24 February 2022
EMA/168280/2022
Human Medicines Division

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

Relvar Ellipta

fluticasone furoate / vilanterol

Procedure no: EMEA/H/C/002673/P46/015

Note

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

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1. Introduction

On 30th November 2021, the MAH submitted a completed study (Study No. HZA114971) for Relvar Ellipta and its duplicate Revinty Ellipta (fluticasone furoate / vilanterol trifenatate), in accordance with Article 46 of Regulation (EC) No. 1901/2006, 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 trifenatate Inhalation Powder [FF/VI]) was 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", as well as for "the symptomatic treatment of adult patients 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), which included a waiver in children under 5 years of age and a deferral in children aged 5-11 years (EMEA-000431-PIP01-08-M04; P/0049/2012). 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 HZA114971 which is part of the PIP EMEA-000431-PIP01-08-M12 (Study 13).

The MAH stated that the study HZA114971 "A Multicentre Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate 50 mcg once daily on Growth Velocity in Prepubertal, Paediatric Subjects with Asthma" is a standalone study. As such, a line listing is not provided.

2.2. Information on the pharmaceutical formulation used in the study

In the hereby submitted study, orally inhaled fluticasone furoate 50 micrograms (FF 50 mcg) or orally inhaled placebo (i.e., lactose) were administered once daily in prepubertal asthmatic children (aged 5 to <9 years) on a background therapy of open-label montelukast. Both FF and placebo, were administered as dry inhalation powder by using the same inhaler device as the Relvar/Revinty products approved in the EU.

The formulation of FF used in the study is not currently approved in the EU. The dose of FF (50 mcg) used in the study HZA114971 was selected from the 2b dose-ranging study HZA106855 of FF in children from 5 to less than 12 years of age with persistent asthma. Both studies are part of the PIP EMEA-000431-PIP01-08-M12 (see, PIP Study 8).

The formulations of montelukast used in the study were the same as the products approved in the EU for the treatment of persistent asthma as add-on therapy in children aged 2 to 5 years (4 mg chewable tablet) and aged 6 to 14 years (5 mg chewable tablet).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for study number HZA114971: "A Multicentre Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate 50 mcg once daily on Growth Velocity in Prepubertal, Paediatric Subjects with Asthma".

2.3.2. Clinical study

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

Description

HZA114971 was a randomised, single-blind (16-week placebo run-in period) / double-blind (52-week treatment period), parallel group, placebo controlled, multicentre study to assess the effect of once daily (OD) orally inhaled fluticasone furoate (FF) 50 mcg on growth velocity in prepubertal asthmatic children on a background therapy of open-label montelukast (OD, 4 mg for subjects who are 5 years old and 5 mg for subjects who are ≥6 years old; from the run-in period through to the end of an 8-week follow-up period).

The purpose of the study was to evaluate the magnitude of effect (with a level of precision) of OD inhaled FF 50 mcg versus OD orally inhaled placebo on growth velocity in prepubertal asthmatic subjects (aged 5 to <9 years) over one year of treatment.

Methods

Objectives

- *Primary:*

To evaluate the magnitude of effect (with a level of precision) of orally inhaled FF 50 mcg versus orally inhaled placebo once daily on growth velocity in prepubertal children over one year of treatment.

- *Secondary:*

To assess the safety of orally inhaled FF 50 mcg once daily.

- *Other:*

To assess the effect of orally inhaled FF 50 mcg once daily on efficacy endpoints, used as a measure of compliance to help identify nonadherence and/or poorly controlled asthma.

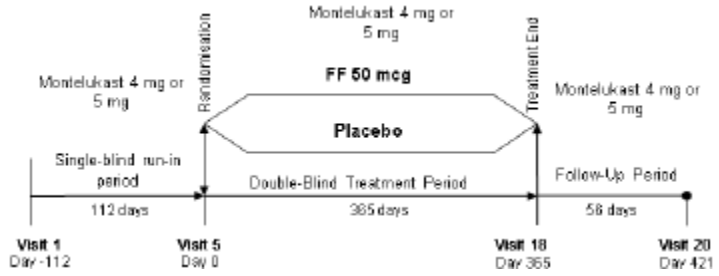
Study design

This was a randomised, single-blind (run-in period) / double-blind (treatment period), parallel-group, placebo-controlled, multicentre study to assess the effect of FF 50 mcg once daily on growth velocity in prepubertal asthmatic children on a background therapy of open-label montelukast. Study randomisation was stratified by country to account for possible differences in medical practices and growth velocity across countries.

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

Eligible participants received a single-blind placebo orally inhaler during a 16-week run-in period. After completing the run-in period, eligible participants were randomly (1:1) allocated to receive orally inhaled FF 50 mcg or orally inhaled placebo for 52 weeks.

Figure 1. Study Schematic



FF = Fluticasone Furoate Inhaled Powder.

*Montelukast 4 mg will be provided to children 5-year old and montelukast 5 mg will be provided to children ≥6 years.

Visit 1 (Day 112): Screening Visit

Visit 5 (Day 0): Randomisation Visit

Visit 18 (Day 365): End of Treatment Period Visit

Visit 20 (Day 421): End of Follow-Up Period Visit

All participants also received open-label montelukast chewable tablets from the run-in period through to the end of the follow-up period. In addition, each participant received albuterol/salbutamol (inhalation aerosol or nebuliser) throughout the entire study period as rescue medication.

Study population /Sample size

<u>Inclusion/exclusion criteria</u>

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.

Re-screening of Individuals who did not meet the criteria for participation in this study (i.e., a screen failure) was permitted. Any re-screened participant had to satisfy all of the protocol-specified inclusion/exclusion requirements at the re-screening visit.

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.
- Celiac 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.

Participants were not eligible if they had any of the prohibited medications listed below according to the timeframes:

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

In addition, albuterol/salbutamol (inhalation aerosol or nebuliser) use was to be withheld for 4 hours prior to the FEV1 measurement at Screening.

Sample size

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

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

Eligible participants were stratified by country and randomised in a 1:1 ratio to orally inhaled FF 50 mcg once daily (plus montelukast open-label) or orally inhaled placebo (plus montelukast open-label). At least 450 participants were to be randomised (approximately 225 per treatment arm). Assuming a withdrawal rate from study treatment of up to 10% within the first 12 weeks, this would still ensure at least 406 eligible participants (approximately 203 per treatment arm) for inclusion in the Growth Population analyses. Assuming a standard deviation (SD) for the growth velocities of 1.2 cm/yr (based

on study FFR101782 to evaluate the effects of a one-year course of fluticasone furoate nasal spray 110 mcg QD on growth in pre-pubescent pediatric subjects with perennial allergic rhinitis), a sample size of 203 eligible participants per treatment arm ensured the width of the CI for the mean treatment difference was no greater than 0.5 cm/yr.

Sample Size Sensitivity

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

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

The shaded area represents the number of participants per treatment group and the SD that correspond to a 95% CI with a width no greater than 0.5 cm/yr.

Sample size re-estimation or adjustment was not planned.

Treatments

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

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

*Single Strip

Each participant also received an albuterol/salbutamol (inhalation aerosol or nebuliser) to be used as needed throughout the entire study period as rescue medication for symptomatic relief of asthma symptoms. Montelukast was locally sourced by the sites.

