NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 204275 S-022
Priority or Standard	Priority
Submit Date(s)	November 14, 2022
Received Date(s)	November 14, 2022
PDUFA Goal Date	May 12, 2023
Division/Office	Division of Pulmonology, Allergy, and Critical Care/Office of Immunology and Inflammation
Review Completion Date	May 10, 2023
Established/Proper Name	Fluticasone furoate/vilanterol
(Proposed) Trade Name	Breo Ellipta
Pharmacologic Class	ICS/LABA
Applicant	GlaxoSmithKline
Doseage form	Oral inhalation powder
Applicant proposed Dosing Regimen	• 50/25 mcg once daily for patients aged 5 to 11 years old • 100/25 mcg once daily for patients aged 12 to 17 years old
Applicant Proposed Indication(s)/Population(s)	Extend indication of maintenance treatment of asthma to include 5-17 years
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	195967001 |Asthma (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Extend indication of maintenance treatment of asthma to include 5-17 years
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	195967001 |Asthma (disorder)|
Recommended Dosing Regimen	• 50/25 mcg once daily for patients aged 5 to 11 years old • 100/25 mcg once daily for patients aged 12 to 17 years old

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OPQ=Office of Pharmaceutical Quality
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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The drug product, fluticasone furoate/vilanterol (FF/VI), is a fixed-dose, inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination dry powder inhaler that is administered with *once daily dosing*. FF/VI 100/25 mcg was initially approved for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) on May 10, 2013. FF/VI was approved on April 30, 2015 for the once daily treatment of asthma in adults 18 years of age and older at doses of 100/25 mcg or 200/25 mcg. Of note, the clinical trial data used to support the approval of FF/VI in patients ≥18 years of age included patients 12 years of age and older; however, FF/VI was not approved in the 12 to 17 year old population due, in part, to concerns that there were a higher number of asthma-related hospitalizations in FF/VI treated patients, compared to patients treated with FF alone, in this age group. In addition, the bronchodilation and exacerbation benefits were also less consistent in the 12 to 17 year old age group, compared to adults. This issue was discussed at an Advisory Committee held on March 19, 2015, where the majority of the committee voted that the submitted data were not adequate to support approval in the 12-17 year old age group (1 for approval to 19 against approval).

This supplemental NDA was submitted to support efficacy and safety of FF/VI for extension of the asthma indication to patients ≥5 years of age, as well as to satisfy PREA-PMR 2904-4 (Section 10):

> *Conduct a randomized, double-blind, parallel-group study to evaluate the efficacy and long-term safety of fluticasone furoate/vilanterol (FF/VI) and fluticasone furoate (FF) in children 5 to less than 18 years of age.*

FF/VI will be the first ICS/LABA combination product approved for children 5-17 years of age with *once daily dosing*, which may improve compliance with maintenance treatment in children.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is **Approval** for FF/VI for the "maintenance treatment of asthma in pediatric patients" aged 5 to 17 years, with a dosing regimen of:

- 50/25 mcg once daily for patients 5 to 11 years old;
- 100/25 mcg once daily for patients 12 to 17 years old.

In this sNDA, the Applicant submitted data from study HZA107116, a phase 3, randomized, double-blind, parallel-group, multicenter trial that evaluated the efficacy and safety of once daily FF/VI inhalation powder, compared to once daily FF inhalation powder alone, in the treatment of asthma in patients 5 to 17 years old currently uncontrolled on ICS. In this trial, 454 patients received FF/VI (337 patients 5 to 11 years old; 117 patients 12 to 17 years old), and 448 patients received FF (336 patients 5 to 11 years old; 112 patients 12 to 17 years old). For

the primary endpoint analysis of weighted mean FEV1 (0 to 4 hours) at Week 12 in patients 5-17 years of age, a statistically significant difference of 0.083 L between treatment groups was observed; results of the subgroup analyses in the 5 to 11 and 12 to 17 year age group was consistent with the overall population. There were no statistically significant differences observed between treatment groups for secondary endpoints, including rescue-free 24-hour periods at 12 weeks, symptom-free 24-hour periods at 12 weeks, change from baseline morning FEV1 at 12 weeks, change from baseline in morning pre-dose PEF at 12 weeks, and change from baseline of ACQ-5 at 24 weeks. The incidence of patients who had a severe asthma exacerbation over the 24-week treatment period was similar in both treatment groups; the number of patients who were hospitalized for asthma was low and balanced between treatment groups. Thus, the finding in the initial pivotal trials that supported approval in adults only of a higher number of asthma-related hospitalizations observed in the FF/VI treatment arm, compared to FF alone, was not replicated in this study. The study did not reveal new safety signals. Overall, study HZA107116 was an adequate and well-controlled trial that demonstrated efficacy of FF/VI, over FF alone, based on a statistically significant improvement in weighted mean FEV1 (0-4 hours) at week 12, although there were no significant benefits in secondary endpoints; no new safety signals were identified.

Confirmatory evidence for efficacy of FF/VI in the maintenance treatment of asthma in pediatric patients 5-17 years of age is provided by the previously demonstrated efficacy of FF/VI in the adult population (≥18 years of age), as well as the clinical experience and scientific knowledge of the effectiveness of other drugs in the same pharmacologic class (i.e., ICS/LABA), including in children ≥5 years of age. Additional supportive evidence for approval of FF/VI in the pediatric population 5 to 17 years of age is provided by 9 supporting pediatric studies, including:

- Clinical pharmacology studies: HZA102942, HZA112777, HZA112776
- Dose-ranging studies: HZA106855, HZA106853
- HPA axis study: HZA107118
- Growth studies: HZA107112, HZA114971
- Device study: 206924

Together, the single adequate and well-controlled trial (HZA107116) and confirmatory evidence provide substantial evidence of efficacy to support approval of this product at the proposed doses in the 5 to 17-year-old population for the maintenance treatment of asthma.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant submitted a supplemental New Drug Application (sNDA) to the extend the asthma indication for FF/VI in the maintenance treatment of asthma, currently approved for patients ≥18 years old, to include pediatric patients 5 to 17 years of age.

Asthma is a chronic lung disease characterized by airway inflammation, bronchoconstriction, and increased airway responsiveness. The goal of asthma treatment is to achieve and maintain disease control and to reduce the future risk of exacerbations. Non-adherence to asthma treatment is a significant risk factor for morbidity, mortality, hospitalization, and reduced quality of life. ICS/LABA combination products for twice daily administration are currently approved for use in children (Section 2.2) and are included in national and international asthma treatment guidelines as part of step-up therapy for disease control. No currently approved ICS/LABA combination product for children (<18 years of age) has an indication for once daily administration. Once-daily ICS/LABA combination product has the potential to improve patient compliance and overall disease management.

To support this supplemental NDA, the Applicant submitted data from one pivotal trial, HZA107116, a Phase 3, randomized, double-blind, parallel-group, multicenter trial to assess the efficacy and safety of FF/VI, compared to FF alone, in patients 5 to 17 years of age. Primary endpoint analysis of weighted mean FEV1 (0 to 4 hours) at Week 12 demonstrated a statistically significant difference of 0.083 L between the FF/VI group and FF group; however, no statistically significant differences were demonstrated in the percentage of rescue-free 24-hour periods, percentage of symptom-free 24-hour periods, change from baseline in morning FEV1, change from baseline in morning PEF, change from baseline in ACQ-5 score, and change from baseline in evening PEF. Asthma-related hospitalizations and exacerbation rates were balanced between the treatment arms.

No new safety signals were identified based on analyses of deaths, SAEs, and AEs. The incidence of SAEs of asthma was low and was balanced between treatment arms.

Based on the safety and efficacy results from study HZA107116, the confirmatory evidence provided by the prior demonstration of the safety and efficacy of FF/VI in the adult population (≥18 years of age), and the clinical experience and scientific knowledge of the effectiveness of other drugs in the same pharmacologic class (i.e., ICS/LABA), the recommended action is Approval of FF/VI for the maintenance treatment of asthma in patients ≥5 years of age.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Asthma is a chronic and potentially life-threatening disease that presents with multiple endotypes. • Airway inflammation and reversible bronchoconstriction are central components of asthma. • Asthma is a cause of significant morbidity and mortality in children, adolescents, and adults. • The goal of asthma treatment is to achieve and maintain asthma control and to reduce the risk of exacerbations.	Asthma is a chronic inflammatory respiratory disease that can affect children, adolescents, and adults. The goal of asthma treatment is to achieve and maintain asthma control and to reduce the risk of exacerbations.
Current Treatment Options	• Inhaled corticosteroids play a central role in the first-line management of patients with persistent asthma. • LABA/ICS fixed-dose combination products are recommended by national and international asthma treatment guidelines for patients with persistent asthma whose disease is more severe or remains uncontrolled despite ICS treatment. • ICS/LABA combination products currently available for children require twice-daily administration. • Adherence with asthma treatment plans is a significant barrier to effective treatment.	FF/VI is approved for the once-daily treatment of asthma in patients 18 years old and older. Availability of a once-daily ICS/LABA combination product for the maintenance treatment of asthma in children 5-17 years of age may improve treatment compliance.
Benefit	• FF/VI was approved on April 30, 2015 for the maintenance treatment of asthma in adults ≥18 years of age based on demonstration of substantial evidence of effectiveness and a favorable benefit-risk assessment in adequate and well-controlled investigations. • FF/VI was studied in children 5-17 years of age in trial HZA107116: there was a statistically significant treatment difference of 0.083 L in weighted mean FEV1 (0 to 4 hours) at Week 12 in patients treated with FF/VI, compared to FF alone. • There were no statistically significant differences observed in secondary endpoints, including rescue-free 24-hour periods,	Results from trial HZA107116 in patients 5 to 17 years of age with persistent asthma demonstrated a significant benefit on the previously agreed primary endpoint of weighted mean FEV1 (0 to 4 hours) at Week 12. There were no statistically significant differences observed in secondary endpoints.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	symptom-free 24-hour periods, morning FEV1, morning PEF, ACQ-5 score, and evening PEF. • The incidence of severe exacerbations over the 24-week treatment period was similar in both treatment arms; asthma-related hospitalizations over 24 weeks were also low and balanced between the FF/VI and FF treatment arms.	Results from HZA107166 and the clinical experience and scientific knowledge of the effectiveness of the pharmacologic class (ICS/LABA) and demonstrated efficacy of FF/VI in patients ≥18 years of age supports efficacy for maintenance treatment on patients 5-17 years of age.
Risk and Risk Management	• The safety profile of FF/VI in pediatric patients 5-17 years of age in trial HZA107116 was consistent with the known risks of both monocomponents. • The safety profile of FF/VI in pediatric patients was consistent with that observed in patients 18 years of age and older. • No new safety signals were identified.	No new or unexpected safety signals were identified in trial HZA107116. No indication for additional risk mitigation was identified.

