasons for Run-in Failure

	Total (N=2402)
Run-in Failures	309 (13%)
Primary Reason for Run-in Failure	
Did not meet continuation criteria	281 (12%)
Investigator discretion	7 (<1%)
Other	1 (<1%)
Protocol deviation	5 (<1%)
Withdrew consent	15 (<1%)

Source: Table 1.4
Abbreviations: N = Number of participants
Note: Run-in failures are withdrawals after Visit 1 (Screening) and prior to randomisation.
Note: For subjects 000011, 002502, 008607, 017902, 019601, 020601 have more than one run-in failure reasons: Other reason was added in error and not included in the table.

Of all 906 participants randomised, a total of 902 participants were randomised and received study intervention (454 participants in the FF/VI group and 448 participants in the FF group) with 673/906 (74%) participants included into the ITT population of the 5 to 11 years old (337 participants in the FF/VI group and 336 participants in the FF group) (Table 4).

Table 4 Summary of Subject Populations

Population	FF/VI	FF	Total
Total			2402
Randomized	455	451	906
Intent-to-Treat (5-17 Years Old)	454 (>99%)	448 (>99%)	902 (>99%)
Intent-to-Treat (5-11 Years Old)	337 (74%)	336 (75%)	673 (74%)

Total: All subjects screened and for whom a record exists on the study database.
Intent-to-Treat (5-17 Years Old): All randomized subjects who received at least a single dose of trial medication.
Intent-to-Treat (5-11 Years Old): A subset of the Intent-to-Treat (5-17 Years Old) Population for subjects <=11 years old at Screening.
Note: Subjects HZA107116.013410 and HZA107116.021401 were randomised twice in error but these subjects are counted only once.

A total of 864/902 (96%) participants completed the study. Prematurely withdrawn were 38/902 (4%) participants, with 21 (5%) participants in the FF/IV group and 17 (4%) in the FF group. See Table 5.

Table 5 Summary of End of Study Record Intent-to-Treat Population (5 to 17 Years Old)

	FF/VI (N=454)	FF (N=448)	Total (N=902)
Completion Status			
Completed	433 (95%)	431 (96%)	864 (96%)
Prematurely withdrawn [1]	21 (5%)	17 (4%)	38 (4%)
Missing	0	0	0
Primary Reason for Withdrawal			
Study closed/terminated	4 (<1%)	3 (<1%)	7 (<1%)
Lost to follow-up	1 (<1%)	0	1 (<1%)
Withdrew consent	16 (4%)	14 (3%)	30 (3%)

Source: Table 1.9
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Number of participants
[1] Prematurely withdrawn is withdrawn from the study.

One participant in the FF/VI group was withdrawn from the study due to the COVID-19 pandemic. None of the participants in either treatment group discontinued the study intervention of the study due to the COVID-19 pandemic.

Recruitment

A total of 2402 participants were screened for the study. The study was conducted at 228 sites in 15 countries. The study was initiated on 20 October 2017 (first participant first visit) and completed on 21 March 2022 (last participant last visit).

Baseline data

The 2 treatment groups were similar with respect to age, race, ethnicity, medical conditions, asthma history, and lung function. A summary of demographic data is shown in Table 6 and Table 7. The majority of the participants (471/902 [52%]) were between 8 and 11 years old (mean [SD] age 10.0 [2.99] years), male (546/902 [61%]), not Hispanic or Latino (651/902 [72%]) with a mean BMI of 18.55 (3.404) kg/m2. The demographic data were comparable between both groups with more male participants in the FF/VI group than in the FF group (289/454 [64%] versus 257/448 [57%], respectively).

Table 6 Summary of Demographic Characteristics Intent-to-Treat Population (5 to 17 Years Old)

		FF/VI (N=454)	FF (N=448)	Total (N=902)
Age (years)	n	454	448	902
	Mean	9.9	10.0	10.0
	SD	3.02	2.97	2.99
	Median	10.0	10.0	10.0
	Min.	5	5	5
	Max.	17	17	17
	≤4 years	0	0	0
	≥5 years to ≤7 years	102 (22%)	100 (22%)	202 (22%)
	≥8 years to ≤11 years	235 (52%)	236 (53%)	471 (52%)
	≥12 years to ≤17 years	117 (26%)	112 (25%)	229 (25%)
	≥18 years	0	0	0
Sex	n	454	448	902
	Female	165 (36%)	191 (43%)	356 (39%)

		FF/VI (N=454)	FF (N=448)	Total (N=902)
	Male	289 (64%)	257 (57%)	546 (61%)
Ethnicity	n	454	448	902
	Hispanic or Latino	120 (26%)	131 (29%)	251 (28%)
	Not Hispanic or Latino	334 (74%)	317 (71%)	651 (72%)
Height (cm)	n	454	448	902
	Mean	142.800	142.870	142.835
	SD	16.4588	16.1150	16.2800
	Median	142.000	142.000	142.000
	Min.	108.00	102.00	102.00
	Max.	187.00	186.00	187.00
Weight (kg)	n	454	448	902
	Mean	38.93	39.49	39.20
	SD	14.275	14.502	14.383
	Median	36.50	38.00	37.45
	Min.	16.0	16.0	16.0
	Max.	89.7	92.0	92.0
BMI (kg/m²)	n	454	448	902
	Mean	18.42	18.68	18.55
	SD	3.332	3.475	3.404
	Median	18.00	18.10	18.10
	Min.	10.4	11.7	10.4
	Max.	29.5	31.9	31.9

Source: Table 1.14
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; SD = standard deviation;
Note: Age is derived by calculating the years between the birth date of the subject and the date of screening. A complete birth date is imputed by using the recorded month and year and assigning a day value of '15'. Age is therefore only approximate.

A summary of race and racial combinations by treatment group for the ITT population is presented in Table 7. The 2 treatment groups were similar with respect to race and racial combinations.

Table 7 Summary of Race and Racial Combinations Intent-to-Treat Population (5 to 17 Years Old)

	FF/VI (N=454)	FF (N=448)	Total (N=902)
n	454	448	902
African American/African Heritage	34 (7%)	40 (9%)	74 (8%)
American Indian or Alaska Native	22 (5%)	29 (6%)	51 (6%)
Asian	32 (7%)	26 (6%)	58 (6%)
Central/South Asian Heritage	8 (2%)	1 (<1%)	9 (<1%)
Japanese/East Asian Heritage/South East Asian Heritage	24 (5%)	25 (6%)	49 (5%)
Mixed Asian Heritage	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White	335 (74%)	320 (71%)	655 (73%)
Multiple	31 (7%)	33 (7%)	64 (7%)

	FF/VI (N=454)	FF (N=448)	Total (N=902)
African American/African Heritage & White/Caucasian/European Heritage	15 (3%)	14 (3%)	29 (3%)
African American/African Heritage & American Indian or Alaska Native	1 (<1%)	0	1 (<1%)
American Indian or Alaska Native & White/Caucasian/European Heritage	13 (3%)	19 (4%)	32 (4%)
African American/African Heritage & Arabic/North African Heritage	2 (<1%)	0	2 (<1%)

Source: Table 1.15
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = Number of participants, n= subset of participants

- *Duration of Asthma Exacerbation and Smoking History*

A summary of the duration of asthma, exacerbation and smoking history is shown in Table 8. Both groups were comparable with regard to mean [SD] duration of asthma (FF/VI 5.84 [3.623] versus FF

5.52 [3.721] years). The majority of participants (686/902 [76%]) had no asthma exacerbation in the last 12 months. All but 1 participant in the FF/VI group never smoked.

Table 8 Summary of Duration of Asthma and Exacerbation and Smoking History Intent-to-Treat Population (5 to 17 Years Old)

	FF/VI (N=454)	FF (N=448)	Total (N=902)
Duration of Asthma (years)			
n	454	448	902
Mean	5.84	5.52	5.68
SD	3.623	3.721	3.673
Median	5.33	5.00	5.04
Min.	0.5	0.5	0.5
Max.	17.0	17.0	17.0
Range of Duration			
n	454	448	902
<6 months	0	0	0
≥6 months to <1 year	22 (5%)	29 (6%)	51 (6%)
≥1 to <5 years	178 (39%)	187 (42%)	365 (40%)
≥5 to <10 years	179 (39%)	170 (38%)	349 (39%)
≥10 years	75 (17%)	62 (14%)	137 (15%)
Number of Exacerbations in Last 12 Months [1]			
n	454	448	902
0	341 (75%)	345 (77%)	686 (76%)
1	79 (17%)	69 (15%)	148 (16%)
2	23 (5%)	25 (6%)	48 (5%)
3	5 (1%)	6 (1%)	11 (1%)
4	3 (<1%)	2 (<1%)	5 (<1%)
>4	3 (<1%)	1 (<1%)	4 (<1%)
Number of Type 1 Exacerbations in Last 12 Months^			
n	454	448	902
0	349 (77%)	350 (78%)	699 (77%)
1	75 (17%)	68 (15%)	143 (16%)
2	19 (4%)	21 (5%)	40 (4%)
3	5 (1%)	6 (1%)	11 (1%)
4	3 (<1%)	2 (<1%)	5 (<1%)
>4	3 (<1%)	1 (<1%)	4 (<1%)
Number of Type 2 Exacerbations in Last 12 Months#			
n	454	448	902
0	442 (97%)	440 (98%)	882 (98%)
1	12 (3%)	7 (2%)	19 (2%)
2	0	1 (<1%)	1 (<1%)
3	0	0	0
4	0	0	0
>4	0	0	0
Smoking History			
n	454	448	902
Never smoked	453 (>99%)	448 (100%)	901 (>99%)
Current smoker	0	0	0
Former smoker	1 (<1%)	0	1 (<1%)

Source: Table 1.17
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation
[1] Includes data for all exacerbations (Type 1 and Type 2).
^Type 1: Required oral/systemic corticosteroids (not involving hospitalisation).
#Type 2: Required hospitalisation.

- *Current and Past Medical Condition*

A summary of the current medical condition is shown in Table 9. The type and frequency of the conditions were comparable between both groups. For all participants of the ITT population at least one current medical condition was reported. All participants in both groups had asthma. The most often reported conditions apart from asthma in both groups were nasal disorder, reported for 252/454 (56%) participants in the FF/VI group and 242/448 (54%) in the FF group, followed by eczema, reported for 73/454 (16%) participants in the FF/VI group and 63/448 (14%) in the FF group. All other reported conditions were reported in less than 1% in both groups.

