NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	205625/S-009
Priority or Standard	Standard
Submit Date(s)	May 4, 2022
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PDUFA Goal Date	March 3, 2023
Division/Office	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review Completion Date	February 28, 2023
Established/Proper Name	fluticasone furoate inhalation powder
(Proposed) Trade Name	ARNUITY ELLIPTA
Pharmacologic Class	Inhaled corticosteroid (ICS)
Applicant	GlaxoSmithKline Intellectual Property Development Ltd. England
Dosage form	Oral Inhalation
Dosing Regimen	For patients aged 12 years and older: one inhalation of 100 mcg or 200 mcg once daily; For patients aged 5 to 11 years old: one inhalation of 50 mcg once daily.
Indication(s)/Population(s)	For once-daily maintenance treatment of asthma as prophylactic therapy in patients aged 5 years and older
SNOMED CT Indication Disease Term	Asthma
Recommendation on Regulatory Action	Approval

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Glossary

AE	adverse event
BRF	Benefit Risk Framework
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CSR	clinical study report
DPI	dry powder inhaler
FDA	Food and Drug Administration
FF 50	Fluticasone furoate 50 mcg
GCP	good clinical practice
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
PI	prescribing information
PMR	postmarketing requirement
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
SAE	serious adverse event
SAP	statistical analysis plan
sNDA	supplemental New Drug Application
SMQ	standard MedDRA query
TEAE	treatment emergent adverse event

1 Executive Summary

Product Introduction

Arnuity Ellipta (fluticasone furoate inhalation powder) is an inhaled corticosteroid (ICS) administered by the Ellipta dry powder inhaler device (DPI). The approved indication is for the maintenance treatment of asthma in patients aged 5 years and older. Pediatric efficacy supplement 009 provides data to evaluate the effect on growth velocity of prepubertal pediatric participants (aged 5 to <9 years) with asthma following administration of once daily inhaled fluticasone furoate (FF) 50 mcg compared to placebo for one year. The pediatric growth study has been conducted and submitted to fulfill a PREA PMR.

2 Conclusions and Recommended Action

This sNDA includes a pediatric growth study to fulfill a PREA PMR for FF 50 (Arnuity Ellipta inhalation powder) which is approved for the maintenance treatment of asthma in patients 5 years of age and older. The pediatric growth study was conducted in accordance with FDA Guidance for Industry in 477 prepubertal children who were 5 to 8 years of age with asthma. The primary endpoint of growth velocity over the 52-week treatment period demonstrated that treatment with FF 50 resulted in a -0.16 cm decrease in growth velocity compared to placebo. The primary analysis for this trial had a 95% confidence interval length of 0.60 cm for the difference in growth velocity between FF 50 and placebo groups. Although slightly larger than the FDA Guidance recommendation for a 95% confidence interval length of 0.5 cm or less, the confidence interval in this study was not considerably wider than 0.5 cm, and the results of the primary analysis were interpretable with reasonable precision in the estimate of treatment effect and were consistent with all growth velocity supportive analyses. The clinical relevance of this small decrease in growth velocity on longer term growth or final adult height is unknown. Given the established benefit on lung function, the benefit/risk assessment for FF 50 in the pediatric population remains favorable.

The recommended regulatory action for this pediatric supplement is Approval. This submission fulfills PMR 2765-3.

Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

This sNDA consists of the final clinical study report to fulfill a PREA PMR (2765-3) to evaluate the effect of Arnuity Ellipta (fluticasone furoate inhalation powder) on the growth velocity of pediatric patients with asthma. Study HZA 114971, was a 52-week randomized, double-blind, parallel-group, placebo-controlled, multicenter study in prepubertal subjects with asthma on a background therapy of open-label montelukast. The study randomized 477 prepubertal subjects (238 to Arnuity Ellipta and 239 to placebo) who were 5 to <8 years (girls) or 5 to <9 years (boys) of age. The study design, sample size, conduct and endpoints were consistent with FDA guidance on conducting growth studies for orally inhaled and intranasal corticosteroids. Over 52 weeks of treatment, FF 50 resulted in a small, but not statistically significant effect on the growth velocity in this population of prepubertal pediatric subjects with asthma compared to placebo. The primary analysis for this trial had a 95% confidence interval length of 0.60 cm for the difference of growth velocity between FF 50 and placebo groups. This was slightly larger than the Growth Guidance recommendation that studies should attain a 95% confidence interval length of 0.5 cm or less. However, the confidence interval was not considerably wider than 0.5 cm and the results of the primary analysis were interpretable with reasonable precision in the estimate of treatment effect and were consistent with all growth velocity supportive analyses. The clinical relevance of this small decrease in growth velocity on longer term growth or final adult height is unknown. Given the established benefit on lung function, the benefit/risk assessment for FF 50 in the pediatric population remains favorable, and healthcare providers should continue to weigh the benefits and potential risks for an individual patient when prescribing. PREA PMR 2765-3 has been fulfilled.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a chronic respiratory disease that affects approximately XX of children in the United States • Symptoms are caused by inflammation and narrowing of small airways and may include shortness of breath, cough, wheeze, and chest pain/tightness • Diagnosis is based on pattern of symptoms, response to therapy over time, and spirometry • Asthma is classified according to frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate	Asthma is a chronic respiratory disease that may have significant impacts on morbidity and quality of life.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Disease severity ranges from mild/infrequent symptoms to severe persistent symptoms that impact activity level and quality of life • Asthma exacerbations lead to missed days of school/work and may require urgent medical visits, increased therapy, and occasionally hospitalization	
Current Treatment Options	• Many treatment options are available for asthma • Treatment guidelines recommend a tailored step-wise approach for achieving asthma control • ICS-containing controller medications are the preferred first-line therapy	While numerous treatment options exist, ICS-containing therapies such as FF 50 (Arnuity Ellipta) are considered first-line therapy.
Benefit	• ICS play a principal therapeutic role in asthma management by decreasing airway inflammation • Efficacy data supporting an indication for FF 50 in children ages 5-11 years with asthma demonstrated a significant improvement in morning peak expiratory flow for FF 50 compared to placebo • FF 50 is administered once daily	FF 50 provides a once daily treatment option and has an established benefit on lung function in adult and pediatric patients.
Risk and Risk Management	• ICS have a well-established safety profile in adults and children • The inhaled route of administration has lower exposure and therefore systemic effects of ICS are less common compared to systemic steroids. However, several studies with different active corticosteroid moieties have demonstrated reduced growth velocities over a 1-yr time period of approximately 1 cm/year among active treatment groups exposed to orally inhaled or intranasal corticosteroids compared to placebo or non-corticosteroid control groups. • FF 50 decreased growth velocity by -0.16 cm in prepubertal pediatric subjects with asthma compared to placebo. The primary analysis for this trial had a 95% confidence interval length of 0.60 cm for the difference of growth velocity between FF 50 and placebo groups. The	FF 50 resulted in a small, but not statistically significant decrease in growth velocity over 52 weeks compared to placebo. The clinical relevance of this small decrease in growth velocity on longer term growth or final adult height is unknown. No new safety signals were identified in the study.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	primary analysis was interpretable with reasonable precision in the estimate of treatment effect and was consistent with all growth velocity supportive analyses.	

Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

				Section of review where discussed, if applicable
X	**The patient experience data that were submitted as part of the application include:**			
	X	Clinical outcome assessment (COA) data, such as Childhood Asthma Control Test (cACT)		Section 8 Statistical and Clinical and Evaluation
		X	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	**Patient experience data was not submitted as part of this application.**			

3 Therapeutic Context

Analysis of Condition

Asthma affects over 25 million Americans and is one of the most common chronic diseases of childhood, affecting over 4 million children[1]. Current treatment strategies aim to control symptoms, reduce impairment, and prevent exacerbations. According to asthma treatment guidelines, ICS-containing controller treatments are considered first-line maintenance therapy for pediatric patients, and allow for the control of asthma symptoms, improvement in lung function and decreased airway hyper-responsiveness[2].

Analysis of Current Treatment Options

The armamentarium of approved asthma maintenance therapies for pediatric patients < 12 years of age is shown in Table 1. Arnuity Ellipta (fluticasone furoate inhalation powder) 50 mcg, referred to as FF 50 in this review, was approved in 2018 for the treatment of asthma patients 5 to 11 years old.

Table 1. Currently Available Asthma Maintenance Treatments for Pediatric Patients < 12 years of Age

Drug Class	Non-proprietary Name	Trade Name	Approved Age*
	Fluticasone furoate inhalation powder	Arnuity Ellipta	≥ 5 years old
	Mometasone inhalation powder	Asmanex Twisthaler	≥ 4 years old
	Fluticasone propionate inhalation powder	Flovent Diskus	≥ 4 years old
	Fluticasone propionate	Flovent HFA	≥ 4 years old
	Budesonide inhalation powder	Pulmicort Flexhaler	≥ 6 years old
	Budesonide inhalation suspension	Pulmicort Respules	12 months – 8 year
	Beclomethasone dipropionate	QVAR HFA	≥ 4 years old
ICS/LABA	Fluticasone propionate/ salmeterol	Advair Diskus and HFA Wixela Inhub	≥ 4 years old
	Budesonide/formoterol fumarate	Symbicort HFA Breyna	≥ 6 years old
LAMA	Tiotropium bromide inhalation powder	Spiriva Respimat	≥ 6 years old

[1] Centers for Disease Control and Prevention. Most Recent Asthma Data. Asthma 2020 [cited November 7, 2022]; Available from: https://www.cdc.gov/asthma/most_recent_data.htm
[2] GINA Main Report 2022: https://ginasthma.org/gina-reports/

Leukotriene modifiers	Montelukast	Singulair	≥ 12 months old
	Zafirlukast	Accolate	≥ 5 years old
	Zileuton	Zyflo	≥ 12 months old
Biologics	Dupilumab (anti-IL4 receptor antagonist)	Dupixent	≥ 6 years old
	Mepolizumab (anti-IL5)	Nucala	≥ 6 years old
	Omalizumab (anti-IgE)	Xolair	≥ 6 years old
Xanthines	Theophylline	Multiple drugs, including Theo-24, Theochron, Elixophyllin	Children and adults

*Approved age for asthma indication

Regulatory Background

U.S. Regulatory Actions and Marketing History

NDA 205625 Arnuity Ellipta (fluticasone furoate inhalation powder) was approved in 2014 for the maintenance treatment of asthma in patients aged 12 years and older with the partial waiver of pediatric study requirements for patients less than 5 years of age and with 4 PMRs (2765-1, 2765-2, 2765-4, and 2765-3) for pediatric studies in patients 5 to 11 years old.