1.4. Patient Experience Data

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)- ACQ-5	Section 8.1
		☐	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.**			

2 Therapeutic Context

2.1. Analysis of Condition

Asthma is a common and potentially serious chronic respiratory disease characterized by variable symptoms and airway inflammation. The management of patients with asthma is based on a step-wise treatment approach that entails a continuous cycle of assessment, treatment, and review of the patient's response to medication. Asthma is a potentially life-threatening disease that may be associated with significant morbidity and healthcare utilization.

Despite advances in the treatment of asthma, it remains a serious global health problem. The goal of asthma treatment is to achieve and maintain asthma control and to reduce the risk of exacerbations. Barriers to effective management are numerous and include, among others, accurate diagnosis and severity classification, access to appropriate medications, treatment of co-morbidities, and patient compliance with maintenance treatments. Given that nonadherence to asthma treatment is a significant risk factor for morbidity, mortality, hospitalization, and reduced quality of life, there is a potential compliance benefit for children with a once-daily ICS/LABA combination product.

2.2. Analysis of Current Treatment Options

The diagnosis and management of asthma are outlined by national and international guidelines, most notably The Global Initiative for Asthma (GINA)[1] and The National Asthma Education and Prevention Program (NAEPP)[2]. Inhaled corticosteroids play a central therapeutic role in the management of patients with persistent asthma. Patients with persistent asthma whose disease is more severe or remain uncontrolled despite treatment with ICS are candidates for treatment with LABA/ICS fixed-dose combination products. All ICS/LABA combination products currently approved for children require twice-daily administration:

- Fluticasone/salmeterol approved for ≥4 years of age
- Mometasone/formoterol approved for ≥5 years of age
- Budesonide/formoterol approved for ≥6 years of age

Figure 1 summarizes controller and reliever medications currently approved and marketed in the US.

[1] https://ginasthma.org/
[2] https://www.nhlbi.nih.gov/health-topics/guidelines-for-diagnosis-management-of-asthma

Figure 1. Summary of Approved Asthma Medications

Class	Generic	Brand Name
Inhaled corticosteroids	Beclomethasone Dipropionate Budesonide Ciclesonide Fluticasone furoate Fluticasone propionate Mometasone	Qvar Pulmicort Alvesco Arnuity Ellipta Flovent Asmanex
Combination inhaled corticosteroid/long-acting bronchodilator	Budesonide/formoterol Fluticasone/salmeterol Mometasone/formoterol Fluticasone/vilanterol Fluticasone/vilanterol/umeclidinium	Symbicort Advair Dulera Breo Ellipta Trelegy Ellipta
Combination inhaled corticosteroid/short-acting bronchodilator	Budesonide/albuterol sulfate	Airsupra
Anticholinergics	Tiotropium	Spiriva
Leukotriene Modifiers	Montelukast Zafirlukast Zileuton	Singulair Accolate Zyflo
Biologics	Omalizumab (anti-IgE) Mepolizumab (anti-IL5) Reslizumab (anti-IL5) Benralizumab (anti-IL5R) Dupilumab (anti-IL4R) Tezepelumab (anti-TSLP)	Xolair Nucala Cinqair Fasenra Dupixent Tezspire
Xanthines	Theophylline	Multiple
Short-acting bronchodilators (beta2-agonists)	Albuterol sulfate Levalbuterol	ProAir Proventil Ventolin Vospire ER Xopenex

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The initial NDA 204275 was submitted on June 28, 2014 proposing once daily FF/VI treatment for the maintenance treatment of asthma in patients 12 years and older. A total of 474 patients aged 12 to 17 years old were studied, including 233 adolescents receiving FF/VI. In patients aged 18 years old and older, the primary efficacy variable of weighted mean FEV_1 favored FF/VI over FF alone. However, in patients aged 12 to 17 years old, the FEV_1 response was less apparent for the FF/VI group compared to the FF group. Furthermore, in the analysis of the rate of asthma exacerbations, the numerical trend in adolescents was against FF/VI, compared to FF alone. An Advisory Committee meeting was held on March 19, 2015, and while the Committee voted that there were sufficient data to support approval in adults (16 for approval to 4 against approval), the Committee voted that the data were not adequate to support approval in adolescents (1 for approval to 19 against approval), particularly in the setting of safety concerns with LABAs at that time. On April 30, 2015, the Division approved FF/VI for the maintenance treatment of asthma in patients ≥18 years of age only. The submitted data did not demonstrate an adequate benefit-risk profile to support approval of FF/VI in pediatric patients with asthma 12-17 years old:

- There was a higher number of asthma-related hospitalizations in patients 12-17 years old treated with FF/VI compared to FF alone
- There was a higher risk estimate for exacerbations and numerical trends towards smaller observed treatment effects with respect to lung function in 12-17 year olds
- There were safety concerns surrounding respiratory-related deaths with LABA use as a class at the time of review

Since PREA requirements for study of FF/VI in children 12 to 17 years of age were satisfied, the Division strongly encouraged the conduct of further safety and efficacy trials in 12- 17 year olds and issued 3 PREA post-marketing requirements (PMRs) for studies in patients 5-11 years of age at the time of initial approval for the asthma indication:

- PREA PMR 2904-1: Conduct a randomized, double blind, double-dummy, active- and placebo controlled, 4-period crossover dose-ranging study with vilanterol inhalation powder in children 5 to 11 years of age with asthma. Each treatment period will be of one-week duration with at least one-week washout period between treatment periods.
- PREA PMR 2904-2: Conduct a 12 week randomized, double-blind, active controlled, safety and efficacy study with fluticasone furoate/vilanterol inhalation powder in children 5 to 11 years of age with asthma.
- PREA PMR 2904-3: Conduct a 52 week randomized, double blind, active comparator, safety study with fluticasone furoate/vilanterol inhalation powder in children 5 to 11 years of age with asthma.

After further discussion between the Applicant and the FDA, these 3 PMRs were released and another PMR issued (2904-4). The PMR was as follows:

> Conduct a randomized, double-blind, parallel-group study to evaluate the efficacy and long-term safety of fluticasone furoate/vilanterol (FF/VI) and fluticasone furoate (FF) in children 5 to less than 18 years of age.

Subsequent to the issuing PMR 2904-4, the Applicant submitted a proposed pediatric study request (PPSR) which proposed a study consistent with PMR 2904-4. The Agency then issued a pediatric written request (WR) on December 20, 2017.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Division and GSK have had multiple prior interactions to discuss the proposed FF/VI asthma development program in pediatric patients. Table 1 below provides a timeline of regulatory interactions.

Table 1. Milestone Interactions Between the Agency and the Sponsor (Pediatric Program)

Date of Interaction	Highlights of Interaction
April 30, 2015	• FDA issued a Complete Response letter following NDA 204275 submission. • FDA requested GSK to provide data from a clinical program showing consistent efficacy and balancing safety to support approval of FF/VI in adolescents.
July 21, 2015	• At Type C meeting, FDA requested that GSK clarify future plan for 12 to 17 year old age group. • If GSK planned to conduct further studies in this age group, FDA would consider whether current PREA PMRs (2904-1, 2904-2, 2904-3) in 5-11 year olds may be re-designed to include 12-17 year olds. In this case, FDA would entertain a Written Request.
October 3, 2016	• At Type C meeting, GSK discussed utilizing a single FF/VI study to fulfill pediatric PREA requirements for FF/VI (Study HZA107116). • FDA said that if the scope of the study included pediatrics and adolescents (5-17 years old), FDA would release the 3 previous pediatric PMRs for FF/VI (2904-1, 2904-2, 2904-3) and issue a new PMR (2904-4) with new milestones. • FDA requested GSK to submit a brief synopsis of the study along with proposed timelines.

November 1, 2016	• GSK submitted the requested study synopsis for HZA107116.
December 20, 2017	• FDA issued a Pediatric Written Request under NDA 204275.
August 30, 2022	• At a Type B meeting, FDA agreed with GSK's overall submission strategy, along with content of the submission, the cross-reference strategy, and the proposal to not include any Integrated Summaries of Efficacy or Integrated Summaries of Safety.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Inspections of clinical sites were not requested.

4.2. Product Quality

Product quality was reviewed by the Office of Lifecycle Products, Division of Post-Marketing Activities I. The efficacy supplement was deemed approvable from a CMC perspective.

Executive Summary:
GSK (Applicant) is submitting this sNDA application to obtain marketing approval for Fluticasone Furoate/Vilanterol Inhalation Powder (FF/VI) 50/25 *microgram* for the maintenance treatment of asthma in patients aged 5 years and older.

Fluticasone Furoate/Vilanterol Inhalation Powder 50/25 microgram uses the same input materials, manufacturing process and container closure system as approved for the 100/25 and 200/25 microgram products. The control strategy applied to the 50/25 microgram product is also similar to that approved for the 100/25 and 200/25 microgram products. The drug substances, blister strips, inhaler and container closure are unchanged for the 50/25 microgram product.

Information on the drug substance, Fluticasone Furoate (FF), is provided in GSK's Drug Master File (DMF) 031938: DMF 031938 is adequate

Information on the drug substance, Vilanterol trifenatate (VI), is provided in GSK's DMF 025906: DMF 025906 is Adequate.

The container closure system including the double foil blister (b) (4) inhaler, desiccant and tray for BREO ELLIPTA 50/25 mcg is the same as that in the approved BREO ELLIPTA.

Up to thirty-six months primary stability data are presented for three batches of BREO ELLIPTA 50/25 mcg. The stability data provided support a proposed shelf-life of 24 months.
The supplement provides updated PI. There are no proposed changes to the CMC section 3, 11 and 16.

Overall Manufacturing Inspection Recommendation (OMIR) is " APPROVE (Review by Dr. Ephrem Hunde dated 1/23/23)".

Drug Product (BREO ELLIPTA 50/25 mcg) is Approvable.

4.3. Clinical Microbiology

Not applicable.

4.4. Devices and Companion Diagnostic Issues

The device used for the new FF/VI 50/25 product is identical to that used for the FF/VI 100/25 and 200/25 products.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical pharmacology/toxicology data was submitted with this supplement. Refer to the Nonclinical Pharmacology-Toxicology team memo with labeling recommendations.

6 Clinical Pharmacology

6.1. Executive Summary

Glaxo Smith Kline (GSK) submitted a supplement (S-22) under NDA 204275 seeking an extension of the indication of BREO ELLIPTA (fluticasone furoate/vilanterol trifenatate inhalation powder, FF/VI) for the maintenance treatment of asthma in children 5 to 17 years of age. The proposed dose and dosing regimen is one inhalation of FF/VI 50/25 mcg once daily and one inhalation of FF/VI 100/25 mcg once daily for patients aged 5 to 11 years and 12 to 17 years, respectively.