Table 9 Summary of Current Medical Conditions Intent-to-Treat (5 to 17 Years Old)

Classification	FF/VI (N=454)	FF (N=448)	Total (N=902)
Any condition	454 (100%)	448 (100%)	902 (100%)
Respiratory Disorder			

Classification	FF/VI (N=454)	FF (N=448)	Total (N=902)
Any condition	454 (100%)	448 (100%)	902 (100%)
Asthma	454 (100%)	448 (100%)	902 (100%)
Nephrology And Urology			
Any condition	2 (<1%)	2 (<1%)	4 (<1%)
Renal Disorder	1 (<1%)	2 (<1%)	3 (<1%)
Urinary Tract Disorder	1 (<1%)	1 (<1%)	2 (<1%)
Endocrine			
Any condition	0	2 (<1%)	2 (<1%)
Thyroid Disorder	0	2 (<1%)	2 (<1%)
Dermatology			
Any condition	74 (16%)	64 (14%)	138 (15%)
Eczema	73 (16%)	63 (14%)	136 (15%)
Skin Infection	1 (<1%)	1 (<1%)	2 (<1%)
Psychological Disorders			
Any condition	3 (<1%)	5 (1%)	8 (<1%)
Learning Disabilities	3 (<1%)	5 (1%)	8 (<1%)
Gastroenterology			
Any condition	4 (<1%)	5 (1%)	9 (<1%)
Coeliac Disease	4 (<1%)	5 (1%)	9 (<1%)
Ear Nose and Throat			
Any condition	252 (56%)	242 (54%)	494 (55%)
Ear Disorder	3 (<1%)	1 (<1%)	4 (<1%)
Nasal Disorder	252 (56%)	242 (54%)	494 (55%)
Bone Disease			
Any condition	2 (<1%)	3 (<1%)	5 (<1%)
Bone Disorder	2 (<1%)	3 (<1%)	5 (<1%)
Haematological Disorder			
Any condition	1 (<1%)	3 (<1%)	4 (<1%)
Anaemia	1 (<1%)	2 (<1%)	3 (<1%)
Haemorrhagic	0	1 (<1%)	1 (<1%)
Cardiac Disorder			
Any condition	5 (1%)	4 (<1%)	9 (<1%)
Arrhythmia	3 (<1%)	1 (<1%)	4 (<1%)
Congenital Cardiac Defect	2 (<1%)	3 (<1%)	5 (<1%)

Source: Table 1.18
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = Number of participants

A total of 198/902 (22%) participants reported any medical conditions in their past, 104/454 (23%) participants in the FF/VI group and 94/448 (21%) in the FF group. The type and frequency of past medical conditions were comparable between both groups. Most often eczema was reported, by 43/454 (9%) participants in the FF/VI group and 43/448 (10%) in the FF group, followed by pneumonia by 44/454 (10%) participants in the FF/VI group and 41/448 (9%) in the FF group, ear

disorder by 9 (2%) participants each in the FF/VI group and the FF group, and nasal disorder by 8 (2%) participants each in the FF/VI group and the FF group.

Screening and Baseline Lung Function Test Results

A summary of all lung function parameters at screening is shown in Table 10 and at run-in (Baseline) in Table 11. There was no difference between the treatment groups in the lung function parameters at screening and at baseline.

Table 10 Summary of Screening Lung Function Test Results Intent-to-Treat Population (5 to 17 Years Old)

Visit 1 (Screening)		FF/VI (N=454)	FF (N=448)	Total (N=902)
Pre-bronchodilator FEV1 (L)	n	444	440	884
	Mean	1.599	1.607	1.603
	SD	0.5877	0.5678	0.5776
	Median	1.468	1.514	1.491
	Min.	0.63	0.57	0.57
	Max.	4.13	4.23	4.23
Pre-bronchodilator FEV1 percent predicted (%)	n	444	440	884
	Mean	73.46	73.82	73.64
	SD	10.745	10.818	10.777
	Median	74.60	74.90	74.70
	Min.	50.1	50.1	50.1
	Max.	99.9	99.3	99.9
Pre-bronchodilator FVC (L)	n	444	440	884
	Mean	2.142	2.163	2.153
	SD	0.8680	0.8415	0.8545
	Median	1.955	2.024	1.984
	Min.	0.70	0.66	0.66
	Max.	6.00	5.88	6.00
Pre-bronchodilator FEV1/FVC (%)	n	444	440	884
	Mean	76.34	75.85	76.09
	SD	10.375	9.777	10.079
	Median	76.85	76.30	76.55
	Min.	48.4	41.9	41.9
	Max.	98.8	98.8	98.8
Post-bronchodilator FEV1(L)	n	446	441	887
	Mean	2.029	2.032	2.031
	SD	0.7336	0.6903	0.7120
	Median	1.879	1.915	1.904
	Min.	0.74	0.68	0.68
	Max.	5.05	4.93	5.05
Post-bronchodilator FEV1 percent predicted (%)	n	446	441	887
	Mean	93.20	93.61	93.41
	SD	13.992	13.096	13.548
	Median	93.10	93.90	93.60
	Min.	58.5	59.4	58.5
	Max.	186.3	148.6	186.3
Percent reversibility FEV1 (%)	n	446	441	887
	Mean	27.81	27.73	27.77
	SD	17.277	15.825	16.562

Visit 1 (Screening)		FF/VI (N=454)	FF (N=448)	Total (N=902)
	Median	22.95	22.80	22.90
	Min.	12.1	3.4	3.4
	Max.	187.6	113.2	187.6
Absolute Reversibility in FEV1 (mL)	n	446	441	887
	Mean	426.9	422.7	424.8
	SD	273.97	232.68	254.15
	Median	360.5	363.0	361.0
	Min.	112	47	47
	Max.	2515	1533	2515
Post-bronchodilator FVC (L)	n	446	441	887
	Mean	2.464	2.460	2.462
	SD	0.9527	0.9090	0.9307
	Median	2.248	2.310	2.283
	Min.	0.83	0.70	0.70
	Max.	6.43	6.27	6.43
Post-bronchodilator FEV1/FVC (%)	n	446	441	887
	Mean	83.41	83.70	83.55
	SD	8.093	7.766	7.929
	Median	84.25	84.60	84.50
	Min.	50.6	39.1	39.1
	Max.	99.9	99.0	99.9

Source: Table 1.20

Abbreviations: FF=Fluticasone furoate; FVC = forced vital capacity; FEV1 = forced expiratory volume in 1 second; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation

Table 11 Summary of Baseline Lung Function Test Results Intent-to-Treat Population (5 to 17 Years Old)

Visit 2 (Run-in)				
		FF/VI (N=454)	FF (N=448)	Total (N=902)
Baseline FEV1 (L)	n	449	446	895
	Mean	1.665	1.645	1.655
	SD	0.6061	0.5800	0.5930
	Median	1.565	1.566	1.565
	Min.	0.61	0.57	0.57
	Max.	4.24	4.03	4.24
Baseline FEV1 percent predicted (%)	n	449	446	895
	Mean	76.63	75.83	76.23
	SD	11.275	11.465	11.371
	Median	77.60	76.75	77.30
	Min.	50.1	51.2	50.1
	Max.	99.9	109.1	109.1

Source: Table 1.20

Abbreviations: FF Fluticasone furoate; FEV1 = forced expiratory volume in 1 second; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation

Summary of Run-In Period ACT Scores

A summary of the ACT score at Screening and Visit 3 (randomisation) in the 5 to 17 year old population is shown in Table 12. The mean (SD) ACT scores at screening and baseline were similar between the treatment groups (15.9 [2.56] for the FF/VI group and 15.6 [2.58] for the FF group). Similarly, at randomisation, the ACT scores were similar between the groups (15.4 [2.44] for the FF/VI group and 15.3 [2.13] for the FF group).

Table 12 Summary of Screening and Randomisation Period ACT Scores Intent-to-Treat Population (5 to 17 Years Old)

		FF/VI (N=454)	FF (N=448)	Total (N=902)
Visit 1 (Screening)	n	116	113	229
	Mean	15.9	15.6	15.7
	SD	2.56	2.58	2.57
	Median	16.0	16.0	16.0
	Min.	0	10	0
	Max.	19	19	19
Visit 3 (Randomisation)	n	116	113	229
	Mean	15.4	15.3	15.4
	SD	2.44	2.13	2.29
	Median	16.0	15.0	16.0
	Min.	9	11	9
	Max.	19	19	19

Source: Table 1.22
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation

Number analysed

Number of participants per analysis populations is shown in Table 13.

Table 13 Summary of Subject's Populations

Population	FF/VI	FF	Total
Total			2402
Randomised	455	451	906
Intent-to-Treat (5 to 17 Years Old)	454 (>99%)	448 (>99%)	902 (>99%)
Intent-to-Treat (5 to 11 Years Old)	337 (74%)	336 (75%)	673 (74%)

Source: Table 1.1
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol

Two participants were randomised twice in error but these subjects are counted only once. These participants received the wrong treatment.

Efficacy results

5 to 11 Years Old Population (ITT Population)

- *Primary Endpoint*

The mean change from baseline to Weeks 1 to 12 was larger for the FF/VI treatment than for the FF treatment as shown in Table 14.

Table 14 Summary of Change from Baseline in AM PEF (L/min) Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 11 Years Old)

Weeks 1 to 12		FF/VI (N=337)	FF (N=336)
Baseline (L/min)	**n**	**336**	**336**
	Mean	196.6	197.9
	SD	63.03	63.33
	Median	193.5	193.0
	Min.	73	71
	Max.	373	429
AM PEF (L/min)	**n**	**337**	**335**
	Mean	208.5	206.9
	SD	60.84	65.56
	Median	205.8	199.4
	Min.	82	76
	Max.	360	576
Change from Baseline (L/min)	**n**	**336**	**335**
	Mean	11.9	8.9
	SD	37.63	35.62
	Median	10.3	5.0
	Min.	-142	-132
	Max.	196	257

Source Table 2.31

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

The LS means change from baseline was 12.0 (Std Err: 1.86) L/min for the FF/VI treatment and 8.8 (STD Err 1.86) L/min for the FF treatment (Table 15). For the primary comparison of the primary endpoint analysis of AM PEF (L/min) over Weeks 1 to 12 on- and post-treatment, using ANCOVA with covariates of baseline, region, sex, age and treatment, the difference between treatment of 3.2 L/min did not reach statistical significance (p=0.228) (Table 15).

Table 15 Statistical Analysis of Change from Baseline in AM PEF (L/min) Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 11 Years Old)

Weeks 1 to -12	FF/VI (N=337)	FF (N=336)
n	336	335
LS Mean	209.3	206.1
LS Mean Change (Std Err)	12.0 (1.86)	8.8 (1.86)
FF/VI vs FF		
Difference	3.2	
95% CI	(-2.0, 8.4)	
p-value	0.228	

Source: Table 2.33

Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error

Note: Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

Additional statistical analysis supported this result. Using the repeated measures analysis method adjusted for baseline, region, sex, age, treatment, week, week by baseline interaction and week by treatment group interaction method, gave a treatment difference of 2.5 L/min (95% CI: -2.7,7.6), and using Jump to Reference Multiple Imputation method also give a treatment difference of 2.5 L/min (95% CI: -2.7,7.6). Including only the on-treatment data, an ANCOVA-based statistical analysis resulted in a treatment difference of 3.1 L/min (95% CI: -2.1, 8.3).

The sensitivity analysis that excluded the data from sites with data concerns was consistent with the primary analysis giving a treatment difference of 3.7 L/min (95% CI -1.6, 8.9).

- *Secondary Endpoints*

– Rescue-Free 24-Hour Periods

Over Weeks 1 to 12, the mean change from baseline for the FF/VI treatment was slightly larger than the mean change from baseline for the FF treatment (Table 16).

Table 16 Summary of Change from Baseline in Percentage of Rescue-Free 24-Hour Periods Over Weeks 1 to 12 On- and Post-Treatment Data -Intent-to-Treat Population (5 to 11 Years Old)

Weeks 1 to 12		FF/VI (N=337)	FF (N=336)
Baseline (%)	**n**	**336**	**336**
	Mean	27.7	27.7
	SD	37.73	37.08
	Median	0.0	0.0
	Min.	0	0
	Max.	100	100
Rescue-Free 24-Hour Periods (%)	**n**	**337**	**335**
	Mean	54.8	53.4
	SD	39.93	39.34
	Median	65.1	59.5
	Min.	0	0
	Max.	100	100
Change from Baseline (%)	**n**	**336**	**335**
	Mean	27.3	25.6
	SD	34.40	37.03
	Median	12.1	13.8
	Min.	-90	-100
	Max.	100	100

Source Table 2.37

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; SD = standard deviation

The LS means change from baseline was similar between both treatments, i.e., 27.1 (Std Err 1.75) for the FF/VI treatment and 25.8 (Std Err 1.74) for the FF treatment. The treatment difference observed using the ANCOVA with covariates of baseline, region, sex, age and treatment was: 1.3 (95% CI: -3.6, 6.2).