In 2017, the Applicant submitted a pediatric efficacy supplement (S005) that fulfilled 3 PMRs for pediatric safety and efficacy studies (2765-1, 2765-2, and 2765-4) and expanded the indication to the maintenance treatment of asthma in patients aged 5 years and older. The pediatric efficacy supplement (S005) was approved in 2018.

4 Significant Issues from Other Review Disciplines

None. Arnuity Ellipta is an approved product for pediatric patients 5 years of age and older with asthma. No new data related to product quality, pharmacology toxicology, or clinical pharmacology was submitted or required for this supplement.

5 Sources of Clinical Data and Review Strategy

Table of Clinical Studies

Table 2. Clinical Trial Relevant to this sNDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Safety								
HZA 114971	0288 9809	Randomized, double-blind, parallel group, placebo-control	Fluticasone furoate (FF) 50 mcg or placebo one inhalation once daily on background of montelukast 4 or 5 mg by mouth once daily	Growth velocity (cm/year) over 52 weeks, as determined by stadiometry	52-week treatment duration, 8-week follow-up	N=477: 238 FF 239 PBO	Prepubertal boys 5 to <9 years and girls 5 to <8 years with asthma ≥6 months	67 sites in 6 countries (US, Argentina, Poland, Romania, Russia, South Africa)

Review Strategy

The sNDA submission contains one PREA PMR study, HZA114971, to evaluate the effect of inhaled fluticasone furoate 50 mcg versus placebo once daily on growth velocity in prepubertal children over one year of treatment. As efficacy has already been demonstrated in pediatric patients 5-11 years of age, the clinical review focuses on the safety data related to growth; however, efficacy outcomes captured in the study are discussed briefly in this review.

6 Statistical and Clinical Evaluation

Trial HZA114971

Protocol Description

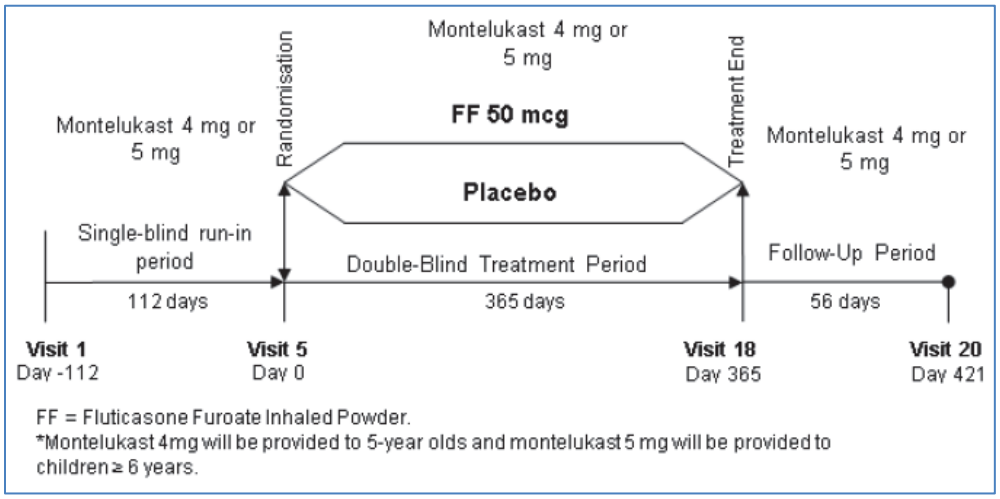
Title

A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Effects of a One-Year Regimen of Orally Inhaled Fluticasone Furoate (FF) 50 mcg once daily on Growth Velocity in Prepubertal, Pediatric Subjects with Asthma

Trial Design

Study HZA114971 was a randomized, single-blind (run-in period)/double-blind (treatment period), parallel-group, placebo-controlled, multicenter phase 4 study to assess the effect of FF 50 mcg (Arnuity Ellipta) once daily on growth velocity in prepubertal subjects with asthma on a background therapy of open-label montelukast. The Study Schematic is shown in Figure 1 below. The study, in its entirety, was 533 days and included a 16-week run-in period, a 52-week double-blind treatment period, and an 8-week follow-up period. All subjects received open-label oral montelukast daily per age-based dosing. During the single-blind run-in period, all subjects received a placebo Ellipta inhaler (to which subjects were blinded) for use once daily. During the double-blind treatment period, subjects who remained eligible for the study were randomized to receive either Arnuity Ellipta (hereafter referred to as FF 50) or placebo via the Ellipta inhaler administered as one inhalation once daily. Study visits occurred every 4 weeks throughout the entire study. The schedule of study assessments is shown in Table 20.

Figure 1. HZA114971 Study Schematic



Source: HZA114971 CSR, Figure 1, p18

Reviewer comment: The study design is consistent with recommendations in the FDA *Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children*[3], which include:

- A baseline period of at least 16 weeks to assess baseline growth velocity
- A treatment period of at least 48 weeks to assess the primary endpoint of growth velocity
- A follow-up period of at least 8 weeks to assess potential for short-term catch-up growth
- A control arm with a clinically appropriate non-steroidal medication

Study Population

The protocol specified that approximately 900 pediatric asthma patients would be screened to randomize at least 450 and achieve 406 evaluable subjects with approximately 203 evaluable subjects per treatment group. At screening (Visit 1), subjects who met the inclusion criteria were enrolled in the run-in period of the study. At Visit 5, only subjects who met the randomization criteria entered the double-blind treatment period and were randomized to FF 50 or placebo treatment arms.

Key Inclusion Criteria

Demographics

1. Male or female
2. Age:

[3] Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children, 2007. https://www.fda.gov/media/71624/download

   a. Males between 5 and <9 years old
   b. Females between 5 and <8 years old
3. Pre-pubertal (Tanner Stage 1)
4. Height between 3% and 97% percentile based on US CDC charts
5. Body weight and body mass index between 3rd and 97th centile based on US CDC charts

Disease and Severity

6. A documented history of symptoms consistent with a diagnosis of asthma for at least 6 months prior to Visit 1 (Screening)
7. A pre-bronchodilatory FEV1 at Visit 1 (Screening) of ≥60%. There should be no SABA use within 4 hours of this measurement[4]
8. Ability to replace current SABA treatment with study supplied rescue albuterol/salbutamol provided at Visit 1 (Screening) for use as needed for the duration of the study
9. A cACT score of >19
10. At least one course of inhaled or oral corticosteroids for asthma (inhaled or oral) in the past year AND
    a. No ICS use within 6 weeks of Visit 1 (Screening).
    b. No oral corticosteroid use within 12 weeks of Visit 1 (Screening)
11. Use of the following asthma therapies prior to entry into the study:
    a. Short acting beta-agonist (SABA) inhaler alone as needed AND/OR
    b. Regular non-ICS controller medications for asthma (e.g. cromones or leukotriene receptor antagonists).

Consent

12. Written informed consent from at least one parent/care giver (legal guardian) and accompanying informed assent from the subject (where the subject is able to provide assent) prior to admission to the study.

<u>Key Exclusion Criteria</u>

Current Condition and Medical History

1. Growth Criteria:
   a. Any previous or current condition that affects growth, (e.g., sleep disorders, endocrine disorders, skeletal dysplasia, Turner and Noonan syndromes, Marfan, Beckwith–Wiedeman and Sotos syndromes, Klinefelter's syndrome, coeliac disease, inflammatory bowel diseases and renal failure)
   b. Premature adrenarche
   c. Inability to stand due to illness or physical disabilities
2. Disease Criteria:

[4] Only subjects who were unable to perform the FEV1 maneuver at their Visit 1 could, at the discretion of the investigator, attend the clinic to perform the maneuver once more on another day. The repeat FEV1 maneuver must be acceptable and must meet the FEV1 inclusion limits to be eligible for the study.

d. History of asthma exacerbation requiring hospitalization (within 6 months) prior to screening
e. Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved within 4 weeks of Visit 1 and led to a change in asthma management or, in the opinion of the Investigator, is expected to affect the subject's asthma status or the subject's ability to participate in the study
f. Clinical visual evidence of candidiasis at Visit 1 (Screening).
g. Any significant abnormality or medical condition identified at the screening medical assessment that in the Investigator's opinion, preclude entry into the study due to risk to the subject or that may interfere with the outcome of the study.

Concomitant Medications

3. Prior use of any medication or treatment that might affect growth (e.g., amphetamines, anabolic steroids, anticonvulsants, biphosphonates, calcitonin, erythropoietin, estrogens, growth hormone, methylphenidate, phosphate binders, antithyroid drugs or thyroid hormone or testosterone)
4. Use any of the prohibited medications listed below:
    h. Within 2 weeks prior to Visit 1 (Screening) and at any time during the study:
        i. Theophylline
        ii. Any prescription or OTC medication that would significantly affect the course of asthma, or interact with study drug
    i. Within 6 weeks prior to Visit 1 (Screening) and at any time during the study:
        i. Intranasal, inhaled and high potency topical corticosteroids
        ii. Oral or inhaled long-acting beta2-agonists (LABAs), including LABA-containing combination products (e.g. SERETIDE™, Symbicort, Dulera)
        iii. Potent Cytochrome P450 3A4 (CYP3A4) inhibitors (Clarithromycin, atazanavir, indinavir, itraconazole, ketoconazole, nefazadone, nelfinavir; ritonavir; saquinavir; telithromycin, troleandomycin, voriconazole, mibefradil, cyclosporine)
    j. Within 12 weeks prior to Visit 1 (Screening) and at any time during the study:
        i. Systemic, oral, or depot corticosteroids
        ii. Anti-IgE (e.g. Xolair) and anti-IL 5
        iii. Immunosuppressive medications (Immunotherapy for the treatment of allergies is allowed during the study provided it was initiated at least 4 weeks prior to Visit 1 and the subject remains in the maintenance phase throughout the study)

Contraindications

5. Known hypersensitivity to corticosteroids, leukotrienes, or any excipients in the ELLIPTA inhaler and study tablets
6. History of severe milk protein allergy

Diagnostic Assessment and others

7. Participation in a clinical trial and receipt of an investigational product within 30 days, 5 half-lives or twice the duration of the biological effect of the investigational product (whichever is longer) prior to the first dosing day in the current study
8. Exposure to more than 4 investigational medicinal products within 12 months prior to the first dosing day
9. Immediate family members of the participating Investigator, sub-Investigator, study coordinator, or employee of the participating Investigator
10. Parent or Guardian with a history of known or suspected psychiatric disease, intellectual deficiency, substance abuse or other condition (e.g. inability to read, comprehend or write) which may affect:
    k. validity of consent to participate in the study
    l. adequate supervision of the subject during the study
    m. compliance of subject with study medication and study procedures (e.g., completion of daily diary, attending scheduled clinic visits)
    n. subject safety and well-being
11. Children who are wards of the government or state

<u>Randomization Criteria (assessed at Visit 5)</u>

1. Growth
    a. Prepubertal (Tanner Stage 1)
    b. Body weight and body mass index between the 3rd and 97th percentile based on the US CDC standard statistics or any local standards outside the US
    c. Baseline growth velocity between the 3rd and 97th percentile based on North America Longitudinal Standard Growth Velocity charts
    d. Bone age within 2 years of subject's chronological age as determined by hand/wrist x-ray during the baseline period
2. Disease Changes
    a. No new medical conditions that would have been exclusionary at Visit 1 (Screening)
3. Medications
    a. No corticosteroid uses during the baseline period that would likely have a systemic effect
    b. No use of any prohibited medications during the baseline period
4. Study Compliance:
    a. Demonstrated ability to comply with all study procedures during the run-in study period, including proper study drug administration during the randomisation visit
    b. Compliance with single-blind placebo treatment (defined as at least 80% of the time during the last 30 days of the run-in period) as recorded in the daily diary and based on the dose counter

Reviewer comment: *The inclusion/exclusion criteria are consistent with the recommendations in the FDA Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the*

Effects on Growth in Children, including the enrollment of pre-pubertal patients greater than 3 years of age, to minimize the effects of normal physiological growth acceleration.