Outcomes/endpoints

Safety

- To evaluate the magnitude of effect (with a level of precision) of orally inhaled FF 50 mcg versus orally inhaled placebo once daily on growth velocity in prepubertal children over one year of treatment:

  Primary endpoint
  - Growth Velocity (cm/yr) over the double-blind treatment period, as determined by stadiometry.

  Secondary endpoint
  - Proportion of participants below the 3rd percentile of growth velocity.
  - Change in growth velocity quartiles from baseline to endpoint.
  - Growth velocity over the first 12 weeks of double-blind treatment period.
  - Height standard deviation scores (SDS) at each visit.

- To assess the safety of orally inhaled FF 50 mcg once daily:
    - Incidence of adverse events.
    - Incidence of asthma exacerbations.

Efficacy

- To assess the effect of orally inhaled FF 50 mcg once daily on efficacy endpoints, used as a measure of compliance to help identify nonadherence and/or poorly controlled asthma:
    - Change from baseline in the percentage of rescue-free 24-hour periods over the double-blind treatment period.
    - Change from baseline in the percentage of symptom-free 24-hour periods over the double-blind treatment period.
    - Change from baseline in AM peak expiratory flow (PEF) averaged over the double-blind treatment period.
    - Change from baseline in Childhood Asthma Control Test (cACT) score at the end of the double-blind treatment period.

Statistical Methods

Three participant populations were defined:

- Total Population: The Total Population comprised all participants screened and for whom a record exists on the study database and was used for the tabulation and listing of reasons for withdrawal before randomisation (Visit 5).
- Intent-to-Treat (ITT) Population: The ITT Population was defined as all randomised participants who received at least one dose of study treatment. All safety and efficacy (compliance assessments) data analyses used the ITT Population.
- Growth Population: The Growth Population was defined as all ITT participants with height assessments via stadiometry from at least three post-randomisation, on-treatment clinic visits during the double-blind treatment period. This was the primary population for analyses of growth data.

The following subgroups were used in descriptive summaries and/or statistical analyses of growth velocity.

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

No interim analyses are planned during this study.

Results

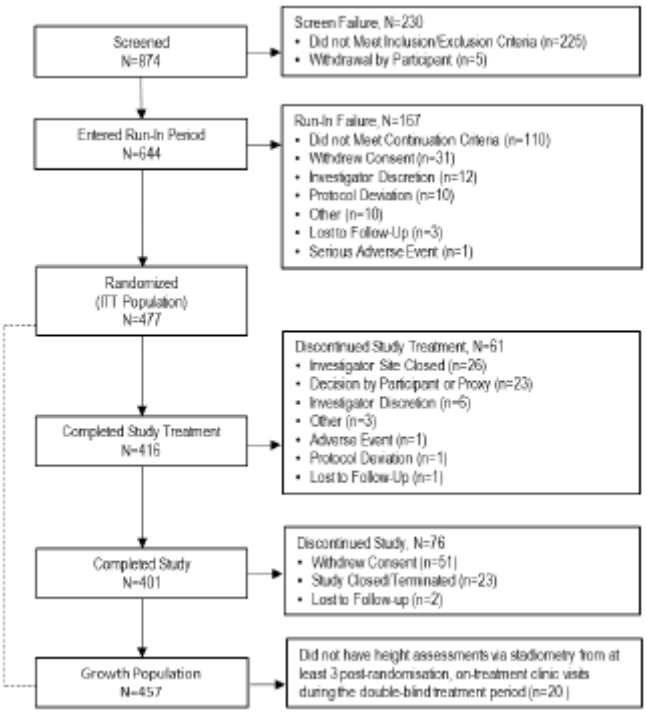
Recruitment/ Number analysed

The study was conducted at 67 sites in 6 countries. The study was initiated on 20 October 2016 (first participant first visit) and completed on 04 June 2021 (last participant last visit).

A total of 874 participants were screened. Of these, 644 entered the run-in period. One participant experienced an SAE during the run-in period and was considered a run-in failure; this participant was not randomised and did not receive any study treatment.

Following the run-in period, a total of 477 participants who met the randomisation criteria were randomised to receive study treatment. A total of 477 (100% of participants randomised) participants were included in the ITT Population and 457 (96% of participants in ITT Population) were included in the Growth Population.

Figure 2. Participant Disposition



Source: Table 1.1, Table 1.2, Table 1.4, Table 1.9, Table 1.10
Total: All participants screened and for whom a record exists in the study database.
Intent-to-Treat: All randomised participants who received at least a single dose of study treatment.
Growth: All ITT participants with height assessments via stadiometry from at least three post-randomisation, on-treatment clinic visits during the double-blind treatment period.
Notes: Screen failures were participants who failed screening and withdrew at Visit 1 (Screening). Run-in failures were withdrawals after Visit 1 (Screening) and prior to randomization. 1 Participant did not meet continuation criteria but was recorded on the disposition form with "investigator discretion" as reason for run-in failure and so was counted under "investigator discretion". Participants may have more than one run-in failure reason specified. Participants were prematurely withdrawn from the study before completing Visit 18, but the early treatment discontinuation form wasn't filled. These participants are not considered as prematurely discontinuing study treatment.

In total, 401 participants completed the study; the proportion of participants who completed the study was slightly lower for the placebo group (82% for the placebo group and 86% for the FF 50 group). A

total of 76 participants withdrew from the study; 43 (18%) in the placebo group and 33 (14%) in the FF 50 group.

Participant status and study disposition are summarised by treatment group in Table 4.

Table 4. Summary of Participant Status and Study Disposition (ITT Population)

	Placebo (N=239)	FF 50 (N=238)	Total (N=477)
Completion Status			
Completed	196 (82%)	205 (86%)	401 (84%)
Prematurely withdrawn[a]	43 (18%)	33 (14%)	76 (16%)
Primary Reason For Study Withdrawal			
Study closed/terminated[b]	12 (5%)	11 (5%)	23 (5%)
Lost to follow-up	1 (<1%)	1 (<1%)	2 (<1%)
Withdrew consent	30 (13%)	21 (9%)	51 (11%)

Source: Table 3.9
a Prematurely withdrawn = withdrawn from the study.
b Participants were from the 3 sites closed prematurely due to suspected ICH GCP noncompliance (see Section 5.2.3).

Baseline data

The two treatment groups were similar with respect to age, race, ethnicity, medical conditions, asthma history, and lung function.

All participants were children between the ages of 4 and 9 years (age was calculated approximately, as date of birth was imputed), and the mean (±SD) age between groups was similar, 6.1 (1.07) for the placebo group and 6.3 (1.02) for the FF 50 group. The majority of the participants were White (412/477 [86%]) and male (299/477 [63%]). The mean BMI of participants was similar between treatment groups, 16.36 (1.70) for the placebo group and 16.52 (1.73) for the FF 50 group.

Demographic characteristics were similar between the ITT Population and the Growth Population.

All participants had asthma, per the enrolment criteria for the study, and this was reported as a current condition. In addition to asthma, the most commonly reported current medical condition was nasal disorder (216/477 [45%] participants), followed by eczema (72/477 [15%] participants). There were 99/477 (21%) participants who reported past medical conditions, being the most commonly reported past medical condition was pneumonia in 40/477 (8%) participants, which was followed by eczema in 30/477 (6%) participants. One participant in the FF 50 group reported arrhythmia as a past medical condition.