Of note, FF/VI 100/25 mcg once daily regimen was initially approved for the maintenance treatment of adults with COPD on May 10, 2013. Later, dosing regimens of 200/25 and 100/25 mcg FF/VI once daily were approved for the treatment of adults with asthma (suppl-1) on April 30, 2015. On the same day, a complete response was issued for FF/VI for treatment in pediatric asthma patients 12 to 17 years of age. In the approval letter for adults, the Agency issued three pediatric post-marketing requirements (PMRs 2904-1, 2904-2, and 2904-3), requesting the Applicant to conduct three pediatric clinical studies in children 5 to 11 years of age with asthma. Of note, FF was also approved in the US as monotherapy (Arnuity Ellipta 100 mcg or 200 mcg once daily for ≥12 years old and 50 mcg once daily 5 to 11 years old) for the treatment of asthma under NDA 205625.

After issuance of 3 PMRs, multiple meetings were held between the Agency and Applicant in which the scope of change of the pediatric PMRs and the design of a planned pediatric study to include adolescent subjects were discussed. Consequently, the Agency released the previously issued 3 pediatric PMRs on April 19, 2017, and added a new pediatric PMR 2094-4:

- Conduct a randomized, double-blind, parallel-group study to evaluate the efficacy (b) nd long-term safety of fluticasone furoate/vilanterol (FF/VI) and fluticasone furoate (FF) in children 5 to less than 18 years of age.

Subsequently, the agency provided a pediatric written request (PWR) on 12/20/2017 in response to the Sponsor's proposed pediatric study request on 7/31/2017. In this PWR, the Agency outlined required information to be derived from the proposed study to fulfill the new pediatric PMR.

The purpose of the current submission is to fulfill this new PMR 2094-4. Alongside seeking the extension of indication of FF/VI to patients aged 5 to 17 years, the Applicant is also requesting a pediatric exclusivity determination for the proposed product under the current supplement.

To support the current submission, the Applicant conducted a pivotal phase 3 efficacy and safety study (HZA 107116) and cross-referenced to 9 more clinical studies submitted before under different NDAs (e.g., 204275, 205625) and supplements. From these 9 studies, the

Sponsor pooled 3 studies (HZA112776, 112777, and 106853) to conduct a population PK analysis to support this pediatric supplement. Of note, HZA106853, a phase 2b dose-ranging study of vilanterol conducted in 5 – 11 years old, is reviewed under this supplement while other clinical pharmacology relevant studies were reviewed before under different NDAs/supplements.

The estimated FF systemic exposures (Cmax and AUC0-24h) at steady state in pediatric subjects with asthma (5 to 11 years old) following the proposed 50/25 mcg FF/VI is only about the half value when compared to adult and adolescent subjects with asthma following the approved 100 mcg FF monotherapy.

Cross-study comparison demonstrates that VI does not affect the PK of FF when co-administered with FF in children 5 to 11 years of age with asthma. Therefore, it is reasonable to extrapolate the HPA axis suppression results from Arnuity Ellipta (NDA 205625) to Breo Ellipta in children 5 to 11 years of age (i.e., no difference between once-daily treatment with inhaled fluticasone furoate 50 mcg compared with placebo on serum cortisol weighted mean (0 to 24 hours) and serum cortisol AUC0-24h following 6 weeks of treatment).

The projected systemic exposure (Cmax and AUC) of VI in children 5 to 11 years of age with asthma following the proposed 50/25 mcg FF/VI is within the range of popPK model-estimated exposure in adult and adolescent subjects with asthma following the approved 100/25 and 200/25 mcg FF/VI treatment.

Cross-study comparison demonstrates that FF reduces VI Cmax by 55% without affecting VI AUC value when co-administered with VI. The clinical meaning of this observation is unclear as VI is not approved as a monocomponent for treating asthma.

6.1.1. Recommendations

The Clinical Pharmacology data provided by the Applicant in this submission is acceptable, and the Clinical Pharmacology review team recommends approval of NDA 204275-S22 for FF/VI combination therapy at doses of 100/25 mcg for adolescents 12-17 years old and 50/25 mcg for pediatric subjects aged 5 – 11 years old with asthma, as a regimen of 1 inhalation once daily.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The general clinical pharmacology information of fluticasone furoate and vilanterol based on the approved drug label of NDA 204275 for combination therapy of FF/VI in adults is listed below. Also refer to the approved drug label of NDA205625 for FF monotherapy in subjects aged ≥ 5 years old with asthma for relevant clinical pharmacology information of FF.

- Absorption:

  Linear pharmacokinetics was observed for fluticasone furoate (200 to 800 mcg) and vilanterol (25 to 100 mcg). On repeated once-daily inhalation administration, steady state of fluticasone furoate and vilanterol plasma concentrations was achieved after 6 days.

  Fluticasone Furoate: Fluticasone furoate plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 0.5 to 1 hour. Absolute bioavailability of fluticasone furoate when administered by inhalation was 15.2%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose is low (approximately 1.3%) due to extensive first-pass metabolism.

  Vilanterol: Vilanterol plasma levels may not predict therapeutic effect. Peak plasma concentrations are reached within 10 minutes following inhalation. Absolute bioavailability of vilanterol when administered by inhalation was 27.3%, primarily due to absorption of the inhaled portion of the dose delivered to the lung. Oral bioavailability from the swallowed portion of the dose of vilanterol is low (<2%) due to extensive first-pass metabolism.

- Distribution:

  Fluticasone Furoate: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 661 L. Binding of fluticasone furoate to human plasma proteins was high (99.6%).

  Vilanterol: Following intravenous administration to healthy subjects, the mean volume of distribution at steady state was 165 L. Binding of vilanterol to human plasma proteins was 93.9%.

- Metabolism

  Fluticasone Furoate: Fluticasone furoate is cleared from systemic circulation principally by hepatic metabolism via CYP3A4 to metabolites with significantly reduced corticosteroid activity. There was no *in vivo* evidence for cleavage of the furoate moiety resulting in the formation of fluticasone.
  Vilanterol: Vilanterol is mainly metabolized, principally via CYP3A4, to a range of metabolites with significantly reduced β1- and β2-agonist activity.

- Elimination

  Fluticasone Furoate: Fluticasone furoate and its metabolites are eliminated primarily in the feces, accounting for approximately 101% and 90% of the orally and intravenously administered doses, respectively. Urinary excretion accounted for

approximately 1% and 2% of the orally and intravenously administered doses, respectively. Following repeat-dose inhaled administration, the plasma elimination phase half-life averaged 24 hours.

Vilanterol: Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and feces (approximately 70% and 30% of the recovered radioactive dose, respectively). The plasma elimination half-life of vilanterol, as determined from inhalation administration of multiple doses of vilanterol 25 mcg, is 21.3 hours in subjects with COPD and 16.0 hours in subjects with asthma.

- Specific Populations

Fluticasone Furoate: FF/VI showed lack of effect of severe renal impairment on FF exposure following repeat doses of FF/VI (200/25). No dose adjustment is warranted in patients with renal impairment.

Following repeat dosing of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days, there was an increase of 34%, 83%, and 75% in fluticasone furoate systemic exposure (AUC) in subjects with mild, moderate, and severe hepatic impairment (HI), respectively, compared with healthy subjects. Increased FF systemic exposure was associated with 34% decrease in serum cortisol in participants with moderate HI, but increased by 14% in severe HI following FF/VI, 100 mcg/12.5 mcg (half dose of that received by the participants with mild and moderate HI), implying no effect on cortisol in participants with severe hepatic impairment. Caution is recommended while using FF in patients with moderate or severe hepatic impairment.

Systemic exposure (AUC0-24h) to inhaled fluticasone furoate 200 mcg was 27% to 49% higher in healthy subjects of Japanese, Korean, and Chinese heritage compared with white subjects. Similar differences were observed for subjects with COPD or asthma. However, there is no evidence that this higher exposure to fluticasone furoate results in clinically relevant effects on urinary cortisol excretion or on efficacy in these racial groups. Age and gender did not show any clinically relevant effect on the PK of FF.

Vilanterol: Vilanterol systemic exposure (AUC0-24h) was increased by 56% in subjects with severe renal impairment compared with healthy subjects. There was no evidence of greater beta-agonist class-related systemic effects. No dose adjustment is warranted in patients with severe renal impairment.

Hepatic impairment had no effect on vilanterol systemic exposure (Cmax and AUC0-24h on Day 7) following repeat-dose administration of fluticasone furoate/vilanterol 200 mcg/25 mcg (100 mcg/12.5 mcg in the severe impairment group) for 7 days. In line with this lack of increase in VI systemic exposure, no clinically relevant effects of the FF/VI combination on beta-adrenergic systemic effects (heart rate or serum potassium) were noted in participants with varying degrees of hepatic impairment compared with healthy participants.

In subjects with asthma, vilanterol Cmax is estimated to be higher (3-fold) and AUC0-24h is comparable for those subjects from an Asian heritage compared with subjects from a non-Asian heritage. However, the higher Cmax values are similar to those seen in healthy subjects. Age and gender did not show any clinically relevant effect on the PK of VI.

- Drug Interaction Studies

Inhibitors of Cytochrome P450 3A4: The exposure (AUC) of fluticasone furoate and vilanterol were 36% and 65% higher, respectively, when coadministered with ketoconazole 400 mg compared with placebo. The increase in fluticasone furoate exposure was associated with a 27% reduction in weighted mean serum cortisol (0 to 24 hours). The increase in vilanterol exposure was not associated with an increase in beta-agonist–related systemic effects on heart rate or blood potassium. Caution should be exercised when considering the coadministration of FF or FF/VI with long-term ketoconazole and other known strong CYP3A4 inhibitors.
Inhibitors of P-glycoprotein: Fluticasone furoate and vilanterol are both substrates of P-glycoprotein (P-gp). Coadministration of repeat-dose (240 mg once daily) verapamil (a potent P-gp inhibitor and moderate CYP3A4 inhibitor) did not affect the vilanterol Cmax or AUC in healthy subjects. Drug interaction trials with a specific P-gp inhibitor and fluticasone furoate have not been conducted.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

BREO ELLIPTA® (fluticasone furoate/vilanterol, FF/VI, or BREO) was first approved for the maintenance treatment of COPD (100/25 mcg once daily) on May 10, 2013 under the current NDA. FF/VI was later approved for the treatment of asthma in adults (≥18 years old) under the supplement-1 of this NDA on April 30, 2015 at the dosage regimen of one inhalation of 100/25 or 200/25 once daily. The label indicates that the patients who do not respond adequately to BREO 100/25 may get additional improvement in asthma control if dose is increased to 200/25.

In the current supplement, the Applicant is proposing the following treatment regimens:

- Maintenance treatment of asthma in adolescent patients 12 to 17 years old: one inhalation of FF/VI 100/25 mcg once daily
- Maintenance treatment of asthma in pediatric patients 5 to 11 years old: one inhalation of FF/VI 50/25 mcg once daily.

Therapeutic Individualization
No therapeutic individualization is needed based on the submitted clinical pharmacology data.