Consistent results were seen when using the repeated measures analysis method (1.4 [95% CI: -3.5, 6.3]) and the Jump to Reference Multiple Imputation method (1.4 [95% CI: -3.5, 6.3]). Also, regarding the on-treatment data only the treatment difference observed was 1.2 (95% CI: -3.7, 6.1).

The sensitivity analysis that excluded the data from sites with data concerns was consistent with the primary analysis giving a treatment difference of 1.5 (95% CI: -3.5, 6.4).

– Symptom-Free 24-Hour Periods

The baseline data of the symptom-free 24-hours period were similar for both treatments. The mean (SD) change from baseline over Weeks 1 to 12 in the percentage of symptom-free 24-hour periods was 27.2 (33.16%) for the FF/VI treatment and 25.8 (34.94%) for the FF treatment (Table 17).

Table 17 Summary of Change from Baseline in Percentage of Symptom-Free 24-Hour Periods Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat population (5 to 11 Years Old)

Weeks 1 to 12		FF/VI (N=337)	FF (N=336)
Baseline (%)	**n**	**336**	**336**
	Mean	13.1	13.4
	SD	23.31	25.90
	Median	0.0	0.0
	Min.	0	0
	Max.	100	100
Symptom-Free 24-Hour Periods (%)	**n**	**337**	**335**
	Mean	40.1	39.2
	SD	37.17	35.70
	Median	37.0	37.8
	Min.	0	0
	Max.	100	100
Change from Baseline (%)	**n**	**336**	**335**
	Mean	27.2	25.8
	SD	33.16	34.94
	Median	14.9	13.6
	Min.	-58	-86
	Max.	100	100

Source Table 2.43

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; SD = standard deviation

The treatment difference observed using the ANCOVA with covariates of baseline, region, sex, age and treatment was 1.3% (95% CI: -3.6, 6.3).

Consistent results were seen when using the repeated measures analysis method (1.3 (95% CI: -3.6, 6.3), and the Jump to Reference Multiple Imputation method (1.3 (95% CI: -3.7, 6.3).

- AM FEV1

FEV1 was measured at Visit 2 (Run-in visit) and Visit 4 to Visit 6. The baseline data of the AM FEV1 were similar for both treatments (mean [SD] AM FEV1 for FF/VI was 1.413 [0.3744] L and for FF 1.424 L [0.3998]).

At Visit 4, the changes from baseline in AM FEV1 showed a difference between FF/VI and FF with a mean (SD) change from baseline of 0.237 (0.2682) L for the FF/VI treatment and 0.187 (0.2758) L for the FF treatment (Table 18).

At Visit 5 and 6, the difference between the changes from baseline in AM FEV1 between FF/VI and FF treatments were smaller (Table 18).

Table 18 Summary of Change from Baseline in Morning FEV1 (L) On- and Post-Treatment Data - Intent-to-Treat (5 to 11 Years Old) Population

Visit 2 (Run-in)		FF/VI (N=337)	FF (N=336)
Baseline FEV1 (L)	n	332	334
	Mean	1.413	1.424
	SD	0.3744	0.3998
	Median	1.369	1.387
	Min.	0.61	0.57
	Max.	2.46	2.51
Visit 4 (Week 4)			
FEV1 (L)	n	308	316
	Mean	1.652	1.605
	SD	0.4660	0.4548
	Median	1.603	1.584
	Min.	0.68	0.52
	Max.	3.27	3.02
Change from Baseline in FEV1 (L)	**n**	**306**	**315**
	Mean	0.237	0.187
	SD	0.2682	0.2758
	Median	0.203	0.122
	Min.	-0.62	-0.48
	Max.	1.84	1.23
Visit 5 (Week 8)			
FEV1 (L)	n	254	257
	Mean	1.662	1.617
	SD	0.4686	0.4920
	Median	1.639	1.603
	Min.	0.49	0.60
	Max.	3.19	4.44
Change from Baseline in FEV1 (L)	n	252	255
	Mean	0.260	0.231
	SD	0.3075	0.3306
	Median	0.232	0.166
	Min.	-0.79	-0.69
	Max.	1.36	2.58
Visit 6 (Week 12)			
FEV1 (L)	n	310	306
	Mean	1.679	1.666
	SD	0.4886	0.4833
	Median	1.643	1.619
	Min.	0.69	0.53
	Max.	3.16	3.57
Change from Baseline in FEV1 (L)	n	307	304
	Mean	0.263	0.245
	SD	0.3029	0.3192
	Median	0.218	0.193
	Min.	-0.63	-0.44
	Max.	1.49	1.71

Source Table 2.47
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; SD = standard deviation

At Visit 4 (Week 4), the difference between FF/VI treatment and FF treatment, using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visitby-baseline interaction and visit-by-treatment group interaction, was 0.060 L (95% CI: [0.020, 0.099]) (Table 19).

At Visit 5 (Week 8), the difference between treatments using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment group interaction, decreased to 0.037 L (95% CI: (-0.010, 0.084) (Table 19).

At Visit 6 (Week 12), the difference between treatments using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment group interaction, was 0.028 L (95% CI: -0.017, 0.073) (Table 19).

Table 19 Statistical Analysis of Change from Baseline in Morning FEV1 (L) On- and Post-Treatment Data - Intent-to-Treat (Population 5 to 11 Years Old)

	FF/VI (N=337)	FF (N=336)
Visit 4 (Week 4)		
n [1]	325	327
n [2]	306	315
LS Mean	1.653	1.594
LS Mean Change (Std Err)	0.238 (0.0143)	0.178 (0.0142)
FF/VI vs FF		
Difference	0.060	
95% CI	(0.020, 0.099)	
p-value	0.003	
Visit 5 (Week 8)		
n [1]	325	327
n [2]	252	255
LS Mean	1.670	1.633
LS Mean Change (Std Err)	0.255 (0.0168)	0.218 (0.0168)
FF/VI vs FF		
Difference	0.037	
95% CI	(-0.010, 0.084)	
p-value	0.123	
Visit 6 (Week 12)		
n [1]	325	327
n [2]	307	304
LS Mean	1.678	1.650
LS Mean Change (Std Err)	0.263 (0.0162)	0.235 (0.0162)
FF/VI vs FF		
Difference	0.028	
95% CI	(-0.017, 0.073)	
p-value	0.226	

Source: Table 2.48.
Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error
Note: Repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment group interaction.
[1] Number of subjects with analysable data for one or more visits.
[2] Number of subjects with analysable data on the given visit.

- ACQ-5

The mean (SD) values of the ACQ-5 score at baseline were similar in both treatments (mean [SD] score in FF/VI was 1.91 [0.808], in FF was 1.83 [0.784]). The improvement in asthma control based on the results of ACQ, was similar for both treatments. At Visit 6 (Week 12), the changes from baseline were slightly larger for the FF/VI treatment (mean [SD] change -1.15 [0.930]) than for the FF treatment (mean [SD] change -1.00 [0.865]), and also at Visit 9 (Week 24), for the FF/VI treatment (mean change [SD] -1.25 [0.944]) and for the FF treatment (mean [SD] change -1.13 [0.975]) (Table 20).

Table 20 Summary of Change from Baseline in ACQ-5 Score On- and Post Treatment Data - Intent-to-Treat Population (5 to 11 Years Old)

Visit 3 (Randomisation)		FF/VI (N=337)	FF (N=336)
Baseline ACQ-5 Score	n	326	330
	Mean	1.91	1.83
	SD	0.808	0.784
	Median	2.00	1.80
	Min.	0.0	0.0
	Max.	4.0	4.8
Visit 6 (Week 12)			
ACQ-5 Score	n	325	321
	Mean	0.77	0.82
	SD	0.724	0.715
	Median	0.60	0.80
	Min.	0.0	0.0
	Max.	3.0	3.6
Change from Baseline in ACQ-5 Score	n	315	317
	Mean	-1.15	-1.00
	SD	0.930	0.865
	Median	-1.20	-1.00
	Min.	-4.0	-3.2
	Max.	2.4	1.8
Visit 9 (Week 24)			
ACQ-5 Score	n	299	289
	Mean	0.66	0.69
	SD	0.683	0.752
	Median	0.40	0.40
	Min.	0.0	0.0
	Max.	3.2	3.4
Change from Baseline in ACQ-5 Score	n	291	286
	Mean	-1.25	-1.13
	SD	0.944	0.975
	Median	-1.20	-1.20
	Min.	-3.8	-4.0
	Max.	1.4	2.2

Source: Table 2.50

Abbreviations: ACQ = Asthma control questionnaire; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

The treatment difference at Visit 9 (Week 24), using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment interaction analysis method, was -0.02 (95% CI: -0.13, 0.09).

- Weighted Mean FEV1 (0 to 4 hours) for 5 to 11 years old population

The mean (SD) change from baseline to Visit 6 (Week 12) was larger for the FF/VI treatment than for the FF treatment, of 0.340 (SD 0.2963) L for the FF/VI treatment and 0.286 (SD: 0.3091) L for the FF treatment (Table 21).

Table 21 Summary of Weighted Mean FEV1 (0 to 4 hours) (L) at Week 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 11 Years Old)

Visit 2 (Run-in)		FF/VI (N=337)	FF (N=336)
Baseline FEV1 (L)	**n**	**332**	**334**
	Mean	1.413	1.424
	SD	0.3744	0.3998
	Median	1.369	1.387
	Min.	0.61	0.57
	Max.	2.46	2.51
Visit 6 (Week 12)			
Weighted Mean FEV1 (L)	n	289	291

Visit 2 (Run-in)		FF/VI (N=337)	FF (N=336)
	Mean	1.762	1.711
	SD	0.4977	0.4817
	Median	1.735	1.657
	Min.	0.71	0.69
	Max.	3.23	3.60
Change from Baseline in Weighted Mean FEV1 (L)	n	286	289
	Mean	0.340	0.286
	SD	0.2963	0.3091
	Median	0.298	0.236
	Min.	-0.26	-0.44
	Max.	1.80	1.73

Source: Table 2.53

Abbreviations: FEV_1 = forced expiratory volume in 1 second; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

Using the ANCOVA method for statistical analysis of weighted mean FEV1 (0 to 4 hours) at Week 12 on- and post-treatment, with covariates of baseline, region, sex, age and treatment, a treatment difference of 0.073 L (95% CI: 0.028, 0.118) was observed (Table 22).

Table 22 Statistical Analysis of Weighted Mean FEV1 (0 to 4 hours) (L) at Week 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 11 Years Old)

Visit 6 (Week 12)	FF/VI (N=337)	FF (N=336)
n	286	289
LS Mean	1.772	1.700
LS Mean Change (Std Err)	0.349 (0.0161)	0.276 (0.0160)
FF/VI vs FF		
Difference	0.073	
95% CI	(0.028, 0.118)	
p-value	0.002	

Source: Table 2.54

Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error

Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

- Exacerbations

Any asthma exacerbation was reported for 27/337 (8%) participants in the FF/VI group and for 32/336 (10%) participants of the FF group on- and post-treatment. Most of these participants in both groups experienced 1 asthma exacerbation in total. Two asthma exacerbations were reported for 2 (<1%) participants in the FF/VI group and for 5 (1%) participants in the FF group. None of the participants in either group experienced more than 2 asthma exacerbations on- and post-treatment.

In the FF group only, 1 participant permanently discontinued the study intervention due to an asthma exacerbation.

All participants in both treatment groups who had an asthma exacerbation received treatment with systemic or oral corticosteroids. One participant in the FF/VI group and 2 (<1%) participants in the FF group were hospitalised, and none were intubated due to an asthma exacerbation. Three participants in the FF/VI group and one in the FF group were reported as visiting ER due to their asthma exacerbation.