Study Treatments

After Screening/Visit 1, all eligible subjects received open label montelukast and a single (subject) blind placebo Ellipta inhaler administered as one inhalation once daily during the 16-week run-in period. Montelukast dosing was based on age: 4 mg orally once daily for subjects 5 years of age or 5 mg orally once daily for subjects 6 years of age and older.

After the run-in period, subjects meeting randomization criteria were randomized equally to one of two double-blinded treatment arms, inhaled Arnuity Ellipta (FF 50 mcg) one inhalation once daily or inhaled placebo once daily, administered in addition to open-label montelukast for 52 weeks. In the 8-week follow-up period, subjects received open-label montelukast only.

Study drug compliance was assessed through review of the Ellipta dose counter and daily e-diaries at each visit.

Study Assessments

For a complete Schedule of Assessments see Table 17 in Section 19 Appendices.

All study data were categorized as pre-treatment, on-treatment, or post-treatment. The pre-treatment data were collected in the run-in period before the starting of the double-blind treatment. The on-treatment data were collected during the double-blind treatment period and the post-treatment data were collected after the end of the double-blind treatment.

Height
Height (stadiometry) measurements were obtained by trained study personnel at the study center using the study-specific calibrated stadiometry at Visits 1, 3, and 5 during run-in; Visits 6, 7, 8, 9, 12, 15 and 18 during treatment; and Visit 20 during follow-up. Height was measured without socks, shoes or hats in place. Measurements were recorded to the nearest 1/10th of a centimeter in the CRF. For each height assessment, triplicate stadiometry measurements were collected for each subject. Each set of triplicate measurements were averaged to derive one estimated height per subject per visit.

Reviewer comment: *The method for measuring height in the study was consistent with recommendations in t*he *Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children.*

eDiary: asthma symptoms, rescue medication use, peak expiratory flow
Subjects/parents/guardians were issued an eDiary to use every morning throughout the study. In addition to recording study medication compliance, the eDiary captured daily day-time and night-time asthma symptom scores, morning peak expiratory flow (PEF), rescue use of

albuterol/salbutamol (number of inhalations per 24-hour period, excluding preventive use for exercise induced bronchospasm). The recall period was the previous day. Asthma symptoms were scored as follows:

Day-time Symptom Scores
- 0: No symptoms during the day
- 1: Symptoms for one short period during the day
- 2: Symptoms for 2 or more short period during the day
- 3: Symptoms for most of the day which did not affect the child's normal daily activities
- 4: Symptoms for most of the day which did affect the child's normal daily activities
- 5: Symptoms so severe that the child could not perform normal daily activities

Night-time Symptom Scores
- 0: No symptoms during the night
- 1: Symptoms causing the child to wake once (or wake early)
- 2: Symptoms causing the child to wake twice or more (including waking early)
- 3: Symptoms causing the child to be awake for most of the night
- 4: Symptoms so severe that the child did not sleep at all

Asthma exacerbations

An asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroids (tablets, suspension, or injection) for at least 3 days or a single depot corticosteroid injection or an in-patient hospitalization or emergency room (ER) visit due to asthma that required systemic corticosteroids. Investigators evaluated patients and managed exacerbations following current asthma management guidelines. Asthma exacerbations and treatment details were collected and recorded in the eCRF. Asthma exacerbations were not recorded as AEs, unless meeting the definition of an SAE.

Childhood Asthma Control Test (cACT)

The cACT is a 7-item questionnaire developed to measure asthma control in pediatric patients 4-11 years of age[5]. Questions 1 through 4 are to be completed by the child and questions 5 through 7 are to be completed by parents/caregivers (refer to Figure 2 in Section 19 Appendices for a copy of the instrument). The recall period is 4 weeks. The total score ranges from 0 to 27 with a higher score indicating better asthma control. A cACT score below 19 suggests that asthma is not well-controlled.

Study Endpoints

The primary endpoint was the mean difference in growth velocities (cm/year) between FF 50 and placebo treatment groups averaged over the 52-week double-blind treatment period.

[5] Liu AH, Zeiger R, Sorkness C, et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol. 2007;119:817-25.

Secondary growth velocity endpoints included:

- Percentage of subjects with growth velocity below the third percentile during the double-blind treatment period
- Change (shift) in growth velocity quartiles from baseline during the run-in period to end of the double-blind treatment period
- Growth velocity over the first 12 weeks of the double-blind treatment period
- Height standard deviation scores (SDS) at each visit

Growth velocity (cm/year) was calculated for each subject by determining the slope of a regression line fitted to all height measurements recorded for an individual subject during a particular study period (i.e., run-in, double-blind treatment, or follow-up). Growth velocity was calculated for the Growth Population and for the ITT Population (defined below). Baseline, double-blind treatment and follow-up growth velocities were summarized by treatment while statistical analysis was only performed for the double-blind treatment period.

Safety endpoints included incidence of adverse events and asthma exacerbations.

Although not designed to detect significant differences in efficacy, efficacy endpoints included:

- Change from baseline in the percentage of rescue medication-free 24-hour periods over the double-blind treatment period
- Change from baseline in morning Peak Expiratory Flow (PEF) averaged over the double-blind treatment period
- Change from baseline in cACT score at the end of the double-blind treatment period

Statistical Analysis Plan

The *FDA Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children* states that the study objective is to estimate the growth rate and its confidence interval with a high level of precision given that clinically meaningful differences in growth velocity have not been established and therefore, interpreting inferential statistical testing can be difficult. To achieve this, the guidance recommends the following:

- Few dropouts
- Complete follow-up on all patients
- Sample size of 150-200 per arm
- Confidence intervals (CI) of 0.5 cm or less, with the aim of precision of the estimate

Reviewer comment: The Applicant had a larger than required sample size and few dropouts. In the results below, all confidence intervals are greater than 0.5cm, but all are less than 1 cm.

Guidance recommendations for the primary analysis include:

- Calculation of individual patient growth velocities during the baseline, treatment, and follow-up periods using a linear regression model (the preferred methodology to

estimate growth velocity because it considers all height measurements)

- Population: all randomized patients with at least three recorded height measurements during the double-blind treatment period
- Inclusion of baseline height, age, and sex in the ANCOVA model
- Construction of mean difference and 95% CI in growth velocities between the control group and the active treatment group as the primary assessment

Reviewer comment: The Applicant conducted the primary analysis in conformance with these recommendations.

Guidance recommendations for secondary analyses include:

- Subset analyses that exclude:
    - Any patient who exhibits greater than or equal to Tanner Stage 2 characteristics
    - Questionable height measurements
    - Measurements taken after children receive rescue systemic corticosteroids
- Analysis of subjects below a certain percentile of growth velocity
- Categorical or shift analysis showing change in growth velocity percentile for each child from baseline to endpoint
- Analysis of the first 3 months of data
- Summary of growth velocities during the pretreatment and follow-up periods
- Descriptive comparison of the growth velocities based on sex and ethnicity

Reviewer comment: The Applicant conducted the secondary analyses in conformance with these recommendations.

Trial Analysis Populations

The Applicant defined three analysis populations:

1. **Total Population:** All participants screened and for whom a record exists in the study database. This population was used to assess safety, with the exception of the growth analyses.
2. **Intent-to-Treat (ITT) Population:** All randomized participants who received at least one dose of study treatment. This population was used to assess subject disposition, demographics, some secondary growth endpoints and efficacy endpoints.
3. **Growth Population:** All ITT participants who had stadiometric height assessments from at least three post-randomisation, on-treatment clinic visits (i.e., including all available height measurements after randomization (Visit 5) up to and including Week 52 (Visit 18), without exclusion) during the double blind treatment period. To be

included in the Growth Population, the first and third height measurements must have been at least 7 weeks apart. This population was used to assess the primary endpoint.

Primary estimand

The five attributes of the primary estimand as described by the Applicant are noted here:

1. ***Treatment condition of interest and alternative treatment:*** The two treatment arms were Fluticasone Furoate (FF) inhaled powder 50 mcg administered QD in the morning and matching placebo for 52 weeks. Both arms included administration of 4 or 5 mg of montelukast as background asthma therapy during the treatment period, as well as during the 112 day screening period and 56 day follow-up period.
2. ***Targeted population:*** Pre-pubertal male and female subjects ages 5 to <9 years (males) and 5 to <8 (females) with a documented history of asthma for at least 6 months prior to screening with pre-bronchodilatory FEV1 at screening of $\geq$ 60%.
3. ***Variable or endpoint:*** Primary endpoint was the growth velocity (cm/year) over the double-blind treatment period of 52 weeks, as determined by stadiometry.
4. ***Population-level summary:*** The summary measure used for the treatment comparison was an estimate of the mean treatment difference in growth velocity over the double-blind treatment period and a 95% confidence interval (CI).
5. ***Intercurrent event and data handling strategy:***
    a. **Discontinuation of Randomized Treatment**: Participants may prematurely discontinue double-blind treatment and continue in the study.
    b. **Participants Presenting Tanner Stage ≥2**: Participants must be pre-pubertal (Tanner Stage 1) at the time of randomisation but may present physical characteristics of Tanner Stage 2 or higher at any point during the study.
    c. **Use of Rescue Systemic Corticosteroids**: Participants may receive rescue systemic corticosteroids at any point during the study.
    d. **Use of Rescue Inhaled/Intranasal Corticosteroids:** Participants may receive rescue inhaled/ intranasal corticosteroids at any point during the study.