Outstanding Issues
None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Fluticasone furoate is a corticosteroid and vilanterol is a long-acting beta$_2$-adrenergic agonist (LABA). To support the current supplement, the Applicant submitted the data and report from a pivotal phase 3 study (HZA 107116) entitled "A randomized, double-blind, parallel group, multicenter, stratified, study evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder compared to once daily fluticasone furoate inhalation powder in the treatment of asthma in participants aged 5 to 17 years old (inclusive) currently uncontrolled on inhaled corticosteroids". However, the PK of FF or VI was not evaluated in this study. Hence, the Clinical Pharmacology team will not review this study.

In addition, the Applicant cross-referenced to 9 more clinical studies previously conducted in pediatric patients aged 5 – 11 years old to support this supplement. The objectives, study designs, dose, and dosage regimen of these supportive studies along with the pivotal phase 3 study HZA107116 are included in Table 2 (VI and FF/VI studies) and Table 3 (FF studies).

Table 2. Clinical studies involving VI monotherapy and FF/VI combination therapy

Study ID	Objectives	Study design	Study treatment	Remarks
HZA112776	Safety, tolerability, PK, and PD (safety) of VI	Phase 2a, R, DB, PC, 2-way CO, in children (n= 28) aged 5-11 years with persistent asthma	VI 25 mcg or placebo once daily for one week	VI Cmax was higher than that of HZA112777
HZA112777	Safety, tolerability, PK, and PD of FF/VI vs. VI	Phase 2a, R, OL, SD, 2-period CO, in children (n= 26) aged 5-11 years with persistent asthma.	1 inhalation of FF/VI (100/25 mcg) once daily or 1 inhalation of FF (100 mcg) once daily for 14 days	FF exposures are comparable between FF/VI and VI arm
HZA106853	Dose-ranging of VI: dose-response, efficacy, safety	Phase 2b, R, DB, PG, PC, MC study in children (n= 463) aged 5-11 years with persistent uncontrolled asthma. PK samples: pre-dose & 10 – 15 minutes post-dose	Background therapy with ICS: FP 100 mcg BID via ACCUHALER/ DISKUS™, open label. Treatment: Placebo, VI 6.25 mcg, 12.5 mcg, or 25 mcg once daily in the evening for 28 days	No statistically significant improvement of PEF between VI and placebo. No dose-response relationship was observed.
HZA107116;	Comparison of efficacy between FF/VI and FF	Phase 3, R, DB, PG stratified study in children (n= 870) aged 5 – 17 years old ; No PK samples were collected	Open-label FP 100 mcg BID as background therapy. 5-11 yo: FF 50 mcg or FF/VI (50/25 mcg) once daily in the morning for 24 weeks 12-17 yo: FF 100 mcg or FF/VI (100/25 mcg) once daily in the morning for 24 weeks	A pivotal Phase 3 study.

206924	Evaluation of correct and ease of device use	Phase 4, randomized, multicenter, single arm, stratified, placebo-only, open-label study using ELLIPTA Dry Powder Inhaler (DPI)	Placebo only, via ELLIPTA DPI for 28 days	Each age stratum (92% for ages 5-7, and 93% for ages 8-11) demonstrated correct use of the device.

Table 3. Clinical studies involving FF monotherapy

Study ID	Objectives	Study design	Study treatment	Remarks
HZA102942	Safety, tolerability, PK, and PD (serum cortisol) of FF	Phase 2a, R, DB, PC, 2-way CO (FF 100 mcg vs Placebo), in children (n= 27) aged 5-11 years with persistent asthma	One inhalation of FF 100 mcg or Matching Placebo once daily in the morning from day 1 to 14.	FF PK results were similar to HZA112776.
HZA106855	Dose-ranging of FF: dose-response, efficacy, safety	Phase 2b, R, DB, DD, PG, placebo- and active-controlled stratified study in children (n= 596) aged 5-11 years with persistent uncontrolled asthma.	FP 100 mcg BID (Flovent Diskus), FF 25, 50, 100 mcg QD or matching placebo of both FP and FF	All doses were significantly superior to placebo on PEF. No dose response relationship was observed.
HZA107112	Effect of FF on short-term lower leg growth; Safety	Phase 3a, SC R, DB, PC, 2-way CO study in children (n= 60) aged 5-11 years with asthma.	FF 50 mcg or placebo QD for 14 days	No significant difference on knemometry assessment compared to placebo.
HZA107118	Effect of FF on HPA axis	Phase 3a, R, DB, PC, PG, stratified study in children (n= 111) aged 5 – 11 years old with asthma	One inhalation of FF 50 mcg OD or matching Placebo in the morning for 6 weeks	No significant reduction on serum cortisol weighted mean compared to placebo
HZA114971	Effect of FF on growth velocity	R, DB, PC, PG study in children 5-9 years old (n=457)	FF 50 mcg QD	No significant reduction on growth velocity compared to placebo (not powered)

Among these studies tabulated above, Studies HZA106853 and 206924 were submitted under the current supplement, and HZA114971 was submitted previously but not reviewed. The remaining 6 studies were reviewed previously as follows:

- Dr Jianmeng Chen reviewed Study HZA102942, HZA112776 (clin pharm review dated 3/18/2013) and HZA112777 (dated 3/26/2015) under NDA204275.
- Dr Manuela Grimstein reviewed Study HZA106855, HZA107112, and HZA107118 (clin pharm review dated 3/28/2018) under NDA 205625.

No PK samples were collected from Studies HZA107116, HZA 114971, and therefore, the Clinical Pharmaoclogy team will not review these studies. This leaves only Study HZA106853, a vilanterol dose-ranging study submitted and fully reviewed under the current supplement.

In addition, a VI popPK model report (2014N222711_00) was submitted under the current supplement which pooled PK data collected from Studies HZA106853, HZA112776, and HZA112777 to support the PK characteristics of VI in children aged 5 – 11 years old. The review of VI popPK model is attached as OCP Appendix in this review.

VI Dose Ranging Study HZA106853:

Study HZA106853 was a multicenter, randomized, double-blind, parallel-group, placebo-controlled (with rescue medication) study in children aged 5 to 11 years with persistent uncontrolled asthma who were symptomatic on ICS. The primary objective was to evaluate the dose-response, efficacy, and safety of 3 doses of VI inhalation powder administered once daily. This study included a 4-week run-in period after screening. All subjects who entered the run-in period received open-label fluticasone propionate 100 mcg twice daily (FP 100 BD) via a DISKUS/ACCUHALER for the entire study duration (4-week run-in and 4-week treatment). At the end of run-in period, subjects were randomized to receive any of the following treatments: 6.25, 12.5, 25 mcg VI, or placebo once daily for 4 weeks, along with FP 100 BD as a background therapy in all treatment arms. A total of 463 subjects were randomized across 4-treatment arms in 1:1:1:1 ratio, but 375 subjects completed the study (Table 4). All subjects were provided with albuterol/salbutamol to be used as needed for symptomatic relief of asthma symptoms during both the run-in and the treatment periods.

Table 4. Subject Populations (Study HZA106853, ITT Population)

	Number (%) Subjects				
Population	**Placebo**	**VI 6.25**	**VI 12.5**	**VI 25**	**Total**
Total					1208
Randomized	115	116	116	116	463
Intent-to-Treat (ITT)	115 (100)	114 (98)	113 (97)	114 (98)	456 (98)
Per Protocol (PP)	91 (79)	95 (82)	97 (84)	93 (80)	376 (81)
Pharmacokinetic		92 (81)	95 (84)	90 (79)	227 (81)[1]

Source: Table 5, study report of hza106853
Note: All treatments were administered on a constant background of open-label FP 100 BD.
Subjects (b) (6) and (b) (6) received study medication but were not randomized and have not been included in the ITT Population. These subjects were subsequently withdrawn.
1. The denominator for the total PK Population is the total number of subjects in the ITT Population who were randomized to VI treatment (N=341)

The primary endpoint was the mean change from baseline in daily pre-dose peak expiratory flow (PEF) at evening (PM). As one of the secondary endpoints, the change from baseline in evening clinic visit trough (pre-bronchodilator and pre-dose) forced expiratory volume in 1 second (FEV1) at the end of the 4-week treatment period in children was evaluated.

The to-be-marketed formulation and device (ELLIPTA inhaler) for vilanterol were used. A sparse PK sampling scheme was used to collect blood samples at pre-dose and 10 to 15 minutes post-dose during Week 5 (Visit 5). The VI PK result obtained from study was pooled into a VI population PK model . Refer to the pharmacometrics review in OCP appendices for the popPK model review.

The lung function results showed an increase from baseline in LS mean PM PEF averaged over Weeks 1 to 4 (placebo: 4.5 L/min; VI treatment: 8.9 to 11.0 L/min) in all treatment groups. VI treatment did not show a statistically significant improvement on the PEF change from baseline compared with placebo at any of the doses investigated and there was no apparent dose-response relationship observed (Table 5).

Table 5. Dose Ranging Results of VI on Peak Expiratory Flow (PEF) compared to Placebo Group Following 4-Week Once Daily Treatment ITT Population – Study HZA106853

	Placebo N=115	VI 6.25 N=114	VI 12.5 N=113	VI 25 N=114
Change from Baseline in PM PEF (L/min), Weeks 1-4				
n	113	113	112	110
LS mean	215.9	221.4	222.4	220.3
LS mean change (SE)	4.5 (2.53)	10.0 (2.53)	11.0 (2.54)	8.9 (2.56)
Treatment versus Placebo				
Difference		5.5	6.4	4.4
95% CI		-1.6, 12.5	-0.6, 13.5	-2.7, 11.4
p-value		0.127	0.073 [a]	0.227

Source: m2.7.3, summary of clinical efficacy – pediatric asthma, Table 19
ANCOVA = analysis of covariance; BD = twice daily; CI = confidence interval; FP = fluticasone; ITT = intent-to-treat; LS = least square; PEF = peak expiratory volume; N = Number of participants; n= subset of participants; PM = evening; SE = standard error.
Note: All treatments were administered on a constant background of open-label FP 100 mcg BD.
a. Nominal p-value. No statistical inference can be made due to the statistical testing hierarchy.

FF Dose Ranging Study HZA106855:

Study HZA106855 is a phase IIb, randomized, double-blind, parallel-group, placebo- and active-controlled, dose-ranging efficacy and safety study in the target population (575 children aged 5 – 11 years uncontrolled on non-ICS asthma medication and/or low dose ICS) to support the selection of the FF dose for the pediatric development program.

Subjects meeting entry criteria at screening (Visit 1) entered a 4-week run-in period, during which subjects continued with their current asthma medications. After run-in period, subjects were randomized (1:1:1:1) to receive FF 25, 50, 100 mcg once daily via ELLIPTA inhaler, or FP 100 mcg twice daily via the ACCUHALER/DISKUS PLUS inhaler, or matching placebo for a duration of 12-week. FF was administered in the PM while FP was administered in the AM and

PM, with similar administration pattern for the matched placebo. Regardless of treatment, all subjects were provided with albuterol/salbutamol to be used for symptomatic relief of asthma symptoms during the run-in and the treatment periods.