- *Other Endpoints: PM PEF*

The baseline data of PM PEF were similar for both treatments, the mean (SD) AM PEF of the FF/VI treatment was 205.2 (62.70) L/min, for the FF treatment 208.7 (65.62) L/min (Table 23).

Table 23 Summary of Change from Baseline in PM PEF (L/min) Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 11 Years Old)

Weeks 1 to 12		FF/VI (N=337)	FF (N=336)
Baseline (L/min)	n	336	336
	Mean	205.2	208.7
	SD	62.70	65.62
	Median	204.3	203.4
	Min.	70	83
	Max.	362	499
PM PEF (L/min)	n	337	335
	Mean	219.2	216.6
	SD	60.98	66.79
	Median	215.7	209.5
	Min.	84	81
	Max.	376	578
Change from Baseline (L/min)	n	336	335
	Mean	14.1	7.7
	SD	35.79	36.10
	Median	12.4	2.8
	Min.	-132	-139
	Max.	201	279

Source Table 2.58
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

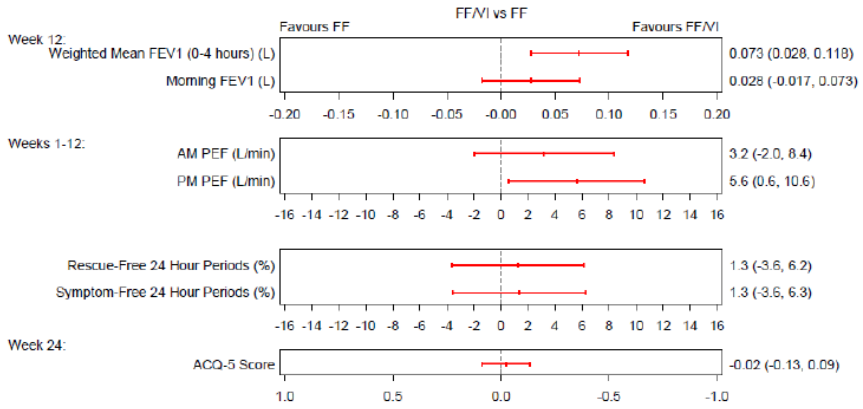
The change from baseline of the PM PEF, measured every evening over Week 1 to 12, was larger in the FF/VI treatment than in the FF treatment. The LS mean change (Std Err) was 13.7 (1.80) L/min for the FF/VI treatment and 8.1 (1.80) L/min for the FF treatment. The ANCOVA- based statistical analysis with covariates of baseline, region, sex, age and treatment showed a treatment difference of 5.6 L/min (95% CI: 0.6, 10.6).

Additional statistical analysis using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, week, week by baseline method and Jump to Reference Multiple Imputation method were consistent with the main analysis.

- *Overview of Treatment Differences for Primary, Secondary and Other Efficacy Endpoints*

Figure 4 gives an overview of the results of the primary, secondary and other endpoints.

Figure 4 Adjusted Treatment Differences for Primary, Secondary and Other Efficacy Endpoints On- and Post-Treatment Data – Intent-to-Treat (5 to 11 Years Old)



Source: Figure 2.20.
Abbreviations: ACQ = Asthma control questionnaire; AM PEF = morning peak expiratory flow; FEV_1 = forced expiratory volume in 1 minute; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol.

5 to 17 Years Old Population (ITT Population)

Primary Endpoint: Weighted mean FEV1 (0 to 4 hours) (L) at Week 12 for 5 to 17 years population

The change from baseline to Visit 6 (Week 12) was larger for the FF/VI treatment than for the FF treatment, shown by a least square (LS) mean change from baseline of 0.406 (Std Err: 0.0165) L for the FF/VI treatment and 0.323 (Std Err: 0.0164) L for the FF treatment (Table 24).

For the primary comparison of the primary endpoint analysis of weighted mean FEV1 (0 to 4 hours) at Visit 6 (Week 12) on- and post-treatment, using ANCOVA with covariates of baseline, region, sex, age and treatment, a statistically significant difference of 0.083 L (95% CI: 0.037, 0.129) between treatments was observed (p<0.001).

Table 24 Statistical Analysis of Weighted Mean FEV1 (0 to 4 hours) (L) at Week 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

Visit 6 (Week 12)	FF/VI (N=454)	FF (N=448)
n	394	397
LS Mean	2.081	1.999
LS Mean Change (Std Err)	0.406 (0.0165)	0.323 (0.0164)
FF/VI vs FF		
Difference	0.083	
95% CI	(0.037, 0.129)	
p-value	<0.001	

Source: Table 2.2
Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error
Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment

Analyses of weighted Mean FEV1 (0 to 4 hours) at Visit 6 (Week 12) using the Jump to Reference (J2R) Multiple Imputation Method and using on-treatment data only showed results consistent with the primary analysis giving treatment differences of 0.074 L (95% CI: 0.029, 0.119) and 0.081 L (95% CI: 0.036, 0.127) respectively.

Results of the statistical analysis of weighted mean FEV1 (0 to 4 hours) at Visit 6 (Week 12) using the tipping point multiple imputation method, showed statistically significant differences for all possibilities.

The sensitivity analysis that excluded the data from sites with data concerns was consistent with the primary analysis giving a treatment difference of 0.080 L (95% CI: 0.034, 0.127).

Secondary Endpoints

- *Rescue-Free 24-Hour Periods*

The baseline in percentage of rescue-free 24-hour periods was similar between both treatments. The mean change from baseline in the percentage of rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period was similar for both treatments (mean [SD] was 25.9 [33.78] for FF/VI treatment and 25.8 [36.55] for FF treatment) (Table 25).

Table 25 Summary of Change from Baseline in Percentage of Rescue-Free 24-Hour Periods Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

Weeks 1 to 12		FF/VI (N=454)	FF (N=448)
Baseline (%)	**n**	**453**	**448**
	Mean	28.7	27.7
	SD	37.97	36.66
	Median	0.0	0.0
	Min.	0	0
	Max.	100	100
Rescue-Free 24-Hour Periods (%)	**n**	**454**	**447**
	Mean	54.5	53.6
	SD	39.98	39.42
	Median	64.2	60.6
	Min.	0	0
	Max.	100	100
Change from Baseline (%)	**n**	**453**	**447**
	Mean	25.9	25.8
	SD	33.78	36.55
	Median	12.0	14.3
	Min.	-90	-100
	Max.	100	100

Source: Table 2.12
Abbreviations; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation

The difference between the treatments in percentage of rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period was -0.3 (95% CI: -4.5, 3.8) (using an ANCOVA with covariates of baseline, region, sex, age and treatment).

These findings are supported by the statistical analysis using the repeated measures method averaged over Weeks 1 to 12 (difference: 0.0 [95% CI: -4.1, 4.2]), and the Jump to Reference method (difference: 0.0 [95% CI: -4.1, 4.2]).

- *Symptom-Free 24-Hour Periods*

The baseline data of the symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period were similar for both treatments. The mean (SD) change from baseline percentage of symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period was also similar between both treatments; FF/VI: 25.7 (32.77) and FF: 24.6 (34.62) (Table 26).

The ANCOVA-based statistical analysis with covariates of baseline, region, sex, age and treatment did not show any difference in symptom-free 24-hour periods between both treatments (difference: 0.0

[95% CI: -4.2, 4.1]). Additional statistical analyses supported the results of the ANCOVA, repeated measures Averaged Over Weeks 1 to 12 and Jump to Reference (J2R) Multiple Imputation Method, difference: 0.4 (95% CI: -3.8, 4.6) in both cases.

Table 26 Summary of Change from Baseline in Percentage of Symptom-Free 24-Hour Periods Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

Weeks 1 to 12		FF/VI (N=454)	FF (N=448)
Baseline (%)	**n**	**453**	**448**
	Mean	13.0	14.5
	SD	23.42	26.47
	Median	0.0	0.0
	Min.	0	0
	Max.	100	100
Symptom-Free 24-Hour Periods (%)	**n**	**454**	**447**
	Mean	38.6	39.1
	SD	36.98	35.94
Weeks 1 to 12		**FF/VI (N=454)**	**FF (N=448)**
	Median	32.7	34.7
	Min.	0	0
	Max.	100	100
Change from Baseline (%)	**n**	**453**	**447**
	Mean	25.7	24.6
	SD	32.77	34.62
	Median	13.9	12.2
	Min.	-58	-86
	Max.	100	100

Source: Table 2.16

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation

- AM FEV1

FEV1 was measured at Visit 2 (Run-in visit) and Visit 4 to 6. The baseline data of the AM FEV1 were similar for both treatments (mean AM FEV1 for FF/VI was 1.665 L and for FF 1.645 L).

At Visit 4 (Week 4), the changes from baseline in AM FEV1 showed a difference between FF/VI and FF with a mean (SD) change from baseline of 0.274 (0.3459) L for the FF/VI treatment and 0.210 (0.3202) L for the FF treatment. (Table 27).

At Visit 5 and 6 (after 8 and 12 weeks), the difference between the changes from baseline in AM FEV1 between FF/VI and FF treatments was smaller than at Visit 4 (Week 4) (Table 27).

Table 27 Summary of Change from Baseline in Morning FEV1 (L) On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

Table 40 Summary of Change from Baseline in Morning FEV1 (L) On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

		FF/VI (N=454)	FF (N=448)
Visit 2 (Run-in)			
Baseline FEV_1 (L)	n	449	446
	Mean	1.665	1.645
	SD	0.6061	0.5800
	Median	1.565	1.566
	Min.	0.61	0.57
	Max.	4.24	4.03
Visit 4 (Week 4)			
Change from Baseline in FEV_1 (L)	n	419	423
	Mean	0.274	0.210
	SD	0.3459	0.3202
	Median	0.222	0.139
	Min.	-1.28	-1.16
	Max.	2.85	1.51
Visit 5 (Week 8)			
Change from Baseline in FEV_1 (L)	n	359	361
	Mean	0.314	0.274
	SD	0.3763	0.3693
	Median	0.274	0.208
	Min.	-1.23	-0.69
	Max.	2.80	2.58
Visit 6 (Week 12)			
Change from Baseline in FEV_1 (L)	n	417	413
	Mean	0.312	0.275
	SD	0.3865	0.3512
	Median	0.254	0.217
	Min.	-1.08	-0.47
	Max.	2.85	2.04

Source: Table 2.20

Abbreviations: FEV1 = forced expiratory volume in 1 second; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n= subset of participants; SD = standard deviation

The difference in AM FEV1 between the FF/VI treatment and the FF treatment, using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit by-baseline interaction and visit-by-treatment group interaction, was 0.035 L (95% CI: -0.010, 0.080) at Visit 6 (Week 12). (Table 28).

Table 28 Statistical Analysis of Change from Baseline in Morning FEV1 (L) On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

	FF/VI (N=454)	FF (N=448)
Visit 4 (Week 4)		
n [1]	442	438
n [2]	419	423
LS Mean	1.929	1.863
LS Mean Change (Std Err)	0.273 (0.0148)	0.207 (0.0148)
FF/VI vs FF		
Difference	0.066	
95% CI	(0.025, 0.107)	
p-value	0.002	
Visit 5 (Week 8)		
n [1]	442	438
n [2]	359	361
LS Mean	1.952	1.916
LS Mean Change (Std Err)	0.296 (0.0163)	0.260 (0.0164)
FF/VI vs FF		
Difference	0.036	
95% CI	(-0.009, 0.082)	
p-value	0.120	
Visit 6 (Week 12)		
n [1]	442	438
n [2]	417	413
LS Mean	1.962	1.926
LS Mean Change (Std Err)	0.306 (0.0161)	0.271 (0.0162)
FF/VI vs FF		
Difference	0.035	
95% CI	(-0.010, 0.080)	
p-value	0.124	

Source: Table 2.21
Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error
Note: Repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment group interaction.
[1] Number of subjects with analysable data for one or more visits.
[2] Number of subjects with analysable data on the given visit.