The mean (±SD) duration of asthma was 3 (±1.85) years, and was similar for both groups. The majority of participants had an asthma duration ranging from ≥1 year to <5 years. The distribution of asthma duration was similar between the treatment groups.

Lung function parameters at Screening (FEV1, predicted FEV1, and percent predicted FEV1) were similar for both groups.

Efficacy results

<u>Rescue-Free 24-hour Periods</u>

Over 1 to 52 weeks, there was little change from baseline in the mean percentage of rescue-free 24-hour periods for both treatment groups, with a change of 3.1% for the placebo group and 2.6% for the FF 50 group (Table 5).

Table 5. Summary of Change from Baseline in Percentage of Rescue-Free 24-Hour Periods Over the Double-Blind Treatment Period (ITT Population

		Placebo (N=239)	FF 50 (N=238)
Baseline (%)	n	239	238
	Mean	85.6	89.8
	SD	30.41	25.24
	Median	100.0	100.0
	Min.	0	0
	Max.	100	100
Double-Blind Treatment Period (%)	n	239	238
	Mean	88.7	92.3
	SD	23.62	19.06
	Median	97.5	98.9
	Min.	0	0
	Max.	100	100
Change from Baseline (%)	n	239	238
	Mean	3.1	2.6
	SD	17.11	19.55
	Median	0.0	-0.3
	Min.	-29	-83
	Max.	91	94

Source: Table 3.1
Note: Baseline was defined as the 6 days prior to randomisation and on the day of randomisation.

Symptom-Free 24-Hour Periods

The change from baseline in the mean number of symptom-free 24-hour periods was higher for the placebo group (5.2%) than the FF 50 group (3.1%).

Table 6. Summary of Change from Baseline in Percentage of Symptom-Free 24-Hour Periods Over the Double-Blind Treatment Period (ITT Population)

		Placebo (N=239)	FF 50 (N=238)
Baseline (%)	n	239	238
	Mean	78.5	81.7
	SD	34.20	33.66

		Placebo (N=239)	FF 50 (N=238)
	Median	100.0	100.0
	Min.	0	0
	Max.	100	100
Double-Blind Treatment Period (%)	n	239	238
	Mean	83.6	84.7
	SD	25.87	26.94
	Median	94.0	95.8
	Min.	0	0
	Max.	100	100
Change from Baseline (%)	n	239	238
	Mean	5.2	3.1
	SD	23.65	24.31
	Median	-0.3	-0.6
	Min.	-82	-86
	Max.	95	95

Source: Table 3.2
Note: Baseline was defined as the 6 days prior to randomisation and on the day of randomisation.

Change from Baseline in Morning Peak Expiratory Flow

A summary of change from baseline in morning PEF during double-blind treatment is presented in Table 7. The mean (±SD) change from baseline for PEF was 6.9 (27.27) for the placebo group and 9.0 (30.70) for the FF 50 group.

Table 7. Summary of Change from Baseline in Morning Peak Expiratory Flow (L/min) Over the Double-Blind Treatment Period (ITT Population)

		Placebo (N=239)	FF 50 (N=238)
Baseline	n	239	238
	Mean	156.0	162.3
	SD	55.94	55.83
	Median	151.9	155.4
	Min.	60	62
	Max.	383	375
Double-Blind Treatment Period	n	239	238
	Mean	162.9	171.3
	SD	53.65	52.69
	Median	155.1	163.8
	Min.	69	70
	Max.	374	338
Change from Baseline	n	239	238
	Mean	6.9	9.0
	SD	27.27	30.70
	Median	7.8	11.1
	Min.	-105	-112
	Max.	102	106

Source: Table 3.3
Note: Baseline was defined as the 6 days prior to randomisation and on the day of randomisation.

Childhood Asthma Control Test Score (cACT)

The mean cACT score at baseline was 23.3 for the placebo group and 23.4 for the FF 50 group. The mean (±SD) change from baseline was similar for both treatment groups, 0.9 (2.83) for the placebo group and 0.7 (3.64) for the FF 50 group (Table 8). One participant had a protocol deviation at Screening, and 7 participants had protocol deviations for the period from inclusion to run-in for a cACT score >19.

Table 8. Summary of Change from Baseline in Childhood Asthma Control Test (C-ACT) Scores at the End of the Double-Blind Treatment Period (ITT Population)

		Placebo (N=239)	FF 50 (N=238)
Baseline	n	239	238
	Mean	23.3	23.4
	SD	2.38	2.35
	Median	23.0	23.0
	Min.	14	16
	Max.	27	27
Visit 18 (Week 52)	n	200	207
	Mean	24.1	24.1
	SD	2.52	3.46
	Median	25.0	25.0
	Min.	14	0
	Max.	27	27
Change from Baseline	n	200	207
	Mean	0.9	0.7
	SD	2.83	3.64
	Median	1.0	1.0
	Min.	-9	-27
	Max.	9	7

Source: Table 3.4
Note: Baseline was defined as the cACT score recorded at Visit 5 (Randomisation).

Safety results

A total of 239 participants in the placebo group and 238 participants in the FF 50 group received at least 1 dose of study treatment. Study treatment exposure was slightly higher for the FF 50 group. The mean (±SD) number of days of exposure was 334.5 (77.46) for the placebo group and 344.0 (61.38) for the FF 50 group indicating that the majority of participants completed approximately one year of treatment. The median (minimum-maximum) number of days of exposure was 364 (4-386) days for the placebo group and 364 (30-386) days for the FF 50 group.

Growth Velocity

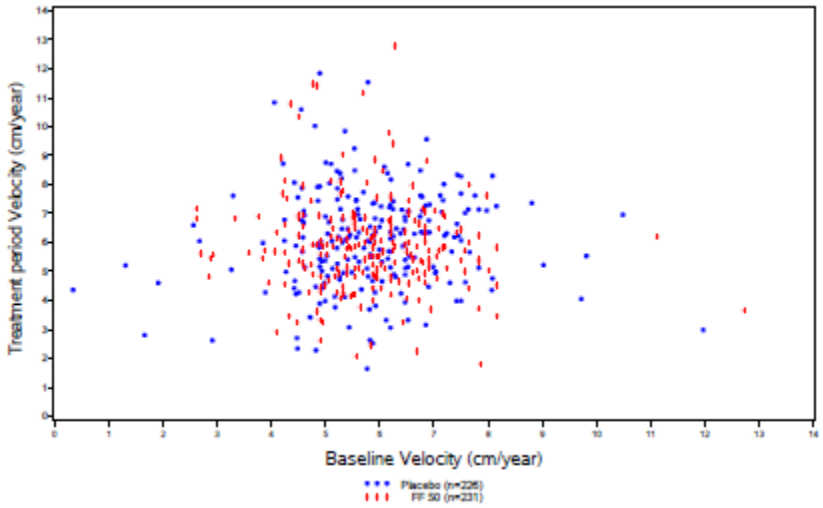
- *Primary Endpoints of Growth Velocity*

The study primary endpoint was growth velocity (cm/yr) over the double-blind treatment period, as determined by stadiometry for the Growth Population.