The primary endpoint was the mean change from baseline in daily pre-dose AM PEF from the patient electronic daily diary averaged over the 12-week treatment period. As one of the secondary endpoints, the change from baseline in evening clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 12-week treatment period in children was evaluated.

The lung function results showed an increase from baseline in LS mean AM PEF averaged over Weeks 1 to 12 (placebo: 3.3 L/min; treatment of FF 25, FF 50, and FF 100 OD: 21.9, 22.8, and 15.8 L/min, respectively) was statistically significant in all FF treatment groups.

Pharmacokinetics of FF:

As mentioned above, FF was also approved as monotherapy (Arnuity Ellipta 50 mcg once daily) for the maintenance treatment of asthma in pediatric patients aged 5 - 11 years old under NDA 205625/supplement-5. To support this pediatric supplement, the Sponsor submitted 3 supportive clinical studies: HZA102942, HZA102777, and HZA106855 under NDA205625, which were reviewed by Dr. Manuela L. T. Grimstein under supplement 5 dated 3/28/2018. The PK of FF in pediatric subjects aged 5 – 11 years with asthma were evaluated based on data from these 3 clinical studies. The clinical pharmacology review of supplement 5 implies that the Sponsor conducted a population PK analysis to compare systemic exposures of FF with those of adolescents and adults. To compare steady state systemic exposures of FF across pediatric, adolescent, and adult subjects, a table is given below.

Table 6. Comparison of systemic exposures of FF at steady state across pediatric, adolescent, and adult subjects with asthma following repeat dosing with FF as monotherapy or in combination with VI (Source: Clin Pharm review dated 03/28/2018 under NDA 205625/Suppl 5)

Population	Study	Dose	N	Cmax (pg/mL)	95% CI	AUC0-24h (pg.h/mL)	95% CI	Cmax (dose-adjusted)	AUC0-24h (dose-adjusted)
5-<12 y	HZA106855 (25, 50, 100 mcg FF)	25	92	5.7	5.1-6.4	47	41-54	0.228	1.88
		50	85	11.6	10.6-12.7	98	87-110	0.232	1.96
		100	77	22.4	19.9-25.3	196	167-230	0.224	1.96
5-<12 y	HZA102942 (100 mcg FF)	100	26	23.6	20.8-26.8	171	142-205	0.236	1.71
5-<12 y	HZA112777 (100 mcg FF and 100/25 mcg FF/VI)	100	26	20.3	17.1-24.2	158	127-196	0.203	1.58

≥12 y	FFA114496 (100 mcg and 200 mcg FF)	100	116	27.0	15.4-50.3	181	118-292	0.270	1.81
		200	115	55.1	32.6-98.2	395	194-918	0.276	1.97

Note: Study HZA112777 explored both 100/50 mcg FF/VI combination and 100 mcg FF while Study FFA114496 tested FF 100 and 200 mcg as monotherapy.
Data are population PK model predicted Cmax and AUC0-24h values (Geometric Mean, 95% confidence interval) following repeat administration of FF 25 mcg, 50 mcg, 100 mcg or 200 mcg once daily in pediatric, adolescents and adults with asthma by study.

Table 6 summarizes the population PK results of FF showing that the systemic exposure of FF at steady state in children 5 to 11 years of age was comparable to that observed in adolescents and adults following the same FF 100 mcg monotherapy once daily dosing. The geometric mean AUC0-24h following 100 FF in children aged 5 to 11 years (196 pg.h/mL, Study HZA106855) was comparable to that in adults and adolescents in (181 pg.h/mL) [Study FFA114496, Original NDA]. Geometric mean Cmax was also similar in children aged 5 to 11 years and adults and adolescents (22 pg/mL and 27 pg/mL, respectively).

Observed PK results from Study HZA112777 demonstrates that FF systemic exposure (Cmax and AUC0-24h) at steady state are comparable when administered as a monocomponent (100 mcg) or in combination with VI (100/25 mcg) when the same device was used (Table 7).

Table 7. Within-study comparison of FF exposures following administration of FF/VI combination and FF alone

Study	PK parameters	FF 100	FF/VI 100/25	Source (PopPK report)
HZA112777 (Asthma (5 – 11 years old)	AUC0–4h, pg.h/mL[a]	83.83 (71.49, 98.30)	86.14 (70.04, 105.96)	HZA112777 CSR; NDA204275/Seq 10
	Cmax, pg/mL[a]	21.16 (14.91, 30.02)	20.73 (15.16, 28.36)	

[a]Geometric mean (95% confidence interval).

In addition, the Study HZA106855 demonstrates that FF systemic exposure increases dose proportionally from 25 mcg to 100 mcg in children 5 to 11 years of age (**Table 5**). Therefore, the systemic exposure of FF (Cmax and AUC0-24h) in children 5 to 11 years of age following the proposed 50/25 mcg FF/VI is projected to be only about half value of systemic exposure in adults and adolescents following the approved 100 mcg, or the dose-adjusted Cmax and AUC0-24h values of FF following FF/VI inhalation are comparable across all pediatric, adolescent, and adult patients with asthma.

Pharmacokinetic results of VI:

In the currently submitted vilanterol dose-ranging study (HZA106853) that evaluated multiple ascending doses of VI ranging from 6.25 – 25 mcg, only 2 PK blood samples (at pre-dose and 10-15 minutes post-dose) were collected at steady state. Besides, a considerable number of

samples were below lower limit of quantitation (LLOQ, 10 pg/mL) in this study, including pre-dose samples of all the dosing arms and post-dose samples of 6.25 mcg and 12.5 mcg dosing cohorts (see pharmacometrics review).

Therefore, the Applicant conducted a popPK analysis by pooling data from HZA106853 (only 25 mcg dosing cohort was included) and two more clinical studies (HZA112776 and 112777) with intensive PK sampling timepoints conducted in children aged 5 – 11 years. Model-predicted PK exposures (e.g., AUC0-24h and Cmax of VI 25 mcg) were estimated and compared with model-predicted corresponding PK parameters observed in adolescents and adults (Table 8).

Table 8. Model-predicted PK parameters of VI in children of 5 – 11 years old with asthma and their comparison with those of healthy subjects, adolescent, and adults with asthma

Treatment	Subjects	N	Cmax (pg/mL); Geometric mean [95% CI]	$AUC_{0\text{-}24h}$ (pg.h/mL); Geometric mean (95% CI)
FF/VI (200/25 mcg)	Healthy subjects (18 – 66 yo)	110	130.5 [118.6, 143.5]	213.9 [197.0, 232.2]
FF/VI (100/25 mcg) or FF/VI (200/25 mcg)	Asthma (12 – 84 years old)	856	49.5 [46.6, 52.5]	168.7 [163.9, 173.5]
VI 25 mcg; FF/VI (100/25 mcg)*	Asthma (5-11 years old)	90	100.6 [30.2, 363.1]	83 [74.8, 92.7]

* VI 6.25 mcg and 12.5 mcg were excluded from popPK analysis.
Source: m.2.7.2 of NDA204275: Table 15 of Summary of clinical pharmacology studies – pediatric asthma.

It shows that model-predicted geometric mean of Cmax in children 5 to 11 years of age is ~2-fold higher and the AUC0-24h is ~2-fold lower at steady state for VI than those predicted in adolescents and adults. However, when compared the observed results from a clinical study in children 5 to 11 years of age with asthma (HZA112777) to the model-predicted exposures in adult and adolescent with asthma at steady state, the pediatric systemic exposures are within the range of adults and adolescents, by considering that the mean plasma concentration of VI in children falls BLQ at 4-8 hours post-dose (Table 9). Of note, the IV PK sampling schedule around Tmax in both studies is identical (10 minutes and 20 minutes postdose).

Table 9. Cross-study comparison of PK parameters of VI when administered alone or with FF

Study	Subjects	N	Cmax (pg/mL) GM [95% CI]	AUC0-4h (pg.h/mL) GM [95% CI]	Source (PopPK report)
HZA112776 (VI 25 mcg)	Asthma (5 – 11 years old)	25	97.44 [64.83, 146.45][@]	110.3 [83.93, 145.5][@]	HZA112776 CSR; NDA204275/Seq 10
HZA112777 (FF/VI [100/25 mcg])	Asthma (5 – 11 years old)	25	44.2 [27.7, 70.7]	119 [102.4, 138.7]	HZA112777 CSR; NDA204275/Seq 10

[@]For 2 subjects, parameters couldn't be derived because of non-calculable concentrations. Hence, AUC was imputed by 0.5 x lowest observed AUC and Cmax was imputed with ½ LLQ (LLQ = 10 pg/mL) for these two subjects

The reason of differences in model predicted exposures between 5 – 11 years old and adolescents as well as adults may be related to high variability due to sparse sampling, higher percentage of samples with BLQ, and limited number of subjects aged 5 – 11 years old with asthma included in popPK analysis, although none of the demographic covariates such as age, race, ethnicity, sex, body weight was identified to have a significant effect on the PK of either FF or VI.

Therefore, the reviewer agrees with the Applicant that the VI systemic exposure in children 5 to 11 years of age following the proposed 50/25 mcg FF/VI is within the range of adults and adolescents following the approved 100/15 or 200/25 mcg FF/VI regimen.

Since the model-predicted systemic exposure of VI is higher in healthy subjects than subjects with asthma, the reviewer collected additional observed VI PK results from healthy subjects in the studies submitted under original review cycles (Table 10) and confirmed this general trend.

This trend is also consistent with the conclusions drawn from the original review of NDA 204275 that "*For VI, the order of relative systemic exposure in COPD and Asthma patients and healthy subjects is, Asthma<healthy subjects≠COPD".* (refer to clin pharm review dated 3/18/2013 by Dr. Jianmeng Chen).

Table 10. Cross-study comparison of VI exposures in adult healthy subjects

Study	N	Dose in mcg (FF/VI)	Day	Cmax (pg/mL) Geometric mean [95% CI]	AUC0-24 (pg.hr/mL) Geometric mean [95% CI]	Sources
HZA111789 (HI Study]	9	200/25	7	246.8 [195.0, 312.5]	511.1 [419.6, 622.6]	HZA111789 CSR, Table 7
HZA113970 (RI Study]	9	200/25	7	152.9 [56.4, 414.5]	386.3 [312.1, 478.3]	HZA113970 CSR, Table 8
HZA105548 (DDI Study]	18	200/25 (from day 5 to 11)	11	120.4 [91.8, 159.2]	78.6 [46.5, 133]	Reviewer's analysis based on dataset, pkcnc.xpt from study HZA105548
HZA102936 (TQT Study]	81[α]	200/25	7	115 [102, 130]	85.0 [71.0, 102]	HZA102936 CSR, Table 17

HI: hepatic impairment; RI: renal impairment, TQT: thorough QT/QTc
[α]Number of subjects (2 for AUC, 1 for Cmax) for whom parameter cannot be derived because of non-calculable concentrations: AUC non-calculable values were imputed by 0.5 x lowest observed AUC (i.e., AUC0–24: 0.5 x 32.4); Cmax non-calculable values were imputed by 0.5 x LLQ (i.e., 0.5 x 10).