- AM PEF

At baseline, the mean AM PEF data were similar in FF/VI treatment and FF treatment (FF/VI 226.7 L/min, FF 224.1 L/min). Over the 12-week treatment period, the mean changes from baseline were larger for the FF/VI treatment than for the FF treatment (FF/VI 14.9 L/min, FF 9.3 L/min) (Table 29).

Table 29 Summary of Change from Baseline in AM PEF (L/min) Over Weeks 112 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

Weeks 1 to 12		FF/VI (N=454)	FF (N=448)
Baseline (L/min)	**n**	**453**	**448**
	Mean	226.7	224.1
	SD	87.94	88.91
	Median	214.3	208.0
	Min.	73	71

Weeks 1 to 12		FF/VI (N=454)	FF (N=448)
	Max.	536	639
AM PEF (L/min)	**n**	**454**	**447**
	Mean	241.5	233.6
	SD	90.82	87.03
	Median	225.5	218.3
	Min.	82	76
	Max.	558	639
Change from Baseline (L/min)	**n**	**453**	**447**
	Mean	14.9	9.3
	SD	39.94	38.95
	Median	11.7	5.0
	Min.	-142	-132
	Max.	213	257

Source: Table 2.8
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

The ANCOVA-based statistical analysis including baseline, region, sex, age and treatment as covariates showed a treatment difference over Weeks 1 to 12 of 6.2 L/min (95% CI: 1.4, 10.9) (Table 30).

Additional statistical analysis provided results consistent with that of the primary ANCOVA analysis for Weeks 1 to 12, repeated measures Averaged Over Weeks 1 to 12 and Jump to Reference (J2R) Multiple Imputation Method.

Table 30 Statistical Analysis of Change from Baseline in AM PEF (L/min) Over Weeks 1 to 12 On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

Weeks 1 to 12	FF/VI (N=454)	FF (N=448)
n	453	447
LS Mean	240.7	234.5
LS Mean Change (Std Err)	15.2 (1.70)	9.0 (1.71)
FF/VI vs FF		
Difference	6.2	
95% CI	(1.4, 10.9)	
p-value	0.011	

Source: Table 2.9
Abbreviations: C. I. = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; LS = least square; N = Number of participants; n= subset of participants; Std Err = standard error
Note: Analysis performed using ANCOVA with covariates of baseline, region, sex, age and treatment.

An additional repeated measures analysis was used to provide an estimate of the treatment effect at Visit 6 (Week 12) using an alternative missing data rule. This showed a treatment difference at Visit 6 (Week 12) of 4.4 L/min (95% CI: -2.2, 11.1).

- ACQ-5

ACQ-5 was assessed at Visit 3 (randomisation), Visit 6 (Week 12) and Visit 9 (Week 24). The mean values of the ACQ-5 score at baseline were similar in both treatments (mean score in FF/VI was 1.90, in FF was 1.82). The improvement in asthma control based on the results of ACQ, was similar for both treatments. At Visit 6 (Week 12), the changes from baseline were slightly larger for the FF/VI treatment (mean change -1.08) than for the FF treatment (mean change -0.96), and at Visit 9 (Week 24), the differences in the changes from baseline of the ACQ-5 score were similar (Table 31).

Table 31 Summary of Change from Baseline in ACQ-5 Score On- and Post-Treatment Data - Intent-to-Treat Population (5 to 17 Years Old)

		FF/VI (N=454)	FF (N=448)
Visit 3 (Randomisation)			
Baseline ACQ-5 Score	n	438	437
	Mean	1.90	1.82
	SD	0.820	0.789
	Median	2.00	1.80
	Min.	0.0	0.0
	Max.	4.2	4.8
Visit 6 (Week 12)			
Change from Baseline in ACQ-5 Score	n	420	422
	Mean	-1.08	-0.96
	SD	0.923	0.863
	Median	-1.00	-0.80
	Min.	-4.0	-3.2
	Max.	2.4	1.8
Visit 9 (Week 24)			
Change from Baseline in ACQ-5 Score	n	385	378
	Mean	-1.21	-1.09
	SD	0.935	0.976
	Median	-1.20	-1.00
	Min.	-3.8	-4.0
	Max.	1.4	2.2

Source: Table 2.23

Abbreviations: ACQ = Asthma control questionnaire; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

Using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, visit, visit-by-baseline interaction and visit-by-treatment interaction analysis method, the treatment difference at Week 24 was -0.01 (95% CI: -0.10, 0.09).

- Exacerbations

Any asthma exacerbation was reported for 33/454 (7%) participants in the FF/VI group and for 38/448 (8%) participants of the FF group on- and post-treatment. Most of these participants with asthma exacerbations in both groups experienced 1 asthma exacerbation in total; 2 asthma exacerbation were reported for 2/454 (<1%) participants in the FF/VI group and for 6/448 (1%) participants in the FF group. None of the participants in either group experienced more than 2 asthma exacerbations on- and post-treatment.

In each group, 1 participant permanently discontinued the study intervention due to an asthma exacerbation; all participants in both groups received systemic or oral corticosteroids for treatment; 2 (<1%) participants in both groups each were hospitalised and none were intubated due to an asthma exacerbation. None of the participants in either group were in an intensive care unit or in a general ward on- and post-treatment, and none were intubated due to an asthma exacerbation.

- *Other Endpoints: PM PEF*

The baseline data of PM PEF were similar for both treatments, the mean AM PEF of the FF/VI treatment was 236.4 L/min, for the FF treatment 235.3 L/min.

Table 32 Summary of Change from Baseline in PM PEF (L/min) Over Weeks 112 On- and Post-Treatment Data - Intent-to-Treat population (5 to 17 Years Old)

Weeks 1 to 12		FF/VI (N=454)	FF (N=448)
Baseline (L/min)	n	453	448
	Mean	236.4	235.3
	SD	89.88	89.51
	Median	224.3	221.4
	Min.	70	83
	Max.	554	636
Week 12 PM PEF (L/min)	n	454	447
	Mean	253.2	244.0
	SD	92.26	88.08
	Median	236.7	232.9
	Min.	84	81
	Max.	572	638
Change from Baseline (L/min)	n	453	447
	Mean	16.9	8.4
	SD	39.88	38.89
	Median	14.5	2.6
	Min.	-132	-139
	Max.	215	279

Source Table 2.27
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Max = maximum; Min = minimum; N = Number of participants; n = subset of participants; PEF = peak expiratory flow; SD = standard deviation

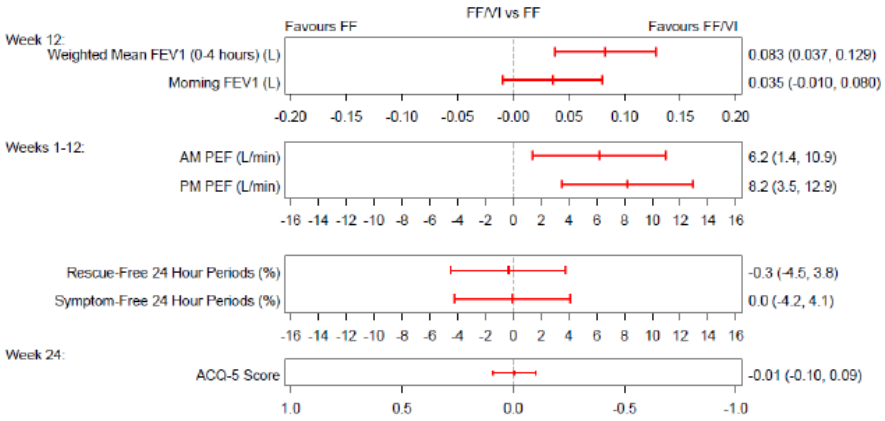
The change from baseline of the PM PEF, measured every evening over Weeks 1 to 12, was larger in the FF/VI treatment than in the FF treatment (Table 32). The LS mean change (Std Err) was 16.8 (1.69) L/min for the FF/VI treatment and 8.6 (1.70) L/min for the FF treatment. The ANCOVA-based statistical analysis with covariates of baseline, region, sex, age and treatment showed a treatment difference of 8.2 L/min (95% CI: 3.5, 12.9).

Additional statistical analysis using the repeated measures analysis adjusted for baseline, region, sex, age, treatment, week, week by baseline method and Jump to Reference Multiple Imputation method were consistent with the main analysis.

- *Overview of Treatment Differences for Primary, Secondary and Other Efficacy Endpoints*

Figure 5 gives an overview of the results of the primary, secondary and other endpoints.

Figure 5 Adjusted Treatment Differences for Primary, Secondary and Other Efficacy Endpoints On- and Post-Treatment Data – Intent-to-Treat Population (5 to 17 Years Old)



Source: Figure 2.10.
Abbreviations: ACQ = Asthma control questionnaire; AM PEF = morning peak expiratory flow; FEV1 = forced expiratory volume in 1 minute; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol.

Safety results

5 to 17 Years Old Population (ITT Population)

- *Adverse Events*

– Overview of Adverse Events

An overview of the AEs occurring during on-treatment is shown in Table 33. Overall, 181/454 (40%) participants in the FF/VI group and 163/448 (36%) participants in the FF group experienced at least 1 AE. In 6 (1%) participants of the FF/VI group and 4 (<1%) participants of the FF group, the investigator considered the AEs to be drug-related. In 3 (<1%) participants of the FF/VI group and 1 participant of the FF group, at least 1 AE led to permanent discontinuation from study intervention or to premature withdrawal from the study. In both groups, at least 1 SAE was reported for 5 (1%) participants in each group. No drug-related SAE, no fatal AE and no drug-related fatal AE were reported.

Table 33 Adverse Event Overview Intent-to-Treat Population (5 to17 Years Old)

On-Treatment	FF/VI (N=454)	FF (N=448)
Any Adverse Event	181 (40%)	163 (36%)
Drug-Related Adverse Events	6 (1%)	4 (<1%)
Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from the Study	3 (<1%)	1 (<1%)
Any Serious Adverse Event	5 (1%)	5 (1%)
Drug-Related Serious Adverse Events	0	0
Fatal Adverse Events	0	0
Drug-Related Fatal Adverse Events	0	0

Source: Table 3.1
Abbreviations: Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants

– Adverse Events by System Organ Class and Preferred Term

In the FF/VI group, the most commonly reported AEs were nasopharyngitis in 47/454 (10%) participants, upper respiratory tract infection in 32/454 (7%) participants, allergic rhinitis in 19/454 (4%) participants, headache in 14/454 (3%) participants, rhinitis in 15/454 (3%) participants, and viral upper respiratory tract infection in 13/454 (3%) participants.

In the FF group, the most commonly reported AEs were nasopharyngitis in 34/448 (8%) participants, upper respiratory tract infection in 25/448 (6%) participants, allergic rhinitis in 6/448 (1%) participants, headache in 9/448 (2%) participants, rhinitis in 6/448 (1%) participants, and viral upper respiratory tract infection in 2/448 (<1%) participants.

– Treatment-Related Adverse Events

Overall, 6/454 (1%) participants in the FF/VI group and 4/448 (<1%) participants in the FF group experienced at least 1 AE, which was considered by the investigator to be drug-related.

The majority of the drug-related AEs occurring were reported at maximum for 1 participant per group, only dysphonia was reported for 2/448 (<1%) participants in the FF group and for 1/454 participant in the FF/VI group.

– Post-Treatment Adverse Events

Only a few participants in both groups experienced at least 1 AE after the treatment period.