    Related to intercurrent events are those which result in missing data. Reasons for missing data include:
    a. **Early Withdrawal from Study**: Participants may prematurely withdraw from the study which results in missing endpoint data.
    b. **Week 52 Height Not Available**: Height information at Week 52 may be unavailable for reasons other than early withdrawal.

The above estimand, therefore, describes the clinical question as follows: The primary trial objective was to demonstrate characterize, as accurately as possible, the estimate of the difference in prepubescent growth velocities between FF 50 mcg against placebo on top of standard of care (montelukast) in pre-pubertal patients aged 5 to 9 with physician diagnosed asthma. Growth velocity was compared between administration of FF 50 mcg OD with matching placebo (both treatments in combination with montelukast) using difference in

population means as a population-level summary, regardless of discontinuation of randomized treatment, subjects presenting Tanner Stage >2, use of rescue systemic, inhaled or intranasal corticosteroids at any time during the study.

Additional pre-specified estimands analyzed by the Applicant

The Applicant conducted the following analyses to explore the robustness of the data:

1. Supportive Estimand I: Similar to the primary estimand, except that only on-treatment data was analyzed.
2. Supportive Estimand II: Similar to the primary estimand, except that only subjects that had not reached Tanner Stage 2 were included in the analysis.
3. Supportive Estimand III: Similar to the primary estimand, except that questionable height measurements were not included in the analysis.
4. Supportive Estimand IV: Similar to the primary estimand, except that height measurements taken after administration of rescue systemic corticosteroids were not included in the analysis.
5. Supportive Estimand V: Similar to Estimand IV, except that height measurements taken after administration of rescue systemic corticosteroids AND rescue inhaled or intranasal corticosteroids were not included in the analysis.
6. Supportive Estimand VI: Similar to Estimands II, III and V, where questionable height measurements and height measurements taken after reaching Tanner Stage 2 or administration of rescue systemic corticosteroids AND rescue inhaled or intranasal corticosteroids were not included in the analysis.
7. Supportive Estimand VII: Similar to Estimand I, except that completers at one year only were used in the analysis.
8. Supportive Estimand VIII: Use the ITT Population, but otherwise similar to the primary estimand.
9. Supportive Estimands IX and X: Missing data sensitivity analyses that use the ITT Population, analysis similar to the primary estimand, but use two approaches with imputation to address missing Week 52 data.

   a). Imputation approach for Supportive Estimand IX: Use the 'worst growth rate' (i.e., smallest growth velocity) from participants from the FF 50 treatment group who complete the double-blind treatment period as the central value for imputations of missing data in the FF treatment group, and the 'worst growth rate' from participants from the placebo group who complete the double-blind treatment period as the central value for imputations of missing data in the placebo treatment group.

   b) Imputation approach for Supportive Estimand X: Use the 'worst growth rate' (i.e. smallest treatment velocity) from participants from the FF 50 treatment group who complete the double-blind treatment period as the central value for imputations of

missing data in the FF treatment group, and assume any data missing in the placebo treatment group are missing at random

The following secondary analyses were also conducted by the Applicant:

10. Supportive Estimand XI: similar to the primary estimand except using data from only the first 12 weeks of the double-blind treatment period.
11. Supportive Estimand XII: similar to the primary estimand for the subgroup of region (US vs non-US sites)
12. Supportive Estimand XIII: uses the primary estimand but with a random effects estimator, where the intercept and slope for the regression of height over time are assumed to be random effects (each subject has their own linear growth over time).

Hypothesis testing

No formal statistical hypotheses were tested in this growth trial.

Primary growth analysis

For each study period (baseline, double-blind treatment, and follow-up), the Applicant calculated growth velocity (cm/year) for each participant based on stadiometry data by fitting a regression line to all height measurements recorded for that participant during the period and determined by the slope of the fitted regression line. These were calculated for the Growth Population and for the ITT Population. The primary endpoint was analyzed using an analysis of covariance (ANCOVA) model adjusting for baseline growth velocity (continuous), age at Visit 1 (continuous), gender (categorical), and country (categorical).

The primary analysis included all available height data, regardless of any intercurrent events that occurred during the study. Missing data was assumed to be missing at random (MAR) and was not imputed. The mean difference in growth velocity over the treatment period between treatments and a 95% confidence interval was used to determine primary results.

The Kenward and Roger method of approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance matrix of the fixed effects was used in the diagnostic analyses of ANCOVA models.

As noted above, Supportive Estimand XIII is the Applicant's sensitivity analysis, which was conducted on the primary endpoint and with the same intercurrent events as described for the primary analysis i.e., all available height data collected during the double-blind treatment period was considered regardless of the occurrence of an intercurrent event.

The mixed effects ANCOVA model for this sensitivity analysis used baseline height (continuous), age at baseline (continuous), gender (categorical), double-blind treatment (categorical), time (days since treatment start, continuous), and the treatment-by-time interaction as explanatory variables. The intercept and slope for the regression of height over time were assumed to be random effects (i.e., each participant has their own linear growth

over time). A 95% confidence interval was constructed for the treatment difference in mean growth velocity over the double-blind treatment period, using the estimate for the treatment-by-time interaction in the mixed effects model.

Secondary growth analyses

The Applicant conducted secondary analyses for the following:

- Percentage of participants with growth velocity below the third percentile during the double-blind treatment period was assessed by comparing the proportion of participants who were and were not below the third percentile by treatment arm.
- Change from baseline in growth velocity quartiles was assessed by the Applicant by comparing the proportion of participants in each treatment group who shifted upward or downward in their growth velocity quartile from baseline to Week 52 . The statistical reviewer further collapsed the Applicant's analysis to assess the proportion of participants who shifted upward or downward in quartiles, regardless of baseline quartile.
- Analysis of growth velocity over the first 12 Weeks of the double-blind treatment period was assessed using descriptive statistics for both treatment arms.
- Height standard deviation scores were assessed using descriptive statistics for both treatment arms.

Subgroup analyses

The Applicant conducted subgroup analyses by gender, ethnicity and region (US and non-US sites). An ANCOVA model, similar to the one for the primary analysis, was used to estimate the mean treatment difference in growth velocity for all participants enrolled in US sites and non-US sites. Gender and ethnicity were assessed with descriptive statistics only.

Efficacy measures

As noted above, efficacy endpoints were collected for the purpose of monitoring compliance and/or poorly controlled asthma. Change from baseline in the percentage of rescue-free 24 hour periods, AM Peak Expiratory Flow (PEF), and cACT score were analyzed with descriptive statistics only.

Protocol Amendments

There were 2 protocol amendments for Study HZA114971.

Amendment 1, dated November 4, 2016, made the following changes:

1. "Local growth charts" was replaced with "US Centers for Disease Control and Prevention

(CDC) charts" for Inclusion Criteria 4 and 5.
2. The time window used for rescheduling the spirometry assessment at Screening (Visit 1) was clarified.
3. "World Health Organization (WHO) growth charts" was replaced with "North America Longitudinal Standard Growth Velocity Charts" for randomization criterion 1c.
4. In the time and events table, body weight measurement was included for Visit 3.
5. The procedure around oropharyngeal exams was clarified.
6. A supportive completers' analysis of growth velocity over the 1-year double-blind treatment period, based on participants who completed the double-blind treatment period while remaining on study treatment, was added.

Amendment 2, dated March 6, 2019, included the following changes:
1. The upper limit of the Forced Expiratory Flow in 1 second (FEV1) in inclusion criterion 7 was removed. Justification for change: FEV1 is often close to or above 100% in young children with controlled asthma. This is due to the variability of asthma with normal spirometry lung function test (LFT) values between asthma attacks in this young population (5-9 years) with controlled asthma. For this reason, an upper limit of 95% had not been used in previous similar studies.
2. Calcitriol was removed from exclusion criterion 3 and the prohibited medications. Justification for change: Children living in regions with low sun exposure especially in winter) can be advised to take calcitriol (synthetic version of Vitamin D3) at prophylactic doses (e.g., 400 IU in Caucasians, 800 IU in black children) to prevent vitamin deficiency and rickets. Excluding children taking calcitriol at prophylactic doses may unnecessarily remove participants likely to benefit from the study treatment.
3. Allowance for re-screening of participants who had previously failed screening was added.

Reviewer's comment: *Most of the protocol revisions were to the eligibility criteria; however, none were expected to have a substantial impact on the study population.*

Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with ICH Good Clinical Practice (GCP), applicable country-specific regulatory requirements, and the guiding principles of the current version of the Declaration of Helsinki.

Of the 67 clinical study sites, three sites located in the US or Poland were suspected of GCP noncompliance. At US site 228101, a quality assurance investigation found evidence of suspected falsification of data including PEF results from the eDiary, AEs, and growth velocity in some subjects. As a result, the site was closed prematurely due to the suspected GCP noncompliance. At US site 228064, data integrity concerns related to lung function data in

another trial being conducted at this site prompted premature closure as a site in Study HZA114971. Similarly, at site 227536 in Poland, GCP noncompliance in another clinical study prompted premature closure of this site in Study HZA114971. The three sites enrolled a total of 63 subjects in Study HZA114971, accounting for 13% (63/477) of randomized subjects in the ITT Population and 12% (56/457) of randomized subjects in the growth population.

The data from these three sites were included in all safety (including growth) and efficacy summaries and analyses (ITT and Growth populations). A sensitivity analysis of the primary endpoint was performed in the Growth Population, excluding data from these 3 sites (Table 11), to explore the impact of these potential GCP noncompliance issues.

Financial Disclosure

See the Financial Disclosure form (Table 21) in Section 19 Appendices.

Data Quality and Integrity

There were quality issues at three investigational sites (see details under Compliance with Good Clinical Practices). The Applicant conducted an additional analysis with these patients removed to assess the impact on the primary statistical analysis (see Table 11). Results with and without patients from these questionable sites were similar, both numerically and in interpretation of results.