A cross-study comparison of observed VI PK results from pediatric Studies HZA112776 and HZA112777 demonstrated that when 25 mcg VI is administered concomitantly with 100 mcg FF in children 5 to 11 years of age, the mean Cmax is only 45% the value of mean Cmax following 25 mcg VI as a mono-component administration, regardless that the same to-be-marketed device was used. However, the VI AUC values are comparable between two treatments in children. This phenomenon is not observed in adult studies (refer to clin pharm review dated

3/18/2013 by Dr. Jianmeng Chen) and the exact cause is unclear. In the clinical pharmacology review for the original NDA 204275, dedicated drug interaction studies HZ105871 and HZA102940 did not identify noticeable effect of FF on PK of VI at 50 and 100 mcg VI dose in healthy subjects.

Effect of FF on the hypothalamic-pituitary-adrenocortical (HPA) axis:

Since FF is a synthetic corticosteroid, it has a potential to suppress HPA axis function. Therefore, the risk of HPA-suppression in children (5-11 years of age) following chronic once daily administration of FF was investigated in the dedicated HPA-axis study HZA107118, which was submitted to NDA 205625/seq0041 and reviewed under supplement 5. Study HZA107118 was a 6-week, double-blind, placebo-controlled, stratified safety study in children 5 to 11 years of age to evaluate the effect of FF on HPA axis function following 50 mcg once daily treatment.
The effects of FF on the HPA axis were assessed primarily based on changes in serum cortisol levels from pre-dose to the end of the 6-week treatment period. The effects of FF on the HPA axis were also assessed based on changes in 24-hour urinary free cortisol levels from pre-dose to the end of the 6-week treatment period. The FF treatment group demonstrated to be noninferior to placebo based on the derived serum cortisol weighted mean (0-24 hour), as the lower limit of the 95% CI was greater than 0.80 (95% CI: 0.8096, 1.0620) (Table 11). Moreover, the safety of inhaled FF on the HPA axis of adult (>18 years of age) and adolescent (12-17 years of age) patients with asthma was also established (Original NDA, Study HZA106851 and meta-analysis 2011N130478_00). The comparable systemic exposure of FF between FF/VI and FF in children 5 to 11 years of age supports the extrapolation of the results and conclusion of HPA axis suppression study HZA107118 from Arnuity Ellipta (NDA 205625) to Breo Ellipta.

Table 11. Analysis of Derived Serum Cortisol Weighted Mean (0-24h) (nmol/L) and Ratio from Baseline (Per Protocol Population)

	Placebo		FF	
	Value (nmol/L)	Ratio from baseline	Value (nmol/L)	Ratio from baseline
Baseline				
n	51		53	
Median	183.50		157.46	
Min	97.2		73.4	
Max	404.6		345.6	
End of Treatment (Week 6)				
n	50		52	
Median	175.63	1.02	151.21	1.01
Min	67.5	0.3	83.7	0.4
Max	538.7	3.8	519.1	4.1
LS mean	173.25	1.05	160.65	0.97
LS mean ratio FF/Placebo				0.93
95% CI				0.8096, 1.0620

Abbreviations: n= number of subjects with value at the visit; LS = Least Square; CI = Confidence Interval
(Source: Table 3 - Clinical Pharmacology review dated 3/28/2018 under NDA 205625/Suppl-5).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Refer to the clinical review and statistical review for more details regarding efficacy assessment.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

No alternative dosing regimen or management strategy is required based on intrinsic factors (e.g., age, race, gender, hepatic impairment, and renal impairment) against the proposed dose and dosing regimen for adolescents and pediatric subjects aged 5 – 11 years old. This is consistent with treatment management strategy in adults as outlined in the approved label of NDA204275 for Breo.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

The proposed management strategy for subjects 5 to 17 years of age regarding drug-drug interactions (e.g., caution should be exercised when FF or FF/VI is coadministered with long-term ketoconazole or other CYP3A4 inhibitors) is consistent with the approved recommendations for adults, which is reasonable. Refer to the approved drug label of NDA 204275 for details.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Figure 2. Clinical Trial to Support NDA 204275-S022

Trial Identifier	Trial Population	Trial Design	Number Treated, Regimen	Primary and Secondary Endpoints	Number of Centers and Countries
HZA107116	Patients 5 to 17 years old with demonstrable airway reversibility and with impaired lung function who were uncontrolled despite treatment with fluticasone propionate	Phase 3, 24-week, randomized, double-blind, parallel-group, multicenter study	902 patients were randomized: 454 received FF/VI, 448 received FF	Primary: Weighted mean FEV1 (0 to 4 hours) at Week 12 Secondary: rescue-free 24-hour periods, symptom-free 24-hour periods, morning FEV1, morning PEF, ACQ-5 score, evening PEF	Centers: 228 Countries: 15

7.2. Review Strategy

The Applicant submitted data from a single pivotal trial, HZA107116, to support efficacy and safety of FF/VI in the maintenance treatment of asthma in children 5 to 17 years of age. HZA107116 was a phase 3, 24-week, randomized, double-blind, parallel-group, multicenter study that was designed to evaluate the efficacy and safety of FF/VI in patients 5 to 17 years old.

A detailed clinical pharmacology review of HZA107116 and supporting data is provided in Section 6.

Analyses of efficacy data from study HZA107116 were performed by the statistical reviewer and are provided in Sections 8.1.2 and 8.1.3, confirming the results submitted by the Applicant. Additional statistical issues are discussed by the statistical reviewer in Section 8.3.

The safety results of pooled data for 5-11 year old patients (FF/VI 50/25) and 12-17 year old patients (FF/VI 100/25) were analyzed and the Applicant's findings were confirmed by the clinical reviewer using JMP. The results of the safety analysis are presented in Section 8.2.

8 Statistical and Clinical and Evaluation

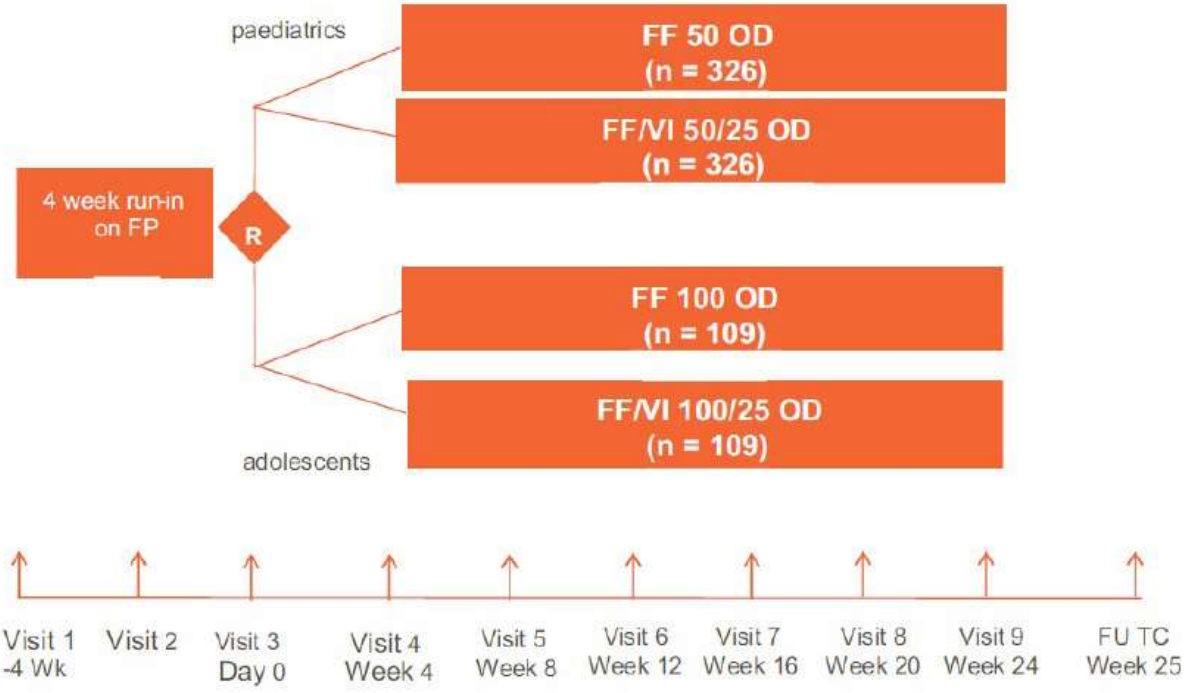
8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. HZA 107116

Trial Design

HZA 107116 was a 24-week, randomized, double-blind, parallel group, multicenter, age-stratified trial evaluating the efficacy and safety of once daily fluticasone furoate/vilanterol inhalation powder, compared to once daily fluticasone furoate inhalation powder, in the treatment of asthma in patients aged 5 to 17 years old currently uncontrolled on inhaled corticosteroids. Following a 4-week run-in period during which all participants received fluticasone propionate 100 mcg twice daily to stabilize control, patients aged 5 to 11 years (paediatrics) were randomized to 24-weeks of treatment with either FF 50mcg or FF/VI 50/25 mcg and patients aged 12-17 years (adolescents) were randomized to 24-weeks of treatment with either FF 100 mcg or FF/VI 100/25 mcg (Figure 3). Based on interactions with the Agency, 25% of the study population were 12-17 years of age. All participants received SABA to be used as needed throughout the trial. The schedule of study assessments were as per Figure 4.

Figure 3. Study schematic



Source: Applicant's CSR HZA107116, p. 29.