In the FF/VI group (n=454), for 2 (<1%) participants, nasopharyngitis was reported and for 1 participant each pneumonia, varicella infection, and stomatitis; in the FF group (n=448), a COVID-19 infection, an upper respiratory infection and extrasystoles were reported by a total of 2 (<1%) participants, of which extrasystoles and upper respiratory infection were reported by 1 participant.

– Adverse Events and COVID-19 Pandemic

All COVID-19 infections occurred in the group of the 5 to 11 years Old.

- *Deaths*

No death occurred during the study (Table 33).

- *Other Serious Adverse Events*

The number of participants experiencing an SAE was low and similar in each treatment group. Overall, 5/454 (1%) participants in the FF/VI group and 5/448 (1%) participants in the FF group experienced an SAE (Table 34).

Table 34 Summary of On-Treatment Serious Adverse Events Intent-to-Treat Population (5 to 17 Years Old)

System Organ Class Preferred Term	FF/VI (N=454)	FF (N=448)
Any event	5 (1%)	5 (1%)
Respiratory, thoracic and mediastinal disorders		
Any event	2 (<1%)	3 (<1%)
Asthma	2 (<1%)	3 (<1%)
Infections and infestations		
Any event	2 (<1%)	1 (<1%)
Appendicitis	1 (<1%)	0
Gastroenteritis rotavirus	1 (<1%)	0
Helicobacter gastritis	0	1 (<1%)
Sinusitis	0	1 (<1%)
Gastrointestinal disorders		
Any event	1 (<1%)	0
Intestinal obstruction	1 (<1%)	0

Source: Table 3.9
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants

- *Treatment-Related Serious Events*

None of the SAEs reported were considered by the investigator to be drug-related.

- *Other Significant Adverse Events*

– Adverse Events Leading to Permanent Discontinuation

For 3/454 (<1%) participants in the FF/VI group, the AEs of intestinal obstruction, lethargy and insomnia led to permanent discontinuation, and for 1 participant in the FF group the AE of dysphonia led to discontinuation.

– Adverse Events of Special Interest

A summary of all AEs of special interest (AESIs) is shown in Table 35. Slightly more participants (44/454 [10%]) participants in the FFV/VI group experienced at least 1 AESI than in the FF group (37/448 [8%] participants).

The majority of AESIs reported were similar in type and frequency in both groups, with the exception of hypersensitivity events and glucose events, which were reported in more participants in the FF/VI group. Of the hypersensitivity events, allergic rhinitis was the most commonly reported for 19/454 (4%) participants in the FF/VI group and for 6 (1%) participants in the FF/448 group. Effects on glucose were reported for 3 (<1%) participants in the FF/VI group and none in the FF group. The set of symptoms of effects on glucose, reported in the FF/VI group comprised increased blood glucose, hyperglycaemia, and weight decreased.

Table 35 Summary of On- and Post-Treatment Adverse Events of Special Interest Intent-to-Treat Population (5 to 17 Years Old)

Special Interest Term Subgroup Preferred Term	FF/VI (N=454)	FF (N=448)
Any event	44 (10%)	37 (8%)
Hypersensitivity		
Any event	23 (5%)	13 (3%)
Rhinitis allergic	19 (4%)	6 (1%)
Conjunctivitis allergic	2 (<1%)	2 (<1%)
Eczema	1 (<1%)	2 (<1%)
Urticaria	1 (<1%)	1 (<1%)
Angioedema	1 (<1%)	0
Dermatitis allergic	0	1 (<1%)
Dermatitis atopic	1 (<1%)	0
Multiple allergies	0	1 (<1%)
LRTI excluding infective pneumonia (SMQ)		
Any event	8 (2%)	8 (2%)
Bronchitis	6 (1%)	8 (2%)
Lower respiratory tract infection	2 (<1%)	0
Tracheitis	1 (<1%)	0
Asthma/bronchospasm [1]		
Any event	4 (<1%)	5 (1%)
Asthma	4 (<1%)	5 (1%)
Decreased bone mineral density and associated fractures		
Any event	4 (<1%)	1 (<1%)
Radius fracture	2 (<1%)	0
Clavicle fracture	0	1 (<1%)
Foot fracture	1 (<1%)	0
Wrist fracture	1 (<1%)	0
Local steroid effects		
Any event	4 (<1%)	4 (<1%)
Dysphonia	1 (<1%)	2 (<1%)
Oropharyngeal pain	1 (<1%)	2 (<1%)
Oral candidiasis	1 (<1%)	1 (<1%)
Stomatitis	1 (<1%)	0
Infective pneumonia [1]		
Any event	1 (<1%)	4 (<1%)
Pneumonia	1 (<1%)	3 (<1%)
Pneumonia mycoplasma	0	1 (<1%)
Cardiovascular effects		
Any event	1 (<1%)	3 (<1%)
Cardiac arrhythmia		
Any event	1 (<1%)	3 (<1%)
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)
Electrocardiogram PR prolongation	0	1 (<1%)
Extrasystoles	0	1 (<1%)
Effects on glucose [1]		
Any event	3 (<1%)	0
Blood glucose increased	1 (<1%)	0
Hyperglycaemia	1 (<1%)	0
Weight decreased	1 (<1%)	0

Source: Table 3.13
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants;
[1] This special interest term or subgroup was defined using Special MedDRA Queries.

– Serious Adverse Events of Special Interest

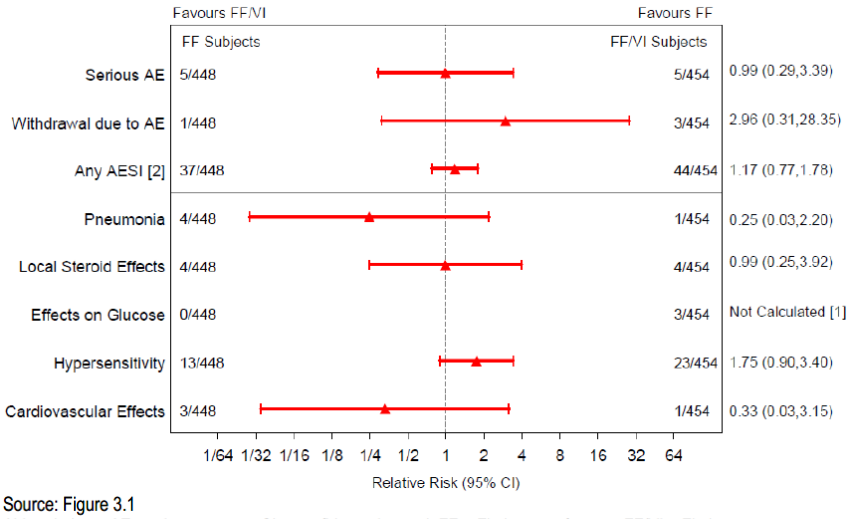
Serious AESIs comprised 2/454 cases of asthma in the FF/VI group and 3/448 cases of asthma in the FF group.

All serious AESIs in the FF group were of severe intensity and considered by the investigator not to be drug-related.

– Summary of Risks for FF/VI Versus FF Treatment

In Figure 6, the risks for FF/VI treatment and FF treatment with regard to safety are presented.

Figure 6 Summary of Risks for FF/VI vs. FF Intent-to-Treat population (5 to 17 Years Old)



Source: Figure 3.1
Abbreviations: AE = adverse event; CI = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol;
Note: W/D due to AE includes events leading to permanent discontinuation of study drug or withdrawal from the study.
[1]: Not calculated if either or both treatment groups have no events
[2]: 'Tremor' not presented as there were no events in this study

- *Clinical Laboratory Evaluations*

– Evaluation of Fasting Blood Glucose Pre- and Post-Treatment

Fasting blood glucose was assessed at Screening and at Visit 9. The summary data are shown in Table 36. For both treatments, a slight decrease of the fasting blood glucose can be observed (Table 37). The LS mean change (Std Err) was similar in both treatments (FF/VI: -0.14 [0.024]; FF: -0.14 [0.023]). There was also no statistically relevant difference for the changes from baseline between both treatments (p=0.970).

Table 36 Summary of Fasting Glucose (mmol/L) Intent-to-Treat Population (5 to 17 Years Old)

Lab Test	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Glucose (mmol/L)	FF/VI	454	Visit 1 (Screening)	439	5.12	0.491	5.10	2.5	8.2
			Visit 9 (Week 24)	382	5.00	0.505	5.00	3.3	8.5
			Maximum post-baseline	389	5.01	0.536	5.00	3.3	8.6
	FF	448	Visit 1 (Screening)	431	5.13	0.502	5.10	3.4	7.9
			Visit 9 (Week 24)	398	4.99	0.499	5.00	2.8	7.5
			Maximum post-baseline	405	5.00	0.498	5.00	2.8	7.5

Source: Table 3.19
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Lab = laboratory; Max = maximum; Min = minimum; N = number of participants; n = subset of participants; SD = standard deviation
Note: Maximum post-baseline results include scheduled, unscheduled, Early Treatment Discontinuation and Early Study Withdrawal Visits.

Table 37 Summary of Change from Baseline in Fasting Glucose (mmol/L) Intent-to-Treat (5 to 17 Years Old)

Lab Test	Treatment	N	Visit	n	Mean	SD	Median	Min.	Max.
Glucose (mmol/L)	FF/VI	454	Visit 9 (Week 24)	370	-0.12	0.587	-0.10	-3.3	3.4
			Maximum post-baseline	376	-0.11	0.610	-0.10	-3.3	3.4
	FF	448	Visit 9 (Week 24)	388	-0.15	0.626	-0.10	-3.0	2.6
			Maximum post-baseline	395	-0.14	0.620	-0.10	-3.0	2.6

Source: Table 3.20

Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; Lab = laboratory; Max = maximum; Min = minimum; N = number of participants; n = subset of participants; SD = standard deviation

Note: Maximum post-baseline results include scheduled, unscheduled, Early Treatment Discontinuation and Early Study Withdrawal Visits.

- *Other Safety Evaluations*

– ECG Recordings

ECG Values and Change from Baseline

During the study, ECG recordings were taken at Screening and at Visit 9. Apart from the RR interval which showed slight differences between both treatments at Screening and at Visit 9, the median values of the parameters at Screening and Visit 9 seem to be similar between both treatments. Similarly, the changes from baseline were similar between both treatments and all parameters.

Statistical analysis of heart rate at Week 9 did not show a difference between both treatments (difference 0.0, 95% CI -1.6, 1.6).

Regarding the individual data, each 1 participant in either group showed prolonged QT intervals, which constituted an AE. In addition, in 1 participant in the FF group, a prolongation of the PR interval constituted an AE. The prolonged QT intervals were considered by the investigator to be related to the study drug, the PR prolongation to be not related to the study drug. All AEs were assessed as mild in their intensity. The AEs of prolonged QT intervals were resolving at the end of the study, the PR prolongation was resolved.

Interpretation of ECG Recordings

In the FF/VI group, the number of participants with abnormal ECG recording was similar at screening and Week 9, 65/453 (14%) participants versus 64/402 (16%) participants. In the FF group, 61/448 (14%) participants showed an abnormal ECG result at screening, and at Visit 9, number of participants with abnormal ECG results decreased to 49/398 (12%).

ECG Data with Potential Clinical Importance

At screening, Visit 9 and any time post-baseline, ECG findings of clinical importance comprised sinus bradycardia, idioventricular rhythm, ectopic supraventricular rhythm and right bundle branch block for both treatments. No further ECG findings of clinical importance were reported at any timepoint for either treatment.