Baseline mean (SD) growth velocity was similar between the two treatment groups (5.839 [1.398] cm/yr for the placebo group and 5.801 [1.263] cm/yr for the FF 50 group). During treatment, the least squares (LS) mean growth velocity was 6.065 cm/yr for the placebo group (n=226) and 5.905 cm/yr for the FF 50 group (n=231); the LS mean difference (MD) in growth velocity was –0.160 cm/yr, (95% CI -0.462, 0.142).

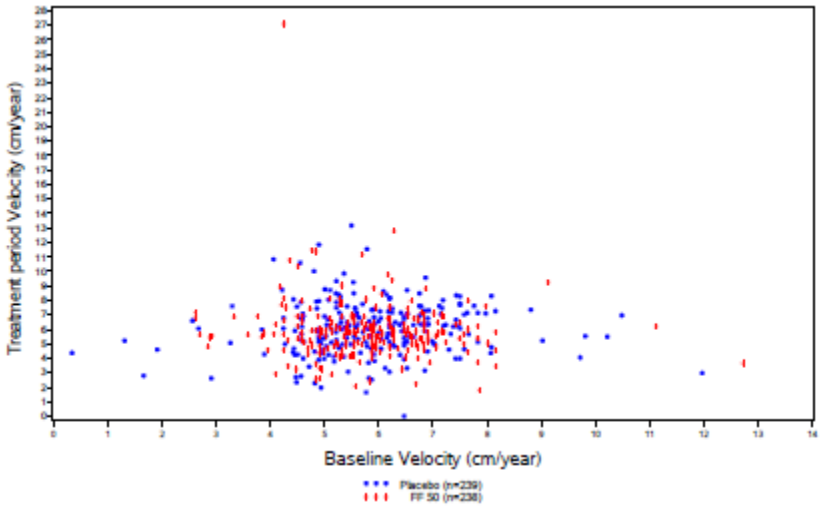
The relationship between the baseline period growth velocity and treatment period growth velocity for each participant is illustrated below by a scatter plot of growth velocity during the treatment period for the Growth Population (Figure 3.a) and for the ITT Population (Figure 3.b). The relationship was similar for both placebo and FF 50, and the velocity was similar when looking at baseline and the treatment period.

Figure 3.a. Distribution of Double-Blind Treatment vs Baseline Growth Velocity Using On- and Off-Treatment Height Measurements - Growth Population



Note: n is the number of subjects with non-missing baseline and double-blind treatment growth velocity.

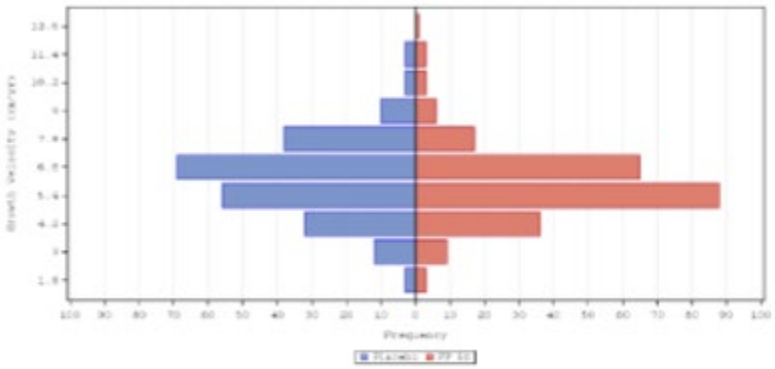
Figure 3.b. Distribution of Double-Blind Treatment vs Baseline Growth Velocity Using On- and Off-Treatment Height Measurements - Intent-to-Treat Population



Note: n is the number of subjects with non-missing baseline and double-blind treatment growth velocity.

The distribution of growth velocities during the treatment period is provided in Figure 4.

Figure 4. Growth Velocity (cm/yr) Over the Double-Blind Treatment Period (Growth Population)



Source: Figure 2.2

A summary of growth velocity using only on-treatment data is provided in Table 9.

Table 9. Summary of Growth Velocity (cm/yr) Using On-Treatment Height Data (Growth Population)

	Placebo (N=226)		FF 50 (N=231)	
	Raw	Change	Raw	Change
Baseline				
n	226		231	
Mean	5.839		5.801	
SD	1.3975		1.2631	
Median	5.817		5.826	
Min.	0.34		2.61	
Max.	11.97		12.72	
Treatment				
n	226	226	231	231
Mean	6.147	0.307	5.867	0.066
SD	1.7465	2.1800	1.5831	2.1322
Median	6.176	0.283	5.794	-0.096
Min.	1.64	-8.99	1.81	-9.06
Max.	11.84	6.95	13.22	6.93

Source: Table 2.4

Using only on-treatment height data, the LS mean growth velocity was 6.118 cm/yr for the placebo group and 5.896 cm/yr for the FF 50 group, similar to the primary analysis; the LS MD in growth velocity was -0.222 cm/yr, 95% CI (-0.528, 0.084).

Growth Velocity Supportive Analyses

Additional supportive analyses were also conducted for the primary endpoint. Statistical analyses showed that the treatment differences on LS mean growth velocities for all of these supportive analyses ranged from -0.027 to -0.357 cm/yr (Table 10) and the results were generally consistent with the primary analysis. The LS MD from each supportive analysis was contained within the bounds of the upper and lower limits of the 95% CI for the primary analysis [-0.160 cm/yr, 95% CI (-0.462, 0.142)].

Table 10. Summary of Growth Velocity Supportive Analyses

Analysis of Growth Velocity (cm/yr)	Placebo (N=226)	FF 50 (N=231)	FF 50 vs. Placebo
	LS mean (SE)		LS Mean Difference (95% CI)
Primary Endpoint			
On- and Off-Treatment Height Data (Primary Estimand) – Growth Population	n=226 6.065 (0.1090)	n=231 5.905 (0.1078)	-0.160 (-0.462, 0.142)
Supportive Analyses			
On- and Off-Treatment Height Data (Primary Estimand) Excluding Sites with Data Concerns – Growth Population	n=198 6.124 (0.1172)	n=203 5.928 (0.1157)	-0.195 (-0.520, 0.129)
On- and Off-Treatment Height Data (Supportive Estimand VIII) – Intent-to-Treat Population	n=239 6.043 (0.1280)	n=238 5.967 (0.1283)	-0.075 (-0.432, 0.282)
On-Treatment Height Data (Supportive Estimand I) – Growth Population	n=226 6.118 (0.1104)	n=231 5.896 (0.1092)	-0.222 (-0.528, 0.084)
Excluding Participants with Tanner Stage >= 2 (Supportive Estimand II) – Growth Population	n=226 6.119 (0.1106)	n=229 5.896 (0.1099)	-0.223 (-0.530, 0.084)
Excluding Questionable Height Measurements (Supportive Estimand III) – Growth Population	n=226 6.119 (0.1105)	n=231 5.904 (0.1093)	-0.215 (-0.521, 0.092)
Excluding Height Measurements Taken after Receiving Rescue Systemic Corticosteroids (Supportive Estimand IV) – Growth Population	n=222 6.045 (0.1198)	n=230 5.983 (0.1177)	-0.062 (-0.393, 0.269)
Excluding Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids (Supportive Estimand V) – Growth Population	n=217 6.000 (0.1269)	n=223 5.949 (0.1252)	-0.051 (-0.402, 0.300)
Excluding Participants with Tanner Stage >= 2 and/or Questionable Height Measurements and/or Height Measurements Taken after Receiving Rescue Inhaled and/or Intranasal and/or Systemic Corticosteroids (Supportive Estimand VI) – Growth Population	n=217 5.998 (0.1269)	n=222 5.972 (0.1254)	-0.027 (-0.379, 0.325)
Completers of One Year of Double-Blind Study Treatment (Supportive Estimand VII) – Growth Population	n=193 6.169 (0.1194)	n=198 5.910 (0.1179)	-0.259 (-0.590, 0.072)