Figure 4. HZA107116 Schedule of Assessments

Procedure	Screening	Pre-Randomi-sation	Randomi-sation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post last visit)
Visit	V1[a]	V2	V3	V4	V5	V6	V7	V8	V9			V10
Week	Week -4 to Day 0		0	4	8	12	16[b]	20[c]	24			25
Day (All visits except V2 to occur within -5 to +2 days of specified day)	-28	-5 (-2 to +2)	0	28	56	84	112	140	168			175
Type of Visit	Clinic only	Home or Clinic	Clinic only	Home or Clinic	Home[b], Video-call or Clinic	Clinic only	Video-call or clinic	Video-call, Phone-call or Clinic	Home or Clinic	Home or Clinic	Home or Clinic	Video-call, Phone-call
Informed consent and assent	X											
Pharmacogenetics consent and assent	X	X	X									
Inclusion and exclusion criteria	X											
Randomisation criteria			X									
Demography	X											
Medical history	X											
Asthma history	X											
Exacerbation history	X											
Full physical including height and weight	X											

Procedure	Screening	Pre-Randomi-sation	Randomi-sation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post last visit)
Visit	V1[a]	V2	V3	V4	V5	V6	V7	V8	V9			V10
Week	Week -4 to Day 0		0	4	8	12	16[b]	20[c]	24			25
Day (All visits except V2 to occur within -5 to +2 days of specified day)	-28	-5 (-2 to +2)	0	28	56	84	112	140	168			175
Type of Visit	Clinic only	Home or Clinic	Clinic only	Home or Clinic	Home[b], Video-call or Clinic	Clinic only	Video-call or clinic	Video-call, Phone-call or Clinic	Home or Clinic	Home or Clinic	Home or Clinic	Video-call, Phone-call
Efficacy Assessments												
Electronic patient diary [d]	X	X	X	X	X	X				X	X	
FEV1	X	X		X	X	X				X	X[e]	
FEV1 review of the overread only			X									
Serial FEV1						X						
Lung function (FEV1) reversibility testing[f]	X											
cACT/ACT	X		X									
ACQ			X			X			X			
Safety Assessments												
Oropharyngeal examination	X		X						X	X	X[g]	

Procedure	Screening	Pre-Randomi-sation	Randomi-sation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post last visit)
Visit	V1[a]	V2	V3	V4	V5	V6	V7	V8	V9			V10
Week	Week -4 to Day 0		0	4	8	12	16[b]	20[c]	24			25
Day (All visits except V2 to occur within -5 to +2 days of specified day)	-28	-5 (-2 to +2)	0	28	56	84	112	140	168			175
Type of Visit	Clinic only	Home or Clinic	Clinic only	Home or Clinic	Home[b], Video-call or Clinic	Clinic only	Video-call or clinic	Video-call, Phone-call or Clinic	Home or Clinic	Home or Clinic	Home or Clinic	Video-call, Phone-call
Concomitant medication review	X		X	X	X	X	X	X	X	X	X	X
12-lead ECG	X								X	X	X[h]	
Vital signs	X											
AE review			X	X	X	X	X	X	X	X	X	X
SAE review	X		X	X	X	X	X	X	X	X	X	X
Exacerbation review			X	X	X	X	X	X	X	X	X	X
Laboratory Assessments												
Blood draw for testing glucose[i]	X								X	X	X[i]	
Pregnancy test	X								X	X	X	
Pharmacogenetic sample (saliva)[k]				X	X	X	X	X	X			
Study intervention												

Procedure	Screening	Pre-Randomi-sation	Randomi-sation	Treatment Period (Days, Weeks)						ETD	EW	FU TC (7 days post last visit)
Visit	V1[a]	V2	V3	V4	V5	V6	V7	V8	V9			V10
Week	Week -4 to Day 0		0	4	8	12	16[b]	20[c]	24			25
Day (All visits except V2 to occur within -5 to +2 days of specified day)	-28	-5 (-2 to +2)	0	28	56	84	112	140	168			175
Type of Visit	Clinic only	Home or Clinic	Clinic only	Home or Clinic	Home[b], Video-call or Clinic	Clinic only	Video-call or clinic	Video-call, Phone-call or Clinic	Home or Clinic	Home or Clinic	Home or Clinic	Video-call, Phone-call
Dispense standardised FP run-in medication	X											
Return FP run-in medication			X									
Dispense SABA rescue inhaler	X											
Return SABA rescue inhaler									X		X	
Treatment assignment (randomisation) via IVRS			X									
Dispense double-blind study intervention via IVRS/IWRS			X	X	X	X	X[l]	X				
Return double-blind study intervention				X	X	X	X	X	X	X	X	

Abbreviations: AE=adverse event; ACT=Asthma control test; cACT=Childhood asthma control test; ACQ=Asthma Control Questionnaire; ECG=electrocardiogram; ETD=early treatment discontinuation; EW=early withdrawal; FEV1=forced expiratory volume in 1 second; FP=fluticasone propionate; FU=follow-up; IVRS=interactive Voice Response System/Interactive Web Response System; SABA= short-acting beta agonist; SAE=serious adverse event; TC=telephone call; V=Visit.

a. Prior to any study activities at Visit 1, including fasting for the blood glucose test, written informed consent was obtained from at least 1 parent/care giver (legal guardian) and accompanying informed assent from the participant (where the participant was able to provide assent).
b. Week 16 (Visit 7) could have been parent only visit.
c. Week 20 (Visit 8) could have been a telephone call if there were no problems with compliance.
d. Asthma symptom scores, peak expiratory flow (PEF), rescue albuterol/salbutamol usage were recorded on the electronic patient diary. To be completed every day in the morning and evening from Visit 1 through to Visit 6 only.
e. FEV1 was not required at the Early Withdrawal Visit or Early Treatment Discontinuation Visit if these visits have occurred after Visit 6.
f. Following administration of 2 to 4 inhalations of albuterol/salbutamol. Reversibility testing included a baseline spirometry and repeat spirometry within 15 to 40 minutes after inhalation of 400 µg of salbutamol. The reversibility test was considered positive if participants show improvement of FEV1 ≥12% after administration of salbutamol.
g. Oropharyngeal examination was not required at the Early Withdrawal Visit if examination had been performed at Early Treatment Discontinuation Visit.
h. A 12-lead ECG was not required at the Early Withdrawal Visit if it had been measured at the Early Treatment Discontinuation Visit.
i. A blood draw was not required at the Early Withdrawal Visit if it had been collected at the Early Treatment Discontinuation Visit.
j. A central laboratory was used.
k. Informed consent for optional substudies, e.g., genetics consent was to be obtained before collecting a sample. Sample to be obtained post-randomisation.
l. Two inhalers to be dispensed at Visit 7 as Visit 8 could have been a telephone call only visit if there were no problems with compliance.

Study Population

The study population consisted of approximately 900 asthma patients 5 to 17 year of age uncontrolled on inhaled corticosteroids.

Key Inclusion Criteria:

1) Between 5 to 17 years of age with a history of symptoms consistent with a diagnosis of asthma for at least 6 months

2) Pre-bronchodilator FEV1 >50% to ≤100% predicted normal

3) Lung function reversibility defined as an increase of ≥12% in FEV1 within 15 to 40 minutes following 2 to 4 inhalations of albuterol/salbutamol inhalation

4) Uncontrolled asthma, with a cACT/ACT score ≤19.

5) Receiving stable asthma therapy (SABA or SAMA inhaler plus ICS [total daily dose ≤FP 250 mcg or equivalent])for at least 4 weeks prior to Visit 1

Key Exclusion Criteria:

1) History of life threatening asthma

2) Any asthma exacerbation requiring oral steroids within 6 weeks of Visit 1

3) A culture documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that has not resolved within 4 weeks of Visit 1 and which led to a change in asthma management or, in the opinion of the investigator, is expected to affect the participant's asthma status or the participant's ability to participate in the study.

4) Clinical visual evidence of oropharyngeal candidiasis

5) Present use of any tobacco products

6) Severe obesity (BMI above the 99th centile based on the CDC charts).

7) Any significant abnormality or medical condition identified at the screening medical assessment (including serious psychological disorder) that in the investigator's opinion, preclude entry into the study due to risk to the participant or that may interfere with the conduct and/or outcome of the study.

Study Endpoints

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

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

Statistical Analysis Plan

Analysis Sets

- Intent-to-Treat (ITT) Population (5-17 Years Old) included all randomized participants who received at least one dose of study treatment. Randomized participants were assumed to have received study treatment unless definitive evidence to the contrary exists. Outcomes were to be reported according to the randomized treatment allocation. This population was used for efficacy analyses.

Estimands

The primary objective was to compare the efficacy of once daily FF/VI (FF/VI 50/25mcg for 5-11 years old; FF/VI 100/25mcg for 12-17 years old) with once daily FF (FF 50mcg for 5-11 years; FF 100mcg for 12-17 years) in the ITT (5-17 years old) Population.

The primary estimand for the primary endpoint (weighted mean FEV1 (0-4 hours) (L) at Week 12) is described below:

- Treatment: FF/VI 50/25mcg, FF/VI 100/25mcg, FF 50mcg, FF 100mcg
- Population: All randomized asthmatic participants (5 to 17 years old) who received at least one dose of study treatment
- Variable: Weighted mean FEV1 (0-4 hours) (L) at Week 12
- Intercurrent Events: Discontinuation of randomized treatment, Increased use of rescue medication. Treatment policy stratgegy was used for these intercurrent events.
- Population-level Summary: The mean difference between treatment groups

A supplementary estimand for the primary endpoint was proposed, whereby a hypothetical strategy was applied for the intercurrent event of treatment discontinuation (i.e., if all participants had stayed on their randomized treatment) and a treatment policy strategy was applied for the intercurrent event of rescue medication use.

The primary estimand for the key secondary endpoints was defined in a similar manner as the primary endpoint.

The Applicant termed their primary estimand “effectiveness-type estimand”. The supplementary estimand was termed “efficacy-type estimand”.

Sample Size Calculation

Approximately 870 participants aged 5-17 years old were to be randomised in a ratio of 1:1 for this study, among which 652 participants were 11 years old or less and 218 participants were 12-17 years old at screening.

The sample size calculation was based on the primary efficacy endpoint of weighted mean FEV1 (0-4 hours). The sample size allowed for up to 20% of participants to not contribute to the primary endpoint giving a total of 348 evaluable participants per arm. The standard deviation was assumed to be 280 mL for 5-11 year olds and 500 mL for 12-17 year olds based on previous studies. Using the assumed representation across the age ranges, a standard deviation of 348 mL was assumed for the 5-17 years old population based on a weighted average of the variances (i.e. assuming equal means). The sample size of 870 would have 93% power to detect a treatment difference of 90 mL at the two-sided 5% significance level.

Details of the sample size calculation were not provided in the Reporting and Analysis Plan (RAP). The calculation above is provided in the Clinical Study Protocol. Refer to Clinical Study Protocol Amendment 04 for details.

Primary Effiacay Analysis

- *Endpoint Derivation*

The individual serial FEV1 assessments at Week 12 (Visit 6) were performed pre-dose and post-dose after 30 minutes and 1, 2, 3 and 4 hours of blinded study drug administration. The weighted mean FEV1 was calculated over the nominal 0-4 hours post-dose period. Values from postdose assessments which were before the time of dosing or 4.5 hours after the time of dosing based on actual times were excluded from the calculation. Both the pre-dose and final value (4-hour) as well as one of the intermediate (30 minutes, 1, 2 and 3 hour) values had to be present for the weighted mean to be calculated. Otherwise the endpoint was treated as missing. If one or more observations were missing between 2 non-missing observations (but within the constraints noted above), the value(s) was linearly interpolated between the 2 non-missing values. The weighted means were derived by calculating the area under the FEV1 time curve (AUC) over the nominal timepoints using the trapezoidal rule, and then dividing by the actual time between dosing and the final assessment. For post-dose observations, the actual time of assessment relative to the time of dosing was used for the calculation. AUC was calculated as follows:

$$AUC_{(t0\text{-}tL\ hrs)} = \frac{1}{2}\sum_{i=0}^{L-1}(C_i + C_{i+1})(t_{i+1} + t_i)$$

where,

i = collected measurement,
L = last collected measurement,
Ci = result of collected measurement i,
t_i = actual time of assessment for collected measurement i.