Subject Disposition

A total of 874 subjects were screened for the study, of whom 225 did not meet eligibility criteria and 5 withdrew prior to enrollment, resulting in a total of 644 subjects who entered the single-blind run-in period. Following completion of the run-in period, 167 subjects did not enter the double-blind treatment period due to the following reasons: failure to meet randomization criteria (110), withdrawal of consent (31), investigator discretion (12), protocol deviations and other reasons (23), and one SAE (acute tonsillitis). Four hundred seventy-seven (477) subjects completed the 16-week run-in period, continued to meet eligibility criteria, and were randomized to double-blinded treatment with FF 50 or placebo. The ITT Population included all 477 randomized subjects. As shown in Table 3, 401/477 (84%) of subjects completed the study with a higher proportion of premature withdrawals from the study in the placebo arm (18%) compared to the FF 50 arm (14%). The primary reasons for premature study withdrawal are listed in the table below. The 16% subject withdrawal rate was influenced by the closure of three study sites for suspected GCP noncompliance, which contributed 5% of subjects in each treatment arm to this overall proportion. A higher proportion of placebo subject withdrew consent, potentially suggesting that withdrawal may have been effected by lack of efficacy. That said, a difference of 13% versus 9% is relatively small and should not affect the interpretation of the study results.

Table 3. Subject Disposition, Study Withdrawals, 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: HZA114971 CSR, Table 8, page 51.
[a] Withdrawn before the end of the study.
[b] Three sites closed prematurely due to suspected ICH GCP noncompliance.

Table 4. Subject Disposition, Premature Treatment Discontinuations, ITT Population

	Placebo (N=239)	FF 50 (N=238)	Total (N=477)
Study Treatment Stopped Prematurely			
No	205 (86%)	211 (89%)	416 (87%)
Yes	34 (14%)	27 (11%)	61 (13%)
Primary Reason the Study Treatment Was Stopped			
Adverse event	0	1 (<1%)	1 (<1%)
Decision by participant or proxy	14 (6%)	9 (4%)	23 (5%)
Investigator site closed	14 (6%)	12 (5%)	26 (5%)
Investigator discretion	4 (2%)	2 (<1%)	6 (1%)
Lost to follow-up	0	1 (<1%)	1 (<1%)
Protocol deviation	1 (<1%)	0	1 (<1%)
Other	1 (<1%)	2 (<1%)	3 (<1%)

Source: HZA114971 CSR, Table 9, p52

Exposure

Table 5 summarizes subject exposure in the study. The mean and median exposures as well as range of exposures are similar across treatment groups. The majority of subjects (84% in placebo group and 87% in FF 50 group) received study drug for ≥337 days; the duration of exposure in the study appears adequate for the evaluation of growth velocity.

Table 5. Subject Exposure, ITT Population

	Placebo (N=239)	FF 50 (N=238)
Exposure (days)[a]		
n	239	238
Mean	334.5	344.0
SD	77.46	61.38
Median	364.0	364.0
Min.	4	30
Max.	386	386
Range of Exposure (days)		
≤28 days	3 (1%)	0
29-56 days	3 (1%)	3 (1%)
57-84 days	4 (2%)	3 (1%)
85-112 days	2 (<1%)	0
113-140 days	1 (<1%)	1 (<1%)
141-168 days	2 (<1%)	2 (<1%)
169-196 days	5 (2%)	2 (<1%)
197-224 days	2 (<1%)	6 (3%)
225-252 days	2 (<1%)	2 (<1%)
253-280 days	8 (3%)	4 (2%)
281-308 days	3 (1%)	4 (2%)
309-336 days	5 (2%)	4 (2%)
337-364 days	133 (56%)	128 (54%)
≥365 days	66 (28%)	79 (33%)
Range of Exposure (months)		
≥3 months	8 (3%)	4 (2%)
≥6 months	10 (4%)	12 (5%)
≥9 months	176 (74%)	167 (70%)
≥12 months[b]	34 (14%)	49 (21%)

Source: HZA114971 CSR, Table 21, page 63.
a Calculated as (treatment stop date – treatment start date + 1)
b The study visit at week 52 (Day 365) had a window of -5/+2 days. A visit that occurred on or after 365 days was categorized as ≥12 months. A visit that occurred prior to Day 365 (including Day 364) was categorized <12 months.

Protocol Violations/Deviations

A protocol deviation was determined to be any change or departure from the approved protocol. Within the ITT Population, 100 (42%) subjects in the placebo group and 92 (39%) subjects in the FF 50 group had protocol deviations (Table 5). The majority of these were for use of prohibited medications or devices and for assessments/procedures, which might affect the study measurement. However, the percentages the protocol violation/deviation were similar in both placebo and FF 50 groups. These protocol deviations were unlikely to have a significant effect on overall results of the study.

Table 6. Summary of Protocol Violations/Deviations, ITT Population

	Placebo (N=239)	FF 50 (N=238)	Total (N=477)
Any Deviation	100 (42%)	92 (39%)	192 (40%)
Informed consent	12 (5%)	10 (4%)	22 (5%)
Assessments and/or procedures	33 (14%)	42 (18%)	75 (16%)
Eligibility criteria not met	20 (8%)	20 (8%)	40 (8%)
Prohibited medication or device	47 (20%)	30 (13%)	77 (16%)
Wrong study treatment/ administration/ dose	6 (3%)	2 (<1%)	8 (2%)
Visit, assessment or timepoint window	7 (3%)	8 (3%)	15 (3%)

Source: HZA114971 CSR, Table 11, page 53.

Demographic Characteristics

As shown in Table 7, subject demographics were similar between the FF 50 and placebo groups. Although subjects not meeting the age criteria were enrolled and randomized into the study, the overall number was small (two subjects < 5 years and two subjects 9 years of age) and balanced across treatment groups. Two subjects at Tanner Stage ≥2 were excluded from the Growth Population, on which the measures of the primary endpoint (growth velocity) were calculated and analyzed.

Table 7. Demographic Characteristics of ITT Population

Demographic Parameters	Placebo N=239	FF 50 N=238	Total N=477
Sex (%)			
F	84 (35%)	94 (39%)	178 (37%)
M	155 (65%)	144 (61%)	299 (63%)
Age, years			
Mean (SD)	6.1 (1.07)	6.3 (1.02)	6.2 (1.05)
Median	6	6	6
Range (Min., Max.)	(4, 9)	(4, 9)	(4, 9)
< 5years (%)	1 (<1%)	1 (<1%)	2 (<1%)
5 (%)	86 (36%)	64 (27%)	150 (31%)
6 (%)	68 (28%)	68 (29%)	136 (29%)
7 (%)	51 (21%)	75 (32%)	126 (26%)
8 (%)	32 (13%)	29 (12%)	61 (13%)
9 (%)	1 (<1%)	1 (<1%)	2 (<1%)
Tanner Stage* ≥2 (%)	0	2 (<1%)	2 (<1%)
Race** (%),			
White/Caucasian	204 (85%)	201 (84%)	405 (85%)
African American	13 (5%)	13 (5%)	26 (5%)
Asian	0	1 (<1%)	1 (<1%)
Multiple/Mixed Race	22 (10%)	23 (10%)	45 (9%)
Ethnicity			
Hispanic/Latino	66 (28%)	68 (29%)	134 (28%)
Not Hispanic/Latino	173 (72%)	170 (71%)	343 (72%)
Region***			

US	75 (16%)	75 (16%)	150 (31%)
Non-US	164 (67%)	163 (68%)	327 (69%)
Argentina	15 (3%)	15 (3%)	30 (6%)
Poland	36 (8%)	34 (7%)	70 (15%)
Romania	8 (2%)	8 (2%)	16 (3%)
Russia	86 (18%)	86 (18%)	172 (36%)
South Africa	19 (4%)	20 (4%)	39 (8%)
Height (cm)			
Mean (SD)	122.1 (8.4)	122.7 (8.4)	122.4 (8.4)
Median	121.5	122.5	122.0
Min.	103.3	103.6	103.3
Max.	141.4	143.2	142.2
Weight (kg)			
Mean (SD)	24.6 (4.7)	25.1 (5.0)	24.8 (4.8)
Median	23.5	24.5	23.9
Min.	15.9	15.7	15.7
Max.	40.0	39.6	40.0
BMI (kg/m^2)			
Mean (SD)	16.4 (1.7)	16.5 (1.7)	16.4 (1.7)
Median	16.2	16.4	16.3
Min.	12.3	12.1	12.1
Max.	21.3	21.9	21.9

Source: Adapted from HZA114971 CSR, Table 14, page 55
*HZA114971 CSR Table 29, page 73.1.
** HZA114971 CSR Table 1.21, page 151.
*** HZA114971 CSR, page 47 and statistical reviewer's analysis (regions.sas).

Treatment Compliance

Treatment compliance was assessed by the e-Diary record and the dose counter of the Ellipta inhaler. As summarized in Table 8, a majority of subjects in both treatment groups had ≥95% compliance in the run-in and the double-blind treatment period as assessed by e-Diary record and the dose counter of the inhaler. The treatment compliance was satisfactory.

Table 8. Summary of Treatment Compliance, ITT Population

Assessment	**Placebo N=239**	**FF 50 N=238**
e-Diary Recorded Inhaler Use, n (%)		
Run-in Period		
<80%	4 (2%)	12 (5%)
≥80% - <95%	23 (10%)	25 (11%)
≥95% - <105%	212 (89%)	201 (84%)
Double-blind Treatment Period, n (%)		
<80%	2 (<1%)	2 (<1%)
≥80% - <95%	17 (7%)	20 (8%)
≥95% - <105%	220 (92%)	216 (91%)
e-Diary Recorded Montelukast Use, n (%)		

Run-in Period		
<80%	6 (3%)	9 (4%)
≥80% - <95%	12 (5%)	23 (10%)
≥95% - <105%	221 (92%)	206 (87%)
Double-blind Treatment Period		
<80%	6 (3%)	8 (3%)
≥80% - <95%	24 (10%)	25 (11%)
≥95% - <105%	209 (87%)	205 (86%)
Dose Counter Reading, n (%)		
Run-in Period		
<80%	1 (<1%)	3 (1%)
≥80% - <95%	35 (15%)	27 (11%)
≥95% - <105%	196 (82%)	203 (85%)
≥105% - <120%	7 (3%)	5 (2%)
Double-blind Treatment Period		
<80%	3 (1%)	4 (2%)
≥80% - <95%	49 (21%)	48 (20%)
≥95% - <105%	184 (77%)	186 (78%)
≥105% - <120%	3 (1%)	0

Source: Adapted from HZA114971 CSR, Tables 22, 23, page 64, 65

Growth Velocity Endpoints

Primary Endpoint

The results for the primary endpoint of growth velocity over 52 weeks in prepubertal pediatric subjects with asthma between the FF 50 and placebo treatment groups are shown in Table 9.

Table 9. Primary Analysis of Growth Velocity During Double-Blind Placebo-Controlled Treatment Period, Growth Population

Treatment	**Placebo N=226**	**FF 50 N=231**
Growth velocity (cm/year)		
LS mean (SE)	6.06 (0.11)	5.91 (0.12)
LS mean difference		-0.16
95% confidence interval		(-0.46, 0.14)

Source: HZA114971 CSR, Table 25. Confirmed by statistical reviewer.