Analysis of Growth Velocity (cm/yr)	Placebo (N=226)	FF 50 (N=231)	FF 50 vs. Placebo
Using On- and Off-Treatment Height Data - Imputation of Missing Week 52 Height Measurements – Approach I (Supportive Estimand IX) Intent-to-Treat Population	n=239 5.839 (0.1121)	n=238 5.683 (0.1121)	-0.156 (-0.467, 0.156)
Using On- and Off-Treatment Height Data - Imputation of Missing Week 52 Height Measurements – Approach II (Supportive Estimand X) Intent-to-Treat Population	n=239 6.043 (0.1119)	n=238 5.686 (0.1125)	-0.357 (-0.669, -0.045)

Source: Table 2.3, Table 2.5, Table 2.7, Table 2.9, Table 2.11, Table 2.13, Table 2.15, Table 2.17, Table 2.19, Table 2.21, Table 2.23, Table 2.58

Intercurrent Events

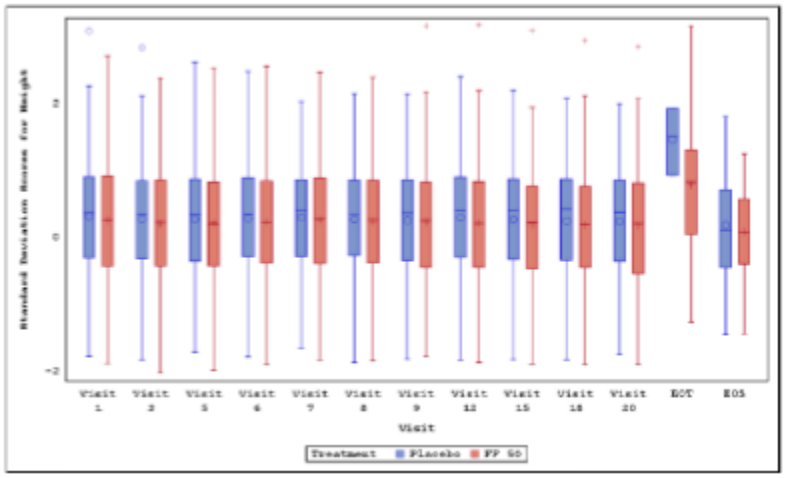
For the ITT Population the percentage of participants with an intercurrent event of rescue systemic corticosteroid use was 10% (25/239) and 7% (16/238) for the placebo and the FF 50 groups, respectively. Similar percentages, 11% (25/226) for the placebo group and 7% (16/231) for the FF 50 group), were seen for the Growth Population for this intercurrent event.

For the intercurrent event of rescue inhaled/intranasal corticosteroids use, the percentage of participants with this intercurrent event were 12% (28/239) and 12% (29/238) for the placebo and the FF 50 groups, respectively for the ITT Population. Similar percentages, 12% (27/226) for the placebo group and 12% (28/231) for the FF 50 group), were seen for the Growth Population.

- *Secondary Endpoints of Growth Velocity*

The Standard Deviation Scores (SDSs) for height showed normal growth in both treatment groups (see, Figure 5). For a given visit during the study, the distributions of SDS were similar between the two treatment groups.

Figure 5. Height Standard Deviation Scores (Growth Population)



Source: Figure 2.1 Abbreviations: EOT=early treatment discontinuation; EOS=early withdrawal from study

The change from baseline in height SDS was within expected variations over the course of one year, and was similar for both treatment groups (-0.02 for the placebo group and -0.04 for the FF 50 group).

The two groups were similar regarding percent of participants below the 3rd percentile of growth velocity, 9% (20/226) in the placebo group and 7% (16/231) in the FF 50 group.

Increases from baseline to endpoint (last 12 weeks on double-blind treatment) in growth velocity quartile occurred in a similar number of participants in the placebo (74/226, 33%) and FF 50 (73/231,

32%) groups; decreases in growth velocity quartile were more common in participants in the FF 50 group (88/231, 38%) than the placebo group (76/226, 34%).

Over the first 12 weeks of double-blind treatment, the LS mean (SD) growth velocity was 6.222 (0.185) cm/yr and 6.281 (0.184) cm/yr for the placebo and FF 50 groups, respectively; for the FF 50 group the LS MD in growth velocity was 0.059 cm/yr, with 95% CI (-0.455, 0.572).

- *Subgroup Analyses of Growth Velocity*

Since the number of participants is not balanced between the regional subgroups (US vs non-US) and the number of participants in one of the subgroups is small, caution should be taken when interpreting the results.

In the US region, the LS mean (SD) was 5.796 (0.243) for the placebo group and 6.055 (0.240) for the FF 50 group; the LS MD for the FF 50 group (95% CI) was 0.259 (-0.419, 0.938). For the non-US region, the LS mean (SD) was 6.180 (0.114) for the placebo group and 5.842 (0.113) for the FF 50 group; the LS MD (95% CI) was -0.338 (-0.654, -0.022).

A summary of growth velocity by gender is provided in Table 11.

Table 11. Summary of Growth Velocity (cm/yr) by Gender (Growth Population)

	Placebo (N=80)		FF 50 (N=93)	
	Raw	Change	Raw	Change
Gender: Female				
Baseline				
n	80		93	
Mean	5.773		5.720	
SD	1.5819		1.3524	
Median	5.798		5.545	
Min.	0.34		2.61	
Max.	11.97		11.12	
Treatment				
n	80	80	93	93
Mean	6.033	0.260	5.644	-0.077
SD	1.8021	2.2119	1.2244	1.8883
Median	6.198	0.108	5.709	0.303
Min.	2.28	-8.99	1.81	-6.04
Max.	11.54	5.75	9.42	4.56
Gender: Male				
Baseline				
n	146		138	
Mean	5.876		5.856	
SD	1.2898		1.2012	
Median	5.825		5.897	
Min.	1.91		2.61	
Max.	10.48		12.72	
Treatment				
n	146	146	138	138
Mean	6.129	0.253	6.031	0.176
SD	1.6380	2.1051	1.7957	2.2916
Median	6.082	0.276	5.843	-0.303
Min.	1.64	-5.67	2.25	-9.06
Max.	11.84	6.95	12.79	6.71

Source: Table 2.32

A summary of growth velocity (cm/yr) by ethnicity (Hispanic or Latino vs Not Hispanic or Latino) during the treatment period is provided in Table 12.