At screening, the number of participants of both treatments were comparable for each finding. At Visit 9 and any timepoint post-baseline, the number of participants with any ECG findings of clinical importance increased from to 51/453 (11%) participants to 63/402 (16%) and 66/408 (16%) participants, respectively, in the FF/VI group, whereas in the FF group, only a slight increase from

49/448 (11%) participants to 50/398 (13%) and 54/414 (13%) participants, respectively, was observed.

Most often, the symptom sinus bradycardia was reported in both groups, whereas all other symptoms were only reported for 1 or 2 participants at any timepoint in either treatment (Table 38).

Table 38 Summary of ECG Findings of Potential Clinical Importance Intent-to-Treat Population (5 to 17 Years Old) – modified

	FF/VI (N=454)	FF (N=448)
Timepoint: Visit 1 (Screening)		
Number of Subjects with an ECG	453	448
Any Abnormality of Potential Clinical Importance	51 (11%)	49 (11%)
Sinus Bradycardia	49 (11%)	47 (10%)
Idioventricular Rhythm	1 (<1%)	2 (<1%)
Ectopic Supraventricular Rhythm	1 (<1%)	0
Right Bundle Branch Block	1 (<1%)	0
Timepoint: Visit 9 (Week 24)		
Number of Subjects with an ECG	402	398
Any Abnormality of Potential Clinical Importance	63 (16%)	50 (13%)
Sinus Bradycardia	59 (15%)	47 (12%)
Ectopic Supraventricular Rhythm	2 (<1%)	1 (<1%)
Idioventricular Rhythm	1 (<1%)	2 (<1%)
Right Bundle Branch Block	2 (<1%)	0
Timepoint: Any time post-baseline		
Number of Subjects with an ECG	408	414
Any Abnormality of Potential Clinical Importance	66 (16%)	54 (13%)
Sinus Bradycardia	62 (15%)	51 (12%)
Ectopic Supraventricular Rhythm	2 (<1%)	1 (<1%)
Idioventricular Rhythm	1 (<1%)	2 (<1%)
Right Bundle Branch Block	2 (<1%)	0

Source: Table 3.25

Abbreviations: ECG = electrocardiogram; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants

Note: Any time post-baseline results include assessments performed at scheduled, unscheduled and Early Treatment Discontinuation and Early Study Withdrawal Visits.

QTc, QTc(F) and QcTB

From all participants in both groups, only 1 participant in the FF/VI group showed a QTc(F) value of >450 to ≤480 ms at screening. All other participants had QTc(F) values of ≤450 ms. At Visit 9 and regarding the maximum value post-baseline, there were 1 participant in the FF/VI group and 2 (<1%) participants in the FF group, who had a QTc(F) value of >450 to ≤480 ms.

Approximately half of the participants in both groups had QTc(F) changes from baseline of 30 ms at maximum. None of them had changes to baseline ≥60 ms in either group.

The statistical analyses of the change from baseline for the QTc(F) data at Week 24 did not reveal a statistically relevant change (LS mean [Std Err]: FF/VI = -1.5 [0.74] ms, FF = -0.2 [0.74] ms). There was also no statistically relevant difference between both treatments (p = 0.204).

Regarding the QTc(B) data, no relevant differences between the QTc(F) and the QTc(B) data could be seen.

– On- and Post-Treatment Pneumonia

For the FF/VI group, no case of on-treatment pneumonia was reported, 1 participant experienced pneumonia during post-treatment. The AE resolved during the observation time, was assessed as moderate in their intensity and not considered by the investigator to be drug-related.

A total of 4 (<1%) participants in the FF group experienced on-treatment pneumonia. All AEs were resolved during the study, were assessed as moderate in their intensity and not considered by the investigator to be drug-related. No post-treatment pneumonia was reported for the FF group.

5 to 11 Years Old Population (ITT Population)

- *Adverse Events*

– Overview of Adverse Events

Overall, 133/337 (39%) participants in the FF/VI group and 122/336 (36%) participants in the FF group experienced at least 1 AE. In 4 (1%) participants of the FF/VI group and 4 (1%) participants of the FF group, the investigator considered the AEs to be drug-related.

In 2 (<1%) participants of the FF/VI group and 1 participant of the FF group, at least 1 AE led to permanent discontinuation from study intervention or to premature withdrawal from the study. In both groups, at least 1 SAE was reported for 4 (1%) participants in each group. No drug-related SAE, no fatal AE and no drug-related fatal AE were reported.

– Adverse Events by System Organ Class and Preferred Term

In the FF/VI group the most commonly reported AEs were nasopharyngitis in 37/337 (11%) participants, upper respiratory tract infection in 23/337 (7%) participants, allergic rhinitis in 14/337 (4%) participants, headache in 9/337 (3%) participants, and rhinitis in 11/337 (3%) participants.

In the FF group the number of participants were smaller regarding all of the most commonly reported AEs than in the FF/VI group. Nasopharyngitis was reported in 27/336 (8%) participants, upper respiratory tract infection in 18/336 (5%) participants, allergic rhinitis in 4/336 (1%) participants, headache in 8/336 (2%) participants, and rhinitis in 4/336 (1%) participants.

– Treatment-Related Adverse Events

Overall, 4 (1%) participants in the FF/VI group and 4 (1%) participants in the FF group experienced at least 1 AE, which was considered by the investigator to be drug-related.

The majority of the drug-related AEs occurring were reported at maximum for 1 participant per group, only dysphonia was reported for 2 (<1%) participants in the FF group.

– Post-Treatment Adverse Events

Only a few participants in both groups experienced at least 1 AE after the treatment period.

In the FF/VI group, for 2 (<1%) participants, nasopharyngitis was reported and for 1 participant each pneumonia, varicella infection, and stomatitis; in the FF group, a COVID-19 infection, an upper respiratory infection and extrasystoles were reported by a total of 2 (<1%) participants, of which extrasystoles and upper respiratory infection were reported by 1 participant.

– Adverse Events and COVID-19 Pandemic

In total, 8/337 (2%) participants in the FF/VI group and 4/336 (1%) participants in the FF group experienced an on-treatment COVID-19 infection. In addition, 1 participant in the FF/VI group had an on-treatment AE of suspected COVID-19 and 1 participant in the FF group had an AE of COVID-19 that occurred post-treatment.

The duration of the COVID-19 infection was between 3 and 46 days, and all AEs were resolved at the end of the study. From the on-treatment AEs, 6 were assessed as mild and 6 as moderate, the post-treatment AE as moderate.

None of these AEs were considered by the investigator to be related to the study drug.

- *Other Serious Adverse Events*

The number of participants in this age group experiencing an SAE was low and similar in each treatment group. Overall, 4/337 participants in the FF/VI group and 4/336 participants in the FF group experienced an SAE (Table 39).

Table 39 Summary of On-Treatment Serious Adverse Events Intent-to-Treat Population (5 to 11 Years Old)

System Organ Class Preferred Term	FF/VI (N=337)	FF (N=336)
Any event	4 (1%)	4 (1%)
Respiratory, thoracic and mediastinal disorders		
Any event	1 (<1%)	3 (<1%)
Asthma	1 (<1%)	3 (<1%)
Infections and infestations		
Any event	2 (<1%)	1 (<1%)
Appendicitis	1 (<1%)	0
Gastroenteritis rotavirus	1 (<1%)	0
Helicobacter gastritis	0	1 (<1%)
Gastrointestinal disorders		
Any event	1 (<1%)	0
Intestinal obstruction	1 (<1%)	0

Source: Table 3.42
Abbreviations: FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = number of participants

- *Treatment-Related Serious Events*

None of the SAEs occurring were considered by the investigator to be drug-related.

- *Other Significant Adverse Events*

– Adverse Events Leading to Permanent Discontinuation

The number of participants with AEs leading to permanent discontinuation is very small in both groups.

For 2 (<1%) participants in the FF/VI group, the AEs of intestinal obstruction and of insomnia led to permanent discontinuation, and for 1 participant in the FF group the AE of dysphonia led to discontinuation.

– Adverse Events of Special Interest

Slightly more participants (31/337 [9%] participants) in the FFV/VI group experienced at least 1 AESI than in the FF group (27/336 [8%)]). The majority of AESIs reported were similar in type and frequency in both groups, with the exception of hypersensitivity events (FF/VI:18/337 [5%] participants versus 9/336 [3%] participants in the FF group).

Of the hypersensitivity events, allergic rhinitis was the most commonly reported or 14/337 (4%) participants in the FF/VI group and for 4/336 (1%) participants in the FF group.

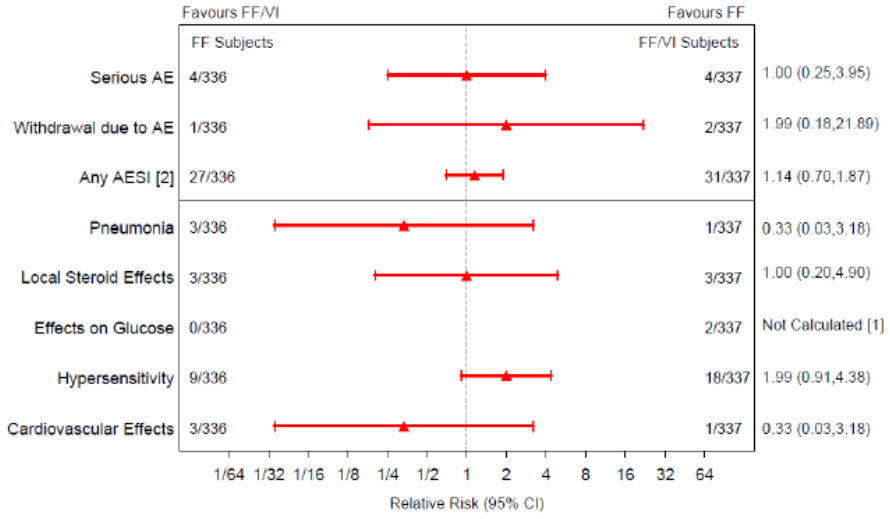
– Serious Adverse Events of Special Interest

Serious AESIs comprised 1 case of asthma in the FF/VI group and 3 cases of asthma in the FF group. All serious AESIs were of severe intensity and considered by the investigator not to be drug-related.

– Summary of Risks for FF/VI Versus FF Treatment

In Figure 7, the risks for FF/VI treatment and FF treatment with regard to safety are presented.

Figure 7 Summary of Risks for FF/VI vs. FF Intent-to-Treat population (5 to 11 Years Old)



Source: Figure 3.2
Abbreviations: AE = adverse event; CI = confidence interval; FF = Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol;
Note: W/D due to AE includes events leading to permanent discontinuation of study drug or withdrawal from the study.
[1]: Not calculated if either or both treatment groups have no events
[2]: 'Tremor' not presented as there were no events in this study

- *Clinical Laboratory Evaluations*

– Evaluation of Fasting Blood Glucose Pre- and Post-Treatment

Fasting blood glucose was assessed at Screening and at Visit 9. For both treatments, a slight decrease of the fasting blood glucose can be observed. The LS mean change (Std Err) was similar in both treatments (FF/VI: -0.14 [0.027] mmol/L; FF: -0.16 [0.026] mmol/L). There was also no statistically relevant difference for the changes from baseline between both treatments (p=0.616).

- *Other Safety Evaluations*

– ECG Recordings

ECG Values and Change from Baseline
During the study, ECG recordings were taken at Screening and at Visit 9. Apart from the RR interval which showed slight differences between both treatments at Screening and at Visit 9, the median values of the parameters at Screening and Visit 9 seem to be similar between both treatments. Similarly, the changes from baseline were similar between both treatments and all parameters.

Statistical analysis of heart rate at Week 9 showed a minor difference between both treatments (difference -0.7, 95% CI [-2.6, 1.2]).