The primary analysis for this trial had a 95% confidence interval length of 0.60 cm for the difference of growth velocity between FF 50 and placebo groups. This was slightly larger than the Growth Guidance recommendation that studies should attain a 95% confidence interval length of 0.5 cm or less. However, the confidence interval was not considerably wider than 0.5 cm and the results of the primary analysis were interpretable with reasonable precision in the

estimate of treatment effect and were consistent with all growth velocity supportive analyses shown below in Table 11. These results suggest there was no clinically or statistically meaningful difference in growth velocity over one year between the two treatment groups.

Results excluding the three sites with data integrity concerns (Table 10) were similar to that of the primary analysis in Table 9, supporting the overall robustness of the results.

Table 10. Analysis of Growth Velocity During Double-Blind Placebo-Controlled Treatment Period, Growth Population Excluding 3 Sites with Data Integrity Concerns

Treatment	**Placebo N=198**	**FF 50 N=203**
Growth velocity (cm/year) LS mean (SE) LS mean difference 95% confidence interval	 6.12 (0.12)	 5.93 (0.12) -0.20 (-0.52, 0.13)

Source: HZA114971 CSR, Table 2.58

Statistical analyses for pre-specified estimands (Table 11) showed that the treatment differences on LS mean growth velocities for all of the supportive analyses ranged from -0.03 cm/year for Estimand 6 (where the subjects who attained Tanner Stage 2, questionable growth measurements or visits where subjects took rescue corticosteroids were removed) to -0.36 cm/year for Estimand 10 (where a method of imputation was used to explore the effects of missing data by use of imputation). The results of these supportive analyses of growth velocity are consistent with the primary endpoint analysis presented in Table 9.

Table 11. Growth Velocity Supportive Analyses

Analyses of growth velocity (cm/year) LS mean (std err)	**Placebo N=226**	**FF 50 N=231**	**LS mean difference (95% CI)**
Estimand 1: On-treatment data only	n=226 6.12 (0.11)	n=231 5.90 (0.11)	-0.22 (-0.53, 0.08)
Estimand 2: Excluded subjects ≥2 Tanner Stage	n=226 6.12 (0.11)	n=229 5.90 (0.11)	-0.22 (-0.53, 0.08)
Estimand 3: Excluded questionable height measurement	n=226 6.12 (0.11)	n=231 5.90 (0.11)	-0.22 (-0.52, 0.09)
Estimand 4: Excluded height measurements after taking rescue systemic corticosteroids	n=222 6.05 (0.12)	n=230 5.98 (0.12)	-0.06 (-0.39, 0.27)
Estimand 5: Excluded height measurements after taking rescue systemic/inhaled /or intranasal corticosteroids	n=217 6.00 (0.13)	n=223 5.95 (0.13)	-0.05 (-0.40, 0.30)

Estimand 6: excluded height measurements in Estimands 2, 3, and 5	n=217 6.00 (0.13)	n=222 5.97 (0.13)	-0.03 (-0.38, 0.33)
Estimand 7: Completers of 52-week double-blind treatment period	n=193 6.17 (0.12)	n=198 5.91 (0.12)	-0.26 (-0.59, 0.07)
Estimand 8: 52-week double-blind treatment period, ITT Population	n=239 6.04 (0.13)	n=238 5.97 (0.13)	-0.08 (-0.43, 0.28)
Estimand 9: 52-week double-blind treatment period, approach 1* to address missing data, ITT Population	n=239 5.84 (0.11)	n=238 5.68 (0.11)	-0.16 (-0.47, 0.16)
Estimand 10: 52-week double-blind treatment period, approach 2* to address missing data, ITT Population	n=239 6.04 (0.11)	n=238 5.69 (0.11)	-0.36 (-0.67, 0.05)

Source: HZA114971 CSR, Table 28

*See Estimands subsection of Statistical Analysis Plan section, above for details.

Intercurrent Events

Estimands 2, 4 and 5 in Table 11 are analyses exploring the intercurrent events, as noted in Table 12. The percentage of subjects with an intercurrent event for treatment discontinuation, rescue inhaled steroids, or rescue intranasal steroids was similar across treatment arms. There were only 2 subjects (<1%) who had a Tanner Stage ≥2 in the FF 50 treatment group. There was a lower percentage of subjects in the FF 50 arm who received rescue systemic steroids (7% and 11% in the FF 50 and placebo arms, respectively), which is to be expected in a year-long placebo controlled trial. Based on the results in Table 11 these intercurrent events do not appear to have significantly affected the growth velocity assessment.

Table 12. Intercurrent Events, Growth Population

	Placebo (N=226)	FF 50 (N=231)	Total (N=457)
Randomised Treatment Discontinuation	24 (11%)	22 (10%)	46 (10%)
Tanner Stage ≥2	0	2 (<1%)	2 (<1%)
Rescue Systemic Corticosteroids Use	25 (11%)	16 (7%)	41 (9%)
Rescue Inhaled/Intranasal Corticosteroids Use	27 (12%)	28 (12%)	55 (12%)

Source: HZA114971 CSR, Table 30, page 73.

Subgroup Analyses of Growth Velocity

Subgroup analyses of the growth velocity (cm/year) during the placebo-controlled treatment period by region, gender, and ethnicity are shown in Table 13. Although the LS mean of the growth velocity in the US region was slightly higher in the FF 50 group than that in the placebo group; however, this may simply reflect higher variability in the smaller subgroup of subjects, and this difference was not statistically significant. In the non-US region, the FF 50 treatment group had a lower growth velocity than that in the placebo group. There was no substantial difference in overall growth velocity between the US and non-US regions.

The average growth velocities during the placebo-controlled treatment period were summarized descriptively for subgroups of gender (male vs. female) and ethnicity (Hispanic/ Latino vs. not Hispanic/Latino). Differences in mean changes of growth velocity between the placebo and FF 50 treatment by gender and ethnicity subgroups were in alignment with the overall population results.

Table 13. Subgroup Analyses of Growth Velocity (cm/year) by Region, Gender, and Ethnicity, Growth Population

	Placebo N=226	**FF 50 N=231**
Region		
United States		
N	70	72
LS mean (std err)	5.80 (0.24)	6.05 (0.24)
LS mean difference		0.26
0.95% confidence interval		(-0.42, 0.94)
Ex-United States		
N	156	159
LS mean (std err)	6.18 (0.11)	5.84 (0.11)
LS mean difference		-0.34
0.95% confidence interval		(-0.65, -0.02)
Gender		
Female		
N	80	93
Mean change (SD)	6.03 (1.80)	5.64 (1.22)
Difference in mean change		-0.39
Male		
N	146	138
Mean change (SD)	6.13 (1.64)	6.03 (1.80)
Difference in mean change		-0.10
Ethnicity		
Hispanic/Latino		
N	62	65
Mean change (SD)	6.20 (2.15)	6.10 (1.84)
Difference in mean change		-0.10
Not Hispanic/Latino		
N	164	166
Mean change (SD)	6.06 (1.49)	5.79 (1.49)
Difference in mean change		-0.27

Source: HZA114971 CSR, Tables 37, 38, 39, pages 77, 79, 80.
Note: Gender and Ethnicity were assessed with descriptive statistics only.

Secondary Growth Velocity Endpoints

Secondary endpoints analyzed by the Applicant were consistent with additional recommended endpoints in the Growth Guidance.

Proportion of subjects with growth velocity below 3rd percentile

Using the *Whole-year Velocity Standard for Height of Boys and Girls*[6] as the reference standard, each subject's growth velocity during the double-blind treatment period was compared to the 3rd percentile value of the age closest to the participant's age at the end of the treatment (i.e., either at Week 52 or at the Early Withdrawal Visit). The number and percentage of subjects whose growth velocity during the double-blind treatment period was below the 3rd percentile were 20 (9%) and 16 (7%) in the placebo and FF 50 treatment groups, respectively. Most subjects had a growth velocity within 97% of range of the reference values, and there was no apparent difference between treatment groups in this endpoint.

Change (shift) from baseline in growth velocity quartiles

Growth velocities for individual subjects were grouped into quartiles (1Q = 1st – 25th percentile, 2Q = 26th – 50th percentile, 3Q = 51st – 75th percentile, 4Q = 76th – 100th percentile) according to the categories in the reference standard, *Whole-year Velocity Standard for Height of Boys and Girls*[7]. Shifts in growth velocity quartile from baseline to the end of the treatment were reported descriptively. Baseline was defined as the slope of a simple linear regression of the average stadiometric height measurements recorded at Visits 1, 3, and 5. Endpoint was defined as the slope of a simple linear regression of the average stadiometric measurements recorded at Visit 12 through Visit 18, including both on and off treatment measurements. Shifts to a higher growth velocity quartile occurred with similar frequency between treatment groups: 73 (32%) FF 50 subjects and 74 (33%) placebo subjects (Table 15). Shifts to a lower growth velocity quartile occurred with greater numerical frequency in the FF 50 (88 subjects, 38%) compared to placebo (76 subjects, 34%) treatment groups. The proportion of subjects with a one- or two-quartile decrease was similar between treatment arms, but slightly higher in the FF 50 arm for a larger three-quartile decrease shift (9% versus 13% in placebo versus FF 50 treatment arms, respectively).

Table 14. Shifts from Baseline in Growth Velocity Quartiles, Growth Population

	Placebo N=226	**FF 50 N=231**
Number of subjects with an endpoint measurement	216	223
Any increased shift	74 (33%)	73 (32%)

[6] Tanner JM, Whitehouse RH Takaishi M. Standards from Birth to Maturity for Height, Weight, Height Velocity, and Weight Velocity: British Children, 1965 Part II. Archives of Disease in Childhood. 1966;41(220):613-35.

One quartile increase	23 (11%)	23 (10%)
Two quartile increase	22 (10%)	22 (10%)
Three quartile increase	29 (13%)	29 (12%)
Any decreased shift	76 (34%)	88 (38%)
One quartile decrease	30 (14%)	34 (15%)
Two quartile decrease	26 (12%)	23 (10%)
Three quartile decrease	20 (9%)	31 (13%)

Source: Statistical reviewer calculations from CSR Table 33

Growth velocity over first 12 weeks of treatment
During the first 12 weeks of double-blind treatment, the LS mean growth velocity was 6.22 cm/year and 6.28 cm/year for the placebo and FF 50 groups, respectively, with a LS mean difference of 0.06 cm/year (95% CI -0.45, 0.57). Although this endpoint result showed a slightly higher growth velocity in the FF 50 arm, the 95% CI is relatively wide indicating low precision of this difference estimate, which is therefore not readily interpretable.