Table 12. Summary of Growth Velocity (cm/yr) by Ethnicity (Growth Population)

	Placebo (N=62)		FF 50 (N=65)	
	Raw	Change	Raw	Change
Ethnicity: Hispanic or Latino				
Baseline				
n	62		65	
Mean	5.465		5.552	
SD	0.9753		1.1944	
Median	5.290		5.425	
Min.	2.91		3.75	
Max.	7.83		11.12	
Treatment				
n	62	62	65	65
Mean	6.195	0.730	6.096	0.544
SD	2.1482	2.2292	1.8440	2.5067
Median	6.329	0.418	5.927	0.483
Min.	1.64	-4.12	2.25	-4.92
Max.	11.84	6.95	11.48	6.71
Ethnicity: Not Hispanic or Latino				
Baseline				
n	164		166	
Mean	5.981		5.899	
SD	1.5055		1.2793	
Median	5.918		5.928	
Min.	0.34		2.61	
Max.	11.97		12.72	
Treatment				
n	164	164	166	166
Mean	6.057	0.076	5.789	-0.110
SD	1.4938	2.0822	1.4893	1.9523
Median	6.087	0.198	5.699	-0.319
Min.	2.51	-8.99	1.81	-9.06
Max.	10.83	6.78	12.79	6.50

Source: Table 2.33

A random coefficient analysis was performed to support the primary analysis findings using an ANCOVA model with height as the dependent variable, and baseline height, age, gender, treatment, time, and treatment-by-time interaction as explanatory variables in the mixed effect model with random intercept and slope. The results of this sensitivity analysis were consistent with those of the primary analysis; the estimated mean (SD) growth velocities were 6.111 (0.110) cm/yr and 5.881 (0.108) cm/yr for placebo and FF 50, respectively, with a treatment difference of -0.230 cm/yr and 95% CI (-0.533, 0.074).

Adverse Events

An overview of AEs by number of events during pre-treatment and on-treatment is presented in Table 13. For both treatment groups, the overall rate of pre-treatment and on-treatment AEs were 33% and 57%, respectively. The majority of the AEs reported were of mild or moderate intensity. A single drug-related AE was reported in the FF 50 group. One participant in each group had an SAE; neither was considered to be related to study treatment. Please note that there may be minor discrepancies in the details of the SAEs included in the clinical narratives compared with the safety tabulations. This is because the data come from 2 different databases (i.e., locked clinical trials database and dynamic SAE database) and have been collected at different points in time.

Table 13. Adverse Events Overview (ITT Population)

	Placebo (N=239)	FF 50 (N=238)
Pre-Treatment		
Any Adverse Event	78 (33%)	79 (33%)
Drug-Related Adverse Events	0	1 (<1%)
Adverse Events Leading to Permanent Discontinuation~ of Study Drug or Withdrawal from the Study	0	0
Any Serious Adverse Event	1 (<1%)	1 (<1%)
Drug-Related Serious Adverse Events	0	0
Fatal Adverse Events	0	0
Drug-Related Fatal Adverse Events	0	0
On-Treatment		
Any Adverse Event	136 (57%)	136 (57%)
Drug-Related Adverse Events	0	1 (<1%)

	Placebo (N=239)	FF 50 (N=238)
Pre-Treatment		
Adverse Events Leading to Permanent Discontinuation~ of Study Drug or Withdrawal from the Study	0	1 (<1%)
Any Serious Adverse Event	6 (3%)	4 (2%)
Drug-Related Serious Adverse Events	0	0
Fatal Adverse Events	0	0
Drug-Related Fatal Adverse Events	0	0

Source: Table 2.37 Note: MedDRA version 24.0.

During the pre-treatment period, 78/239 (33%) participants in the placebo group and 79/238 (33%) participants in the FF 50 group experienced one or more AEs. The overall incidence of AEs on-treatment was 57% for the placebo and FF 50 groups (Table 14). The most frequently reported AEs occurred in the infections and infestations SOC (45% placebo; 47% FF 50). For both treatment groups, the most frequently reported AEs were upper respiratory tract infection, nasopharyngitis, rhinitis and influenza.

One participant in the FF 50 group experienced one or more AEs that led to withdrawal from the study. The incidence of AEs during the follow-up period was similar for the placebo and FF 50 groups (35/239 [15%] and 43/238 [18%] participants, respectively). Overall, during the study period 2/238 (<1%) participants in the FF 50 group experienced one or more AEs that were considered treatment-related by the investigator (Table 15).

Table 14. Summary of On-Treatment Adverse Events >= 3% of Participants in Any Treatment Group (ITT Population)

System Organ Class Preferred Term	Placebo (N=239)	FF 50 (N=238)
Any event	136 (57%)	136 (57%)
Infections and infestations		
Any event	107 (45%)	113 (47%)
Upper respiratory tract infection	33 (14%)	29 (12%)
Nasopharyngitis	25 (10%)	23 (10%)
Rhinitis	18 (8%)	16 (7%)
Bronchitis	12 (5%)	9 (4%)
Influenza	7 (3%)	11 (5%)
Respiratory tract infection viral	4 (2%)	10 (4%)
Pharyngitis	9 (4%)	3 (1%)
Tonsillitis	3 (1%)	6 (3%)
Acute sinusitis	6 (3%)	1 (<1%)
Respiratory, thoracic and mediastinal disorders		
Any event	38 (16%)	30 (13%)
Cough	15 (6%)	12 (5%)
Rhinitis allergic	9 (4%)	8 (3%)
Rhinorrhoea	8 (3%)	3 (1%)
Gastrointestinal disorders		

System Organ Class Preferred Term	Placebo (N=239)	FF 50 (N=238)
Any event	27 (11%)	20 (8%)
Vomiting	6 (3%)	7 (3%)
Diarrhoea	6 (3%)	3 (1%)
Toothache	6 (3%)	1 (<1%)
General disorders and administration site conditions		
Any event	20 (8%)	13 (5%)
Pyrexia	18 (8%)	13 (5%)
Nervous system disorders		
Any event	13 (5%)	10 (4%)
Headache	12 (5%)	10 (4%)
Skin and subcutaneous tissue disorders		
Any event	3 (1%)	13 (5%)
Injury, poisoning and procedural complications		
Any event	8 (3%)	4 (2%)

Source: Table 2.39

- *Drug-Related Adverse Events*

Two (<1%) participants in the FF 50 group were reported with drug-related AEs that included abdominal pain, constipation, oropharyngeal candidiasis, and decreased appetite (more than 1 AE was reported per participant) (Table 15). All of the drug-related AEs were reported as non-serious.

Table 15. Summary Of All Drug-Related Adverse Events (ITT Population

System Organ Class Preferred Term	Placebo (N=239)	FF 50 (N=238)
Any event	0	2 (<1%)
Gastrointestinal disorders		
Any event	0	1 (<1%)
Abdominal pain	0	1 (<1%)
Constipation	0	1 (<1%)
Infections and infestations		
Oropharyngeal candidiasis	0	1 (<1%)
Metabolism and nutrition disorders		
Decreased appetite	0	1 (<1%)

Source: Table 2.42

- *Common Adverse Events*

The incidence of common (occurring in ≥3% of participants in any treatment group) AEs overall was similar between treatment groups (44% [105/239] in the placebo group and 42% [99/238] in the FF 50 group). The most commonly reported PTs were upper respiratory tract infection, nasopharyngitis, rhinitis, and pyrexia (Table 16). A summary of common (occurring in ≥3% of participants in any treatment group) non-serious on-treatment AEs by number of participants and occurrences during treatment is presented in Table 16.