Regarding the individual data, each 1 participant in either group showed prolonged QT intervals, which constituted an AE. In addition, in 1 participant in the FF group, a prolongation of the PR interval constituted an AE. The prolonged QT intervals were considered by the investigator to be related to the study drug, the PR prolongation to be not related to the study drug. All AEs were assessed as mild in their intensity. The AEs of prolonged QT intervals were resolving at the end of the study, the PR prolongation was resolved.

Interpretation of ECG Recordings
In the FF/VI group, the number of participants with abnormal ECG recordings were similar at screening and Week 9, 55/337 (16%) participants versus 53/303 (17%) participants. In the FF group, 49/336 (15%) participants showed an abnormal ECG result at screening, and at Visit 9, number of participants with abnormal ECG results decreased to 40/298 (13%).

ECG Data with Potential Clinical Importance
At screening, Visit 9 and any time point post-baseline, ECG findings of clinical importance comprised sinus bradycardia, idioventricular rhythm, ectopic supraventricular rhythm and right bundle branch block for both treatments. No further ECG findings of clinical importance were reported at any timepoint for either treatment.

At screening, the number of participants with any ECG abnormality of potential clinical importance was similar for both groups (FF/VI: 30 [9%]) versus 32 [10%] participants).

In the FF/VI group, the number of participants with any ECG findings of clinical importance increased from to 30/336 (9%) participants to 49/303 (16%) participants and 52/305 (17%) participants from screening to Visit 9 and any timepoint post-baseline, whereas in the FF group, the number of participants with ECG findings of clinical importance was similar at all timepoints, 32/336 (10%), 30/298 (10%) and 32/307 (10%) participants, respectively.

Most often, the symptom sinus bradycardia was reported in both groups, whereas all other symptoms were only reported for 1 or 2 participants at any timepoint in either treatment.

QTc, QTc(F) and QcTB
At screening all participants in both groups showed QTc(F) values of ≤450 ms. At Visit 9, 1 participant in the FF/VI showed a QTc(F) value within >450 to ≤480 ms. None of the participants in the FF group showed a QTc(F) value above 450 ms at any timepoint.

Approximately half of the participants in both groups had QTc(F) changes from baseline of up to 30 ms, none of them had changes from baseline >60 ms in either group.

The statistical analyses of the change from baseline for the QTc(F) at Week 24 data did not reveal a statistically relevant change (LS mean [SE]: FF/VI = -1.1 [0.86] ms, FF = 0.4 [0.86] ms). There was also no statistically relevant difference between both treatments (p = 0.210).

Regarding the QTc(B) data, no relevant differences between the QTc(F) and the QTc(B) data could be seen.

– On- and Post-Treatment Pneumonia

For the FF/VI group, no case of on-treatment pneumonia was reported, 1/337 participant experienced pneumonia during post-treatment. The AE resolved during the observation time, was assessed as moderate in their intensity and not considered by the investigator to be drug-related.

A total of 3/336 (<1%) participants in the FF group experienced on-treatment pneumonia. All AEs were resolved during the study, were assessed as moderate in their intensity and not considered by the investigator to be drug-related. No post-treatment pneumonia was reported for the FF group.

- *Pregnancies*

No pregnancy was reported in this study.

2.3.3. Discussion on clinical aspects

Fluticasone furoate/vilanterol inhalation powder (FF/VI) is currently approved by the European Commission for the regular treatment of asthma in adults and adolescents aged 12 years and older, where use of a combination product (long-acting beta2-agonist and inhaled corticosteroid) is appropriate.

This Article 46 procedure of Regulation (EC) No1901/2006, concerns the submission of the study number HZA107116 (EudraCT number: 2016-004086-87). This study is part of the EU Paediatric Investigation Plan of FF/VI agreed upon for the treatment of asthma indication in children and adolecescents aged 5 to <18 years (EMEA-000431-PIP01-08-M12).

HZA107116 was a phase 3, randomised, double-blind, stratified, parallel group, multicentre study to evaluate the efficacy and safety of once daily (OD) FF/VI compared to OD FF in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Study randomisation was stratified by age as follows: participants from 5 to 11 years were randomly (1:1) allocated to receive FF/VI 50/25 micrograms or FF 50 micrograms whereas participants from 12 to 17 years were randomly (1:1) allocated to receive FF/VI 100/25 micrograms or FF 100 micrograms. This study was conducted over a total duration of approximately 29 weeks: a 4-week open-label run-in period where all participants received fluticasone propionate (FP) 100 micrograms twice daily, a 24-week double-blind treatment period where participants received FF/VI or FF as described above, and a 1-week follow-up period. Participants received a short-acting beta agonist (SABA; i.e. salbuterol/salbutamol) as needed throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms. The study design is considered acceptable for a phase 3 performed in paediatric asthmatic participants from 5 years of age and older.

The primary objective was to compare the efficacy of OD FF/VI with OD FF in participants with asthma, being the secondary objective the safety assessment of OD FF/VI. In this application, the primary endpoint for the 5 to 11 years population (required by EMA] was change from baseline, averaged over Weeks 1 to 12 of the treatment period, in pre-dose (i.e., trough) morning peak expiratory flow (AM PEF), captured daily via electronic patient diary (eDiary). This was a secondary endpoint for the 5 to17 years population. Weighted mean FEV1 (0 to 4 hours) at Week 12 was a secondary endpoint for the 5 to 11 years population, and the primary endpoint for the 5 to 17 years population. Common efficacy secondary endpoints to both 5 to 11 years and 5 to 17 years populations included change from baseline in: rescue-free 24-hour periods over Weeks 1 to 12 of the treatment period, symptom-free 24-hour periods over Weeks 1 to 12 of the treatment period, AM FEV1 at Week 12, ACQ-5 at Week 24, and incidence of exacerbations over the 24-week treatment period. Secondary safety endpoints common to both 5 to 11- and 5 to 17 years population included incidence of AEs, evaluation of fasting blood glucose pre- and post-treatment, evaluation of ECG at screening and end of treatment. Other endpoint common to both paediatric sub-populations was change from baseline, averaged over Weeks 1 to 12 of the treatment period in PM PEF, captured daily via eDiary.To account for multiplicity across key endpoints, a step-down closed-testing procedure was applied whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. The submitted study methodology appears adequate for its primary objective. Proposed efficacy and safety endpoints appear to be relevant to develop a medicinal product for the treatment of asthma in paediatric subjects from 5 years of age and older.

A total of 2402 participants were screened, of whom 1187/2402 (49%) participants failed screening and 309/2402 (13%) participants failed in the run-in period. Of all 906 participants randomised, a total of 902 participants were randomised and received study intervention (454 in the FF/VI group and 448 in the FF group) with 673/906 (74%) participants included into the ITT population of the 5 to 11 years old (337 participants in the FF/VI group and 336 participants in the FF group). A total of 864/902 (96%)

participants completed the study. The number of screened and randomised subjects as well as the number of subjects per treatment arm, are in agreement with the planned sample size.

The majority of the participants were between 8 and 11 years old (471/902; 52%) (mean [SD] age 10.0 [2.99] years), male (546/902;61%), not Hispanic or Latino (651/902; 72%) with a mean BMI of 18.55 (3.404) kg/m2. The demographic and baseline data with respect to age, race, ethnicity, medical conditions, asthma history, and lung function were comparable between both groups, with more male participants in the FF/VI group than in the FF group (289/454 [64%] versus 257/448 [57%], respectively).

Regarding the primary endpoint (AM PEF) for 5 to 11 years population, the mean change from baseline over Weeks 1 to 12 was larger for the FF/VI treatment than for the FF treatment. The LS means change from baseline was 12.0 (Std Err: 1.86) L/min for the FF/VI treatment and 8.8 (Std Err 1.86) L/min for the FF treatment. For the primary comparison of AM PEF (L/min) over Weeks 1 to 12 on- and post-treatment, using ANCOVA with covariates of baseline, region, sex, age and treatment, the difference between treatment of 3.2 L/min did not reach statistical significance (p=0.228). Although a clinically significant improvement in weighted mean FEV1 (0 to 4 hours) was also seen in the 5 to 11 years old population (representing 2 third of the 5 to 17 years old population) no statistical inference can be made on this endpoint because of the statistical testing hierarchy. Secondary endpoints such as symptom-free 24-hour periods, AM FEV1, ACQ-5, and PM PEF, were similar for both treatments. Any asthma exacerbation was reported for 27/337 (8%) participants in the FF/VI group and for 32/336 (10%) participants of the FF group on- and post-treatment.

As regards of the 5 to 17 years population safety results, 181/454 (40%) participants in the FF/VI group and 163/448 (36%) participants in the FF group experienced at least 1 AE. In 6/454 (1%) participants of the FF/VI group and 4/448 (<1%) participants of the FF group, the investigator considered the AEs to be drug-related. In 3/454 (<1%) participants of the FF/VI group and 1/448 participant of the FF group, at least 1 AE led to permanent discontinuation from study intervention or to premature withdrawal from the study. In both groups, at least 1 SAE was reported for 5 (1%) participants in each group. No drug-related SAE, no fatal AE and no drug-related fatal AE were reported. The majority of the drug-related AEs occurring were reported at maximum for 1 participant per group, only dysphonia was reported for 2 (<1%) participants in the FF group and for 1 participant in the FF/VI group.

For 5 to 11 years population, 133/337 (39%) participants in the FF/VI group and 122/336 (36%) participants in the FF group experienced at least 1 AE. In 4 (1%) participants of the FF/VI group and 4 (1%) participants of the FF group, the investigator considered the AEs to be drug-related. In 2 (<1%) participants of the FF/VI group and 1 participant of the FF group, at least 1 AE led to permanent discontinuation from study intervention or to premature withdrawal from the study. In both groups, at least 1 SAE was reported for 4 (1%) participants in each group. No drug-related SAE, no fatal AE and no drug-related fatal AE were reported. A total of 4 (1%) participants in the FF/VI group and 4 (1%) participants in the FF group experienced at least 1 AE, which was considered by the investigator to be drug-related. The majority of the drug-related AEs occurring were reported at maximum for 1 participant per group, only dysphonia was reported for 2 (<1%) participants in the FF group.

Overall, the study failed to accomplish its primary objective as no significant difference between FF/VI and FF in the 5 to 11 years old population for AM PEF were demonstrated. However, FF/VI was well tolerated for both populations and no new safety concerns were identified during the study.

In agreement with the MAH proposal, it is considered that a type II variation application consisting of the full relevant data package (i.e., containing several studies) should be submitted by March 2023.

3. CHMP overall conclusion and recommendation

In accordance with Article 46 of the regulation (EC) No. 1901/2006, Glaxo Group Ltd hereby submits to the EMA a final study report for study number HZA107116 which is part of the last PIP agreed to FF/VI (PIP EMEA-000431-PIP01-08-M12).

HZA107116 was a phase 3, randomised, double-blind, stratified, parallel group, multicentre study to evaluate the efficacy and safety of once daily fluticasone furoate/vilanterol (as trifenatate) inhalation powder (FF/VI) compared to once daily fluticasone furoate inhalation powder (FF) in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids. Study randomisation was stratified by age as follows: participants from 5 to 11 years were randomly (1:1) allocated to receive FF/VI 50/25 micrograms or FF 50 micrograms whereas participants from 12 to 17 years were randomly (1:1) allocated to receive FF/VI 100/25 micrograms or FF 100 micrograms.

Overall, the study failed to accomplish its primary objective as no significant difference between FF/VI and FF in the 5 to 11 years old population for AM PEF was demonstrated. Nevertheless, FF/VI safety profile observed in the study HZA107116 was consistent with the already known safety profile of FF/VVI in adults and adolescents aged 12 years and older with asthma.

☒ Fulfilled:

No further action required. The MAH has planned to submit a variation application for paediatric studies by March 2023.