Standard Deviation Scores for Height
Each subject's height standard deviation score (SDS) for each visit was calculated as: SDS = [(observed height measurement – standard median height for age at Visit 1) / (standard 95th height percentile for age at the visit – standard 5th height percentile for age at the visit)] /(2 x 1.645). The SDS is a score similar to z-score that estimates how far the measurement is from the average. A large SDS indicates the measurement is far from the average; a small SDS indicates the measurement is close to the average. The change from baseline to end of the treatment in height SDS was summarized by treatment group. Baseline was defined as the height SDS at Visit 5; end of treatment was defined as the height SDS at Visit 18. If either baseline or end of the treatment point values were missing, then the change from baseline in height SDS was not calculated.

The mean SDSs were 0.27 and 0.24 for the placebo group at baseline and end of treatment, respectively. The mean SDSs were 0.21 and 0.18 for FF 50 treatment group at baseline and end of the treatment, respectively. The mean change from baseline in height SDS was small and within the 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 SDS measures and changes suggested that the FF 50 treatment was not associated with large variation of growth velocity measures during the treatment period.

Summary of Secondary Growth Analyses
These analyses of the secondary endpoints were supportive of the primary analysis. The FF 50 treatment at 1 year had a small, but not statistically significant effect on the growth velocity in this population of prepubertal pediatric subjects with asthma. The clinical relevance of this small decrease in growth velocity at 1 year on longer term growth or final adult height is unknown.

Statistical Issues

The primary estimand, as noted in Section 8 describes the clinical question as follows: The primary trial objective was to characterize, as accurately as possible, the estimate of the difference in prepubescent growth velocities between FF 50 mcg against placebo on top of standard of care (montelukast) in pre-pubertal patients aged 5 to 9 with physician diagnosed asthma. Growth velocity was compared between administration of FF 50 mcg QD with matching placebo (both treatments in combination with montelukast) using difference in population means as a population-level summary, regardless of discontinuation of randomized treatment, subjects presenting Tanner Stage >2, use of rescue systemic, inhaled or intranasal corticosteroids at any time during the study.

The Applicant conducted trial and analyses in conformance with the Growth Guidance recommendations. No statistical issues were identified.

Descriptive Efficacy Outcomes

The study was not designed to detect significant differences in efficacy outcomes between FF 50 and placebo treatment groups as efficacy has already been demonstrated in this age group to support an indication in pediatric patients 5 to 11 years of age. However, the Applicant provided descriptive statistics for efficacy outcomes that were captured in the study to monitor asthma control; the results are shown below.

Table 15. Summary of Descriptive Efficacy Endpoints, ITT Population

Measures	Placebo N=239	FF 50 N=238
Number of Rescue-Free 24-hour Periods		
*Baseline Mean (SD)	86 (30)	90 (25)
Double-blind treatment Period Mean (SD)	89 (24)	92 (19)
Change from Baseline (SD)	3 (17)	3 (20)
Number of Symptom-Free 24-hour Periods		
*Baseline Mean (SD)	79 (34)	82 (34)
Double-blind treatment Period Mean (SD)	84 (26)	85 (27)
Change from Baseline (SD)	5 (24)	3 (24)
Morning PEF (Liters/minute)		
*Baseline Mean (SD)	156 (56)	162 (56)
Double-blind treatment Period Mean (SD)	163 (54)	171 (53)
Change from Baseline (SD)	7 (27)	9 (31)
cACT score		
†Baseline Mean (SD)	23 (2)	23 (2)
Double-blind treatment Period Mean (SD)	24 (3)	24 (3)
Change from Baseline (SD)	1 (3)	1 (4)

Source: Adapted from HZA114971 CSR, Tables 53, 54, 55, and 56, pages 91-93
*Baseline defined as 6 days prior to and the day of randomization.
†Baseline defined as cACT score at Visit 5 (randomization)

Over the 52-week double-blind treatment period, efficacy outcomes appear similar between treatment groups; however, the results are difficult to interpret as these measures are not the typical endpoints relied upon to demonstrate efficacy in asthma trials.

Asthma Exacerbations

Few subjects experienced an asthma exacerbation in the trial; however, exacerbations occurred with greater numerical frequency in the placebo group (22, 9%) versus the FF 50 group (7, 3%) during the double-blind treatment period. In the follow-up period, placebo and FF 50 treatment groups experienced a similar number of asthma exacerbations. Results are shown in the table below.

Table 16. Asthma Exacerbations On- and Post-Treatment, ITT Population

	Placebo N=239	**FF 50 N=238**
Double-blind Treatment Period		
Number of exacerbation events	30	8
Number of subjects, n (%)		
Any exacerbation	22 (9)	7 (3)
1 exacerbation	18 (8)	6 (3)
2 exacerbations	1 (<1)	1 (<1)
3 exacerbations	0	0
4 exacerbations	2 (<1)	0
>4 exacerbations	0	0
Permanent treatment discontinuation due to an exacerbation	1 (<1)	1 (<1)
Requiring hospitalization due to exacerbation	1 (<1)	0
ED visit for exacerbation	6 (3)	0
Follow-up Period		
Number of exacerbation events	4	3
Number of subjects, n (%)		
Any exacerbation	4 (2)	3 (1)
1 exacerbation	4 (2)	3 (1)
≥2 exacerbations	0	0
Permanent treatment discontinuation due to an exacerbation	0	1 (<1)
Requiring hospitalization due to exacerbation	1 (<1)	0
ED visit for exacerbation	0	0

Source: HZA114971 CSR, Table 52, page 89

Additional Safety Data

Categorization of Adverse Events

An adverse event (AE) was defined as any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. AEs were coded using the MedDRA coding dictionary (Version 24.0). AEs were summarized for each study period (16-week single-blind run-in/baseline period, 52-week double-blind treatment period, and 8-week follow-up period) and by treatment group. Serious adverse event (SAE) definitions and reporting were consistent with the 21 CFR 312.32(a).

Serious Adverse Events

No deaths occurred in the study. The nonfatal serious adverse events (SAEs) reported in the study are listed in Table 17. SAEs occurred as single events with no particular pattern raising concerns for new safety signals.

Table 17. Nonfatal SAEs by Treatment Period and Group, ITT Population

Treatment Period SAEs by Preferred Term	Placebo N=239	FF 50 N=238
Run-in Period		
Any SAE, n (%)	1 (<1)	1 (<1)
Bone fracture	1 (<1)	0
Tonsillitis	0	1 (<1)
Double-blind Treatment Period		
Any SAE, n (%)	6 (3)	4 (2)
Pneumonia	1 (<1)	1 (<1)
Appendicitis	0	1 (<1)
Gastroenteritis norovirus	1 (<1)	0
Urinary tract infection	1 (<1)	0
Fecaloma	0	1 (<1)
Diabetes mellitus	1 (<1)	0
Hematuria	0	1 (<1)
Testicular appendage torsion	1 (<1)	0
Asthma exacerbation	1 (<1)	0
Follow-up period		
Any SAE, n (%)	1 (<1)	1 (<1)
Asthma exacerbation	1 (<1)	0
Bronchitis	0	1 (<1)

Source: HZA114971 CSR, Tables 46, 2.47, 2.49, pages 85, 277, 279.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject (8-year-old white male) in the FF 50 group prematurely discontinued treatment due to an asthma deterioration AE on post-randomization Day 206. He received oral corticosteroid treatment and fully recovered on Day 218.

Treatment Emergent Adverse Events

The only TEAE that occurred in ≥3% of subjects in FF 50 group and more frequently than placebo was influenza (3% placebo vs 5% FF 50). All other commonly reported TEAEs occurred with similar or greater frequency in the placebo group

Laboratory Findings

There were no clinical laboratory evaluations performed in this study.

Adverse Events of Special Interest

The Applicant designated the following categories of Adverse Events of Special Interest (AESIs) based on the known safety profile of ICS:

- Hypersensitivity
- Lower Respiratory Tract Infection (LRTI) (excluding pneumonia)
- Local steroid effects
- Decreased bone mineral density and associated fractures
- Infective Pneumonia
- Effects on glucose
- Ocular effects/Glaucoma/Lens disorder

The AESIs of on-treatment and post-treatment were summarized in the Table 18 below. The frequency of AESIs between treatment groups was similar. The small numerical difference in hypersensitivity events was not driven by any particular PT.

Table 18. Summary of Treatment-emergent AESIs On- and Post-Treatment, ITT Population

	Placebo N=239	**FF 50 N=238**
Any AESI, n (%)	45 (19%)	44 (18%)
Hypersensitivity[a]	16 (7%)	21 (9%)
LRTI, excluding pneumonia[b]	20 (8%)	17 (7%)
Local Steroid Effects[c]	3 (1%)	5 (2%)
Decreased bone mineral density and associated fractures[d]	4 (2%)	1 (<1%)
Infective Pneumonia[e]	3 (1%)	4 (2%)
Effects on glucose[f]	3 (1%)	1 (<1%)
Ocular effects/Glaucoma/Lens disorder[g]	0	2 (<1%)

Source: HZA114971 CSR, Table 50, page 87.
[a] Includes PTs: rhinitis allergic, conjunctivitis allergic, dermatitis atopic/allergic/contact, eczema, rash, angioedema, urticaria
[b] Based on Standard MedDRA Query; includes PTs: bronchitis, tracheitis, bronchitis viral, viral tracheitis, bacterial tracheitis, lower respiratory tract infection viral, rhinotracheitis, and tracheobronchitis
[c] Includes PTs: oropharyngeal pain, stomatitis, and oropharyngeal candidiasis
[d] Includes PTs: clavicle fracture, facial bones fracture, fibula fracture, forearm fracture, and upper limb fracture
[e] Based on Special MedDRA Query; includes PTs: pneumonia, atypical pneumonia, and pneumonia mycoplasma
[f] Based on Special MedDRA Query; includes PTs: dehydration, diabetes mellitus, and loss of consciousness
[g] Based on Special MedDRA Query; includes PTs: ocular hyperemia, and visual acuity reduced

Safety Summary

The safety of FF 50 observed in this trial was consistent with product labeling. No new safety signals were identified.