Table 16. Summary of Common >=3% On-Treatment Non-serious Adverse Events (Number of Subjects and Occurrences)

System Organ Class Preferred Term	Number of Subjects (%) / Events / Drug-Related Events Placebo (N=239)	 FF 50 (N=238)
Any event	105 (44%) / 243 / 0	99 (42%) / 202 / 0
General disorders and administration site conditions		
Any event	18 (8%) / 23 / 0	13 (5%) / 15 / 0
Pyrexia	18 (8%) / 23 / 0	13 (5%) / 15 / 0
Infections and infestations		
Any event	85 (36%) / 152 / 0	84 (35%) / 143 / 0
Bronchitis	12 (5%) / 13 / 0	9 (4%) / 11 / 0
Influenza	7 (3%) / 8 / 0	11 (5%) / 11 / 0
Nasopharyngitis	25 (10%) / 31 / 0	23 (10%) / 26 / 0
Pharyngitis	9 (4%) / 10 / 0	3 (1%) / 3 / 0
Respiratory tract infection viral	4 (2%) / 7 / 0	10 (4%) / 11 / 0
Rhinitis	18 (8%) / 26 / 0	16 (7%) / 18 / 0
Upper respiratory tract infection	33 (14%) / 57 / 0	29 (12%) / 63 / 0
Nervous system disorders		
Any event	12 (5%) / 24 / 0	10 (4%) / 17 / 0
Headache	12 (5%) / 24 / 0	10 (4%) / 17 / 0
Respiratory, thoracic and mediastinal disorders		
Any event	27 (11%) / 44 / 0	19 (8%) / 27 / 0
Cough	15 (6%) / 23 / 0	12 (5%) / 15 / 0
Rhinitis allergic	9 (4%) / 11 / 0	8 (3%) / 9 / 0
Rhinorrhoea	8 (3%) / 10 / 0	3 (1%) / 3 / 0

Note: Common is defined as >=3% (without rounding) in any treatment.

- *Adverse Events and COVID-19 Pandemic*

The two treatment groups were similar with respect to AEs and SAEs for the pre-pandemic and during pandemic periods.

Serious and Other Significant Adverse Events

SAEs were reported for 6/239 (3%) participants in the placebo group and 4/238 (2%) participants in the FF 50 group. None of the SAEs was considered by the investigator to be related to study treatment and no dose relationship or pattern of events was observed. See, case narratives.

- *Deaths*

No participants died during the study.

- *Other Serious Adverse Events*

Pre-treatment SAEs were reported for 1 participant in each treatment group. The participant in the placebo group had an SAE of fracture, and the participant in the FF 50 group had an SAE of tonsilitis.

Post-treatment SAEs were reported for 1 participant in each treatment group. The participant in the placebo group had an SAE of asthma, and the participant in the FF 50 group had an SAE of bronchitis.

- *Drug-Related Serious Adverse Events*

There were no drug-related SAEs reported during the study.

- *Other Significant Adverse Events*

One participant in the FF 50 group reported an AE of asthma deterioration leading to permanent discontinuation of study treatment or withdrawal from the study. The participant was an 8-year-old white boy with asthma deterioration reported 206 days after the first dose of study treatment, with a

duration of 12 days. The participant was withdrawn from study treatment, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment.

Overall, there were 45/239 (19%) participants in the placebo group and 44/238 (18%) participants in the FF 50 group with Adverse Events of Special Interest (AESIs) during the study. The most frequently reported AESI for both groups was bronchitis (15/239 [6%] participants in the placebo group and 12/238 [5%] in the FF 50 group), followed by allergic rhinitis (12/239 [5%] participants in the placebo group and 9/238 [4%] in the FF 50 group).

Two serious AESIs were reported in each of the treatment groups, during and after treatment. The reported serious AESIs in the placebo group were pneumonia and diabetes mellitus, whereas the serious AESIs reported in the FF 50 group were pneumonia and bronchitis.

Clinical Laboratory Evaluations

There were no protocol-mandated clinical laboratory evaluations performed during this study.

Asthma Exacerbations

During the treatment period, more participants in the placebo group (22/239 participants, 9%) than in the FF 50 group (7/238 participants, 3%) experienced at least one asthma exacerbation (Table 17). This difference is evidence of treatment compliance by participants in the FF 50 group.

One participant in each treatment group permanently discontinued study treatment due to an exacerbation. More participants in the placebo group reported that they took systemic/oral corticosteroids for an exacerbation than in the FF 50 group (22/239 [9%] and 7/238 [3%] participants, respectively). More participants in the placebo group were hospitalised due to an exacerbation, and visited the emergency room due to an exacerbation. After the treatment period, the two treatment groups were similar with respect to asthma exacerbations.

Table 17. Summary of Asthma Exacerbations Over the Double-Blind Treatment Period Using On- and Post-Treatment Data (ITT Population)

	Placebo (N=239)	FF 50 (N=238)
Phase: On-Treatment		
Any asthma exacerbations	22 (9%)	7 (3%)
Number of Asthma Exacerbations	30	8
Exacerbation Frequency		
0	217 (91%)	231 (97%)
1	18 (8%)	6 (3%)
2	2 (<1%)	1 (<1%)
3	0	0
4	2 (<1%)	0
>4	0	0
Permanently Discontinued Study Treatment due to an Exacerbation	1 (<1%)	1 (<1%)
Took Systemic/Oral Corticosteroids for an Exacerbation	22 (9%)	7 (3%)
Hospitalized due to an Exacerbation	1 (<1%)	0
Visited Emergency Room due to an Exacerbation	6 (3%)	0
Took Systemic/Oral Corticosteroids or Hospitalized or Visited Emergency Room	22 (9%)	7 (3%)
Phase: Post-Treatment		
Any asthma exacerbations	4 (2%)	3 (1%)
Number of Asthma Exacerbations	4	3
Exacerbation Frequency		
0	235 (98%)	235 (99%)
1	4 (2%)	3 (1%)
2	0	0
3	0	0
4	0	0
>4	0	0
Permanently Discontinued Study Treatment due to an Exacerbation	0	1 (<1%)
Took Systemic/Oral Corticosteroids for an Exacerbation	4 (2%)	3 (1%)
Hospitalized due to an Exacerbation	1 (<1%)	0
Visited Emergency Room due to an Exacerbation	0	0
Took Systemic/Oral Corticosteroids or Hospitalized or Visited Emergency Room	4 (2%)	3 (1%)

Source: Table 2.56

Pneumonia

Two (<1%) participants in the placebo group (n=239) and 3 (1%) participants in the FF50 group (n=238) reported pneumonia while on treatment. Post-treatment, 1 (<1%) participant in each group reported pneumonia.

For the two participants in the placebo group, one participant was a 5-year-old white girl with pneumonia reported 239 days after the first dose of study treatment, with a duration of 11 days. Study treatment was not changed, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment. The other participant was a 5-year-old white boy with pneumonia reported 195 days after the first dose of study treatment, with a duration of 15 days. Study treatment was not changed, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment. For the three participants in the FF 50 group, the first was a 7-year-old white girl reported with mycoplasmal pneumonia 32 days after the first dose of study treatment, with a duration of 24 days. Study treatment was not changed, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment. The second participant as a 7-year-old white girl reported with pneumonia 181 days after the first dose of study treatment, with a duration of 8 days. Study treatment was not changed, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment. The third participant was a 5-year-old white boy reported with walking pneumonia 230 days after first dose of study treatment, with a duration of 9 days. Study treatment was not

changed, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment.