Conclusions and Recommendations

This sNDA includes a pediatric growth study to fulfill a PREA PMR for FF 50 (Arnuity Ellipta inhalation powder) which is approved for the maintenance treatment of asthma in patients 5 years of age and older. The pediatric growth study was conducted in 477 prepubertal children with asthma in accordance with FDA Guidance for Industry. The primary endpoint of growth velocity over the 52-week treatment period demonstrated that treatment with FF 50 resulted in a -0.16 cm decrease in growth velocity compared to placebo. The primary analysis for this trial had a 95% confidence interval length of 0.60 cm for the difference of growth velocity between FF 50 and placebo groups. Although slightly larger than the FDA Guidance recommendation for a 95% confidence interval length of 0.5 cm or less, the confidence interval in this study was not considerably wider than 0.5 cm, and the results of the primary analysis were interpretable with reasonable precision in the estimate of treatment effect and were consistent with all growth velocity supportive analyses. The clinical relevance of this small decrease in growth velocity on longer term growth or final adult height is unknown. No new safety signals were identified. Given the established benefit on lung function, the benefit/risk assessment for FF 50 in the pediatric population remains favorable, and healthcare providers should continue to weigh the benefits and potential risks for an individual patient when prescribing.

We recommend approval of this pediatric supplement submission which fulfills PMR 2765-3 and revising the PI to incorporate the growth study results in Section 8.4.

7 Advisory Committee Meeting and Other External Consultations

As fluticasone furoate is an ICS, a drug class with a well-established benefit/risk profile, and Arnuity Ellipta is an approved drug product for asthma in pediatric patients, a Pulmonary and

Allergy Drug Advisory Committee meeting was not convened nor required for this application.

8 Pediatrics

This pediatric supplement fulfills the final outstanding PREA requirement, PMR 2765-3. No additional pediatric studies are required.

9 Labeling Recommendations

Prescribing Information

The Applicant submitted proposed labeling to add results of the pediatric growth study to Section 8.4 and revisions to better align language with the approved labels for TRELEGY ELLIPTA (NDA 209482, fluticasone furoate, umeclidinium, and vilanterol inhalation powder) and ANORO ELLIPTA (NDA 203975, umeclidinium and vilanterol inhalation powder).

Table 19. Summary of Major Revisions to the PI

Full Prescribing Information Sections	Rationale for Major Changes Incorporated into the Finalized Prescribing Information (PI)
1 INDICATIONS AND USAGE 2 DOSAGE AND ADMINISTRATION 5 WARNINGS AND PRECAUTIONS	The labeling was revised to provide recommendations and format of the Prescribing Information (PI) to help ensure that the PI was compliant with Physician Labeling Rule (PLR) and current labeling practice. Please refer to the labeling Information Request dated January 10, 2023, for labeling revisions.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	**8.4 Pediatric Use** The pediatric use statement was revised to include all the indicated pediatric population for ages 5 years and older. A statement that describes the information supporting pediatric patients use was also included. <u>Effects on Growth</u> The study results of ARNUITY ELLIPTA 50 mcg on growth velocity from the *PMR 2765-3: A 52-week, randomized, double-blind, parallel group, active controlled, growth study in females 5-<8 years of age and males 5-<9 years of age with asthma,* replaced the study results that evaluated fluticasone furoate 110 mcg nasal spray formulation

	on growth velocity. Language describing the results from a growth study with fluticasone furoate nasal spray was removed given that growth velocity data are now available with Arnuity Ellipta. Because of the different route of administration, FF nasal spray growth velocity study results are less relevant and retaining the information in the PI may cause confusion.

10 Risk Evaluation and Mitigation Strategies (REMS)

No new safety signals were identified; therefore, no additional risk evaluation and management strategies are required.

11 Postmarketing Requirements and Commitment

This supplement fulfills PREA PMR 2765-3. All PMRs associated with NDA 205625 have been fulfilled.

12 DPACC Deputy Director for Safety (DDS) Comments

Arnuity Ellipta (fluticasone furoate), a dry powder inhaled corticosteroid, is currently approved for the once daily maintenance treatment of asthma as prophylactic therapy in patients aged 5 years and older. It was initially approved in the 12 and older population on August 20, 2014. The indication was later expanded to include the patients 5 year and older on May 17, 2018. At initial approval multiple PMRs were issued one of which was a 52-week growth study as follows:

> 2765-3: Conduct a 52-week, randomized, double-blind, parallel group, active controlled, growth study in females 5-<8 years of age and males 5-<9 years of age with asthma.

The Applicant has completed study HZA 114971 to address PMR 2765-3. Data pediatric growth study HZA 114971 was submitted under NDA 205625 supplement 009 to support inclusion these growth data in section 8 of the label.

Study HZA 114971 was a randomized, double-blind, parallel-group, placebo-controlled, multicenter phase 4 study to assess the effect of FF 50 mcg (Arnuity Ellipta) once daily on growth velocity in prepubertal subjects with asthma on a background therapy of open-label

montelukast. The study included a 16-week run-in period where patients received open-label montelukast and placebo Ellipta inhaler. After the run-in period, patients that met eligibility criteria were randomized to FF 55mcg or placebo for a 52-week double-blind treatment period. All patients received open-label montelukast as background therapy during the double-blind treatment period. Included patients had a diagnosis of asthma, were Tanner Stage-1, and were males between 5 and <9 years old and females between 5 and <8 years old. Design of this growth study was consistent with FDA *Guidance for Industry: Orally Inhaled and Intranasal Corticosteroids: Evaluation of the Effects on Growth in Children.*

The primary endpoint was mean difference in growth velocities (cm/year) over the 52-week treatment period between the FF 50mcg and placebo treated groups.

Secondary endpoints included the following:

- Percentage of subjects with growth velocity below the third percentile during the double-blind treatment period
- Change in growth velocity quartiles from baseline during the run-in period to end of the double-blind treatment period
- Growth velocity over the first 12 weeks of the double-blind treatment period
- Height standard deviation scores at each visit

Following the run-in period, 477 patients met eligibility criteria and were randomized (239 to placebo and 238 to FF 50mcg). The majority of patients were white (85%) males (63%) with a mean age of 6.2 years. Treatment compliance with blinded study treatment was high with 91-92% of patients having a greater than 95% compliance.

For the primary endpoint of growth velocity, the least mean square difference between Arnuity Ellipta and placebo was -0.16cm/year (95%CI -0.46,0.14). These data suggest that the effect of Arnuity Ellipta on growth is numerically small and of unclear clinical significance. Subgroup analysis was also performed based on sex, and results were consistent with the primary analysis.

With regard to secondary endpoints, results were consistent with the primary endpoint in that large differences between FF 50mcg and placebo groups were not observed. In the FF 50mcg and placebo groups, the percentage of patients with growth velocity <3rd percentiles were 7% and 9%, respectively. For percentage of patients who experienced shifts from baseline in growth velocity quartiles, results were similar between groups. Regarding growth velocity in the first 12weeks of the treatment period, the LS mean difference between FF 50 mcg and placebo was 0.06cm/year (95%CI -0.45, 0.57). Standard deviation scores for heights at end of treatment were also similar between groups at the end of treatment (FF 50mcg = 0.18 and placebo=0.24). Additionally, change from baseline standard deviation scores were also similar between groups (FF 50mcg = -0.4 and placebo = -0.02).

With regard to safety, no deaths were reported. Serious adverse events were uncommon and balanced between treatment groups. With regard to treatment emergent AEs, they occurred in

57% of patients in both arms and were balanced. The AEs reported were consistent with the underlying disease and those observed in the previously completed Arnuity trials. Safety data from this study did not reveal new safety concerns.

Overall, results from this study do not impact the benefit-risk assessment of this product. The benefit-risk assessment remained positive.

This pediatric supplement submission fulfills the PMR 2765-3. The draft labeling with information from the pediatric growth study is acceptable. The regulatory action is Approval.

13 Appendices

Table 20. Schedule of Assessments

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

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

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

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

*Child Visit – in these visits the child (subject) must attend the clinic.
W/D = Early Withdrawal Visit ; T/D= Early Treatment Discontinuation Visit

Figure 2. Childhood Asthma Control Test (cACT)

Childhood Asthma Control Test for children 4 to 11 years.

How to take the Childhood Asthma Control Test

- Step 1 Let your child respond to **the first 4 questions (1 to 4)**. If your child needs help reading or understanding the question, you may help, but let your child select the response. Complete the remaining **3 questions (5 to 7)** on your own and without letting your child's response influence your answers. There are no right or wrong answers.
- Step 2 Write the number of each answer in the score box provided.
- Step 3 Add up each score box for the total.
- Step 4 Take the test to the doctor to talk about your child's total score.

19 or less If your child's score is 19 or less, it may be a sign that your child's asthma is not controlled as well as it could be. No matter what the score, bring this test to your doctor to talk about your child's results.

Have your child complete these questions.

1. How is your asthma today?

0	1	2	3	SCORE
Very bad	Bad	Good	Very good	

2. How much of a problem is your asthma when you run, exercise or play sports?

0	1	2	3	
It's a big problem, I can't do what I want to do.	It's a problem and I don't like it.	It's a little problem but it's okay.	It's not a problem.	

3. Do you cough because of your asthma?

0	1	2	3	
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time.	

4. Do you wake up during the night because of your asthma?

0	1	2	3	
Yes, all of the time.	Yes, most of the time.	Yes, some of the time.	No, none of the time.	

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5	4	3	2	1	0	
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday	

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5	4	3	2	1	0	
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday	

7. During the last 4 weeks, how many days did your child wake up during the night because of asthma?

5	4	3	2	1	0	
Not at all	1-3 days	4-10 days	11-18 days	19-24 days	Everyday	

TOTAL

The answers below should not be added to the total score. These answers should be discussed with your child's doctor.

In the past 12 months, how many emergency department visits has your child had due to asthma (that did not result in a hospitalization)? _____

In the past 12 months, how many inpatient hospitalizations has your child had due to asthma? _____

ASTHMA ACTION AMERICA®

Financial Disclosure

Application: NDA 205625 S009
Product: ARNUITY ELLIPTA (fluticasone furoate inhalation powder)
Covered Clinical Study (Name and/or Number): HZA114971

Table 21. Financial Disclosure Checklist

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 217		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

The Applicant certified that there was no any financial arrangement with the listed investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a), and no listed investigators had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b).

One [redacted] investigator was identified as having disclosed financial interests. Dr. [redacted] was a [redacted] Investigator for the study [redacted], which recruited [redacted] from a total of 477 subjects for the Study HZA 114971. The attachment of Form FDA 3455 reported that Dr. [redacted] received Honoraria payment of US $32,825.00 from the sponsor. Despite the finding of Dr. [redacted] in Study HZA 114971, there is minimal impact from the [redacted]% of the total subjects) enrolled at [redacted] site on the interpretation of the study data. Review of the documents does not raise concerns regarding the integrity of the submitted data to the current application.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STACY J CHIN
03/01/2023 01:02:43 PM

ROBERT H LIM
03/01/2023 01:04:37 PM