2.3.3. Discussion on clinical aspects

This Article 46 procedure of Regulation (EC) No1901/2006, concerns the submission of a stand-alone study, which is the HZA114971 study: "A Multicentre Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate 50 mcg once daily on Growth Velocity in Prepubertal, Paediatric Subjects with Asthma". Study HZA114971 is part of the EU Paediatric Investigation Plan of fluticasone furoate/vilanterol trifenatate inhalation powder (FF/VI) agreed upon for the treatment of asthma indication (EMEA-000431-PIP01-08-M12; see, PIP Study 13).

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.

HZA114971 was a randomised, single-blind (placebo run-in period) / double-blind (treatment period), parallel group, placebo controlled, multicentre study to assess the effect of once daily (OD) orally inhaled FF 50 mcg on growth velocity in prepubertal (Tanner Stage 1) asthmatic children aged 5 to <9 years on a background therapy of open-label montelukast. After completing a 16-week placebo run-in period, eligible subjects were randomised (1:1) to receive placebo or FF 50 mcg during a 52-week period. All participants received open-label montelukast (OD, 4 mg for subjects who are 5 years old and 5 mg for subjects who are ≥6 years old) as chewable tablets throughout the entire study period (76 weeks: 16-week run-in period; 52-week double-blind treatment period; and 8-week follow-up period). Albuterol/salbutamol (inhalation aerosol or nebuliser) was received as rescue medication from the run-in period through to the end of an 8-week follow-up period.

The primary objective was to evaluate the magnitude of effect (with a level of precision) of orally inhaled FF 50 mcg versus orally inhaled placebo on growth velocity in prepubertal children over one year of treatment. The primary endpoint, growth velocity, was determined by stadiometry over the double blind treatment period. Secondary endpoints included the proportion of subjects below the 3rd percentile of growth velocity, the change in growth velocity quartiles from baseline to endpoint, growth velocity over the first 12 weeks of double-blind treatment period and height standard deviation scores (SDS) at each visit. The primary population for the primary growth analysis was the Growth Population, which only includes randomised patients who received at least one dose of study treatment (ITT population) with height assessments from at least three post-randomisation, on-treatment clinic visits during the double-blind treatment period. The submitted study methodology appears adequate for its primary objective.

Safety of orally inhaled FF 50 mcg OD was also determined by measuring the incidence of adverse events and asthma exacerbations. The assessment of the effect of orally inhaled FF 50 mcg OD on some efficacy endpoints (PEF and asthma symptoms), were used as a measure of compliance to help identify nonadherence and/or poorly controlled asthma. All safety and efficacy (compliance assessments) data analyses used the ITT Population.

239 subjects in the placebo group and 238 subjects in the FF 50 group out of the 874 screened participants entered the run-in period, but only 477 of them met the randomisation criteria to be

randomised to receive study treatment. All 477 randomised participants were included in the ITT Population (239 subjects in the placebo group and 238 subjects in the FF 50 group) and 457/477 participants (96% of participants in ITT Population) were included in the Growth Population (226 subjects in the placebo group and 231 subjects in the FF 50 group). 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 two treatment groups were similar with respect to age, race, ethnicity, medical conditions, asthma history, and lung function. All participants were children between the ages of 4 and 9 years, and the mean (±SD) age between groups was similar, 6.1 (1.07) for the placebo group (n=239) and 6.3 (1.02) for the FF 50 group (n=238). The majority of the participants were White (412/477 [86%]) and male (299/477 [63%]). The mean BMI of participants was similar between treatment groups, 16.36 (1.70) for the placebo group and 16.52 (1.73) for the FF 50 group.

Study treatment exposure was slightly higher for the FF 50 group (344.0 mean days of exposure for the placebo group and 334.5 for the FF 50 group).

Baseline mean growth velocity was similar between the two treatment groups (5.839 cm/yr for placebo [n=226] and 5.801 cm/yr for FF 50 [n=231]). During treatment, the least-squares (LS) mean growth velocity was 6.065 cm/yr for the placebo group and 5.905 cm/yr for the FF 50 group. The LS mean treatment difference for FF 50 versus placebo from the primary analysis was -0.160 cm/yr (95% CI: -0.462, 0.142). The effect on growth after one year did not result in any clinically meaningful drop in height Standard Deviation Scores (SDS) with a mean change from baseline of -0.04 SDS in the FF group and -0.02 SDS in the placebo group. Obtained growth data could suggest that children were still growing along the same centile.

The overall rate of on-treatment adverse events (AEs) was 57% for both treatment groups (136/239 in the placebo group and 136/238 in the FF 50 group). The majority of the AEs reported were of mild or moderate intensity. One participant in each group had an SAE. One participant in the FF 50 group experienced AEs that led to withdrawal from the study, the outcome was recovered/resolved, and the event was considered by the investigator as not related to study treatment. During the study period, 2/238 participants in the FF 50 group experienced one or more drug-related AEs considered as non-serious by the investigator. There were no deaths and no drug-related SAEs reported. Overall, it is considered that no safety signals have been emerged from the study findings.

There were no clear differences between the two groups regarding their measures of compliance. This may be explained by the relatively mild asthma in the children recruited in the study and in part at least by the background montelukast in both groups.

Assuming that the study was not powered to detect any treatment differences, the obtained results suggests that, compared with placebo, a one-year regimen of orally inhaled FF 50 mcg had no effect on growth velocity in prepubertal asthmatic children aged 5 to <9 years on a background therapy of open-label montelukas.

Since the provided results for FF 50 mcg are in line with the approved product information in the EU for FF/VI formulations (100/25 mcg and 200/25 mcg), no regulatory action required at this point.

3. CHMP's overall conclusion and recommendation

In accordance with Article 46 of Regulation (EC) No1901/2006, the MAH submitted a final study report for study number HZA114971 "A Multicentre Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate 50 mcg once daily on Growth Velocity in Prepubertal, Paediatric Subjects with Asthma". This study is part of the EU Paediatric Investigation Plan of fluticasone furoate/vilanterol trifenatate inhalation powder (FF/VI) agreed upon for the treatment of asthma indication (EMEA-000431-PIP01-08-M12).

HZA114971 was a randomised, single-blind (placebo run-in period) / double-blind (treatment period), parallel group, placebo-controlled, multicentre study to assess the effect of once-daily orally inhaled FF 50 mcg on growth velocity in prepubertal asthmatic children aged 5 to <9 years on a background therapy of open-label montelukast.

Assuming that the study was not powered to detect any treatment differences, the obtained results suggests that, compared with placebo, a one-year regimen of orally inhaled FF 50 mcg had no effect on growth velocity in prepubertal asthmatic children aged 5 to <9 years on a background therapy of open-label montelukast.

Since the provided results for FF 50 mcg are in line with the approved product information in the EU for FF/VI formulations (100/25 mcg and 200/25 mcg), no regulatory action is required at this point.

☒ **Fulfilled:**

No regulatory action required.