Weighted mean (WM) was then calculated as follows:

$$WM_{(t0\text{-}tL\ hrs)} = AUC_{(t0\text{-}tL\ hrs)} / (t_L - t_0)$$

- *Statistical Analysis Model*

Statistical analysis was performed using analysis of covariance (ANCOVA) model with effects due to baseline, region, sex, age and treatment group. The analysis included all available data, regardless of whether the participant remained on-treatment or increased use of rescue medication. Missing data were assumed to be missing at random (MAR).

Sensitivity analyses using multiple imputation (MI) methods (Jump to Reference Method, Tipping Point Analysis) were conducted to investigate the impact of missing data and to examine the robustness of the analysis results of the primary endpoint to departures from the assumption that missing data were MAR. The sensitivity analyses were performed for the primary estimand including all data regardless of treatment state.

To evaluate the supplementary estimand, the ANCOVA model for the primary efficacy endpoint was rerun using the data collected up to the time of treatment discontinuation. Data collected

after treatment discontinuation were set as missing. Missing data were assumed to be MAR.

Secondary Efficacy Analyses

Statiscal analysis methods for the key secondary efficacy endpoints are described below:

- Change from baseline in the percentage of rescue-free 24-hour periods over Weeks 1-12
- Change from baseline in the percentage of symptom-free 24-hour periods over Weeks 1-12
- Change from baseline in AM PEF (L/min) over Weeks 1-12

    - Statistical analyses were performed with ANCOVA models with effects due to baseline, region, sex, age and treatment group. The statistical analyses included all available data, regardless of whether the participant remained on-treatment.

- Change from baseline in morning FEV1 (L) at Week 12
- Change from baseline in ACQ-5 at Week 24

    - Statistical analyses were performed with MMRM model which allowed for effects due to baseline (FEV1 or ACQ-5 score), region, sex, age, visit and treatment group. The models also contained a visit-by-treatment interaction term and a visit-by-baseline interaction term. The statistical analyses included all available data, regardless of whether the participant remained on-treatment.

Multiplicity Adjustment

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

The treatment comparisons defined as part of the multiple testing strategy were limited to the specified key comparisons shown in Figure 5.

Figure 5: Statistical Testing Strategy for ITT (5-17 Years Old) Population

Testing of each endpoint is dependent on significance at the 0.05 level having been achieved on the previous endpoint in the hierarchy.	
Primary Efficacy Endpoint	
1) Weighted mean FEV_1 (0-4 hours):	FF/VI vs. FF
Secondary Efficacy Endpoints	
2) Rescue-free 24 hour periods:	FF/VI vs. FF
3) Symptom-free 24 hour periods:	FF/VI vs. FF
4) AM FEV_1:	FF/VI vs. FF
5) AM PEF:	FF/VI vs. FF
6) ACQ:	FF/VI vs. FF

Source: Reporting and Analysis Plan (RAP) Figure 1, p.16

Protocol Amendments

There were a total of 4 protocol amendments. The protocol amendments were reviewed and do not affect the interpretation of the results.

8.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with GCP as required by the ICH guidelines and in accordance with country-specific laws and regulations governing clinical studies of investigational products and data protection. Three study sites were closed during conduct of the trial as a result of suspected noncompliance with GCP. The 3 sites were in the United States, Poland and Mexico. Combined, they screened 80 participants and randomized 30 participants, or 3.3% of the 908 total participants randomized. A sensitivity analysis sensitivity analysis for the primary endpoint was performed by the Applicant, excluding the data for all participants from these three sites, demonstrated no change in the primary efficacy results (Table 28).

Financial Disclosure

For financial disclosure information, refer to Section 15.2.

Patient Disposition

Patients disposition is summarized in Table 12. Nine-hundred six (906) patients were stratified by the participant's age at the screening visit and randomized in a 1:1 ratio to FF/VI and FF in the study. Four patients did not receive any study drug. Among the 902 randomized and who received at least one dose (454 patients in the FF/VI group and 448 patients in the FF group), the overall early treatment discontinuation rate was 4% and the discontinuation rate was comparable between the two groups (17 in the FF/VI group and 15 in the FF group). The primary reason for discontinuation was withdrawal by subject in 16 patients, with 7 (2%) in the FF/VI group and 9 (2%) in the FF group. Two (2) patients (< 1%) and 1 patient (< 1%) discontinued the randomized treatment due to adverse event in the FF/VI and FF groups, respectively. Among 32 patients who discontinued the treatment, 5 completed the study (2 in FF/VI and 3 in FF; based on the reviewer's analysis using adsl.xpt dataset). Overall study withdrawal rate was 4%. A major reason for study discontinuation was "withdrew consent", which provides limited information about the study withdrawal. Among 38 patients who withdrew the study prematurely, 11 patients completed the randomized treatment and 27 discontinued the randomized treatment (based on the reviewer's analysis using adsl.xpt dataset).

Table 12: Patient Disposition (All Randomized Patients)

	Number of Patients, n (%)		
Randomized	**FF/VI (N = 455)**	**FF (N = 451)**	**Total (N = 906)**
Randomized and received at least one dose	**454 (100)**	**448 (100)**	**902 (100)**
Study intervention stopped permanently[1]	17 (4)	15 (3)	32 (4)
Adverse event	2 (<1)	1 (<1)	3 (<1)
Lost to follow-up	1 (<1)	0 (<1)	1 (<1)
Other	3 (1)	1 (<1)	4 (<1)
Physician decision	1 (<1)	2 (<1)	3 (<1)
Protocol deviation	1 (<1)	1 (<1)	2 (<1)
Sponsor terminated study treatment	2 (<1)	1 (<1)	3 (<1)
Withdrawal by subject	7 (2)	9 (2)	16 (<1)
Prematurely withdrawn from the study[2]	21 (5)	17 (4)	38 (4)
Withdrew consent	16 (4)	14 (3)	30 (3)
Study closed/terminated	4 (<1)	3 (<1)	7 (<1)
Lost to follow-up	1 (<1)	0	1 (<1)

Source: Statistical Reviewer
[1] A participant was considered discontinued from study intervention if the participant had been randomised, but intentionally and permanently had stopped taking study intervention during the treatment period.
[2] A participant was considered withdrawn from the study if the participant left the study prior to completing all required visits and the follow-up phone contact.

Number of patients per age cohort is summarized in Table 13.

Table 13: Summary of Patient's Populations (All Randomized Patients)

Population	Number of Patients, n (%)		
Randomized	FF/VI (N = 455)	FF (N = 451)	Total (N = 906)
Intent-to-Treat (5 to 17 Years Old)	454 (>99%)	448 (>99%)	902 (>99%)
5 to 11 Years Old	337 (74%)	336 (75%)	673 (74%)
12 to 17 Years Old	117 (26%)	112 (25%)	229 (26%)

Source: Statistical Reviewer

Protocol Violations/Deviations

In total, 11% of patients had important protocol deviations. The majority of these were eligibility criteria not met or informed consent. None of these deviations were considered to impact the interpretation of study results.

Table of Demographic Characteristics

Patients' demographic and baseline characteristics in the ITT population are relatively balanced between treatment arms and are summarized in Table 14.

Table 14. Demographic and Baseline Characteristics, HZA107116 (ITT Population 5 – 17 Year Old)

	FF/VI (n=454)	FF (n=448)	Total (n=902)
Age			
Mean	9.9	10.0	10.0
Min	5	5	5
Max	17	17	17
≥5 years to ≤11 years	337 (74%)	336 (75%)	673 (75%)
≥12 years to ≤17 years	117 (26%)	112 (25%)	229 (25%)
Sex			
Female	165 (36%)	191 (43%)	356 (39%)
Male	289 (64%)	257 (57%)	546 (61%)
Race			
African American/African Heritage	34 (7%)	40 (9%)	74 (8%)
American Indian or Alaska Native	22 (5%)	29 (6%)	51 (6%)
Asian	32 (7%)	26 (6%)	58 (6%)
Native Hawaiian or other Pacific Islander	0	0	0
White	335 (74%)	320 (71%)	655 (73%)
Multiple	31 (7%)	33 (7%)	64 (7%)
Duration of Asthma			
Mean (years)	5.84	5.52	5.68

<6 months	0	0	0
≥6 months to <1 year	22 (5%)	29 (6%)	51 (6%)
≥1 year to <5 years	178 (39%)	187 (42%)	365 (40%)
≥5 years to <10 years	179 (39%)	170 (38%)	349 (39%)
≥10 years	75 (17%)	62 (14%)	137 (15%)
Screening Lung Function			
Mean pre-bronchodilator FEV1 (L)	1.599	1.607	1.603
Pre-bronchodilator FEV1 percent predicted (%)	73.46	73.82	73.64
Mean percent reversibility FEV1 (%)	27.81	27.73	27.77

Source: CSR, Tables 1.14, 1.15, 1.17, 1.20

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The two treatment groups were similar with respect to age, race, ethnicity, medical conditions, asthma history, and lung function. The majority of patients were between 8 and 11 years old (52%), male (61%), and not Hispanic or Latino (72%). The majority of patients (76%) had no asthma exacerbation in the last 12 months. The most often reported medical conditions apart from asthma in both groups were nasal disorder (56% in the FF/VI group, 54% in the FF group), followed by eczema (16% in the FF/VI group, 14% in the FF group). There was no difference between treatment groups in lung function parameters at screening and at baseline. The medications taken by more than 10% of patients were fluticasone propionate (96% in the FF/VI group, 95% in the FF group), followed by salbutamol (91% in the FF/VI group, 88% in the FF group), followed by budesonide (25% in the FF/VI group, 26% in the FF group).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Mean overall treatment compliance was 96.6% in both treatment groups. The baseline in percentage of rescue-free 24-hour periods was similar between treatment groups. The mean change from baseline in the percentage of rescue-free 24-hour periods over Weeks 1 to 12 was 25.9% for the FF/VI group and 25.8% for the FF group.

Efficacy Results – Primary Endpoint

Table 15 summarizes the primary endpoint result. The primary endpoint of weighted mean FEV1 was derived by calculating the area under the FEV1 time curve (AUC) over the nominal timepoints (0-4 hours post-dose period) at Week 12 using the trapezoidal rule, and then dividing by the actual time between dosing and the final assessment. The primary analysis was conducted in the ITT population 5-17 years old.

FF/VI met statistical significance for the primary endpoint at α=0.05 significance level, demonstrating an improvement over FF in weighted mean FEV1 at Week 12 with the difference in LS means of 0.08 [95% CI: 0.04, 0.13; p-value = <0.01].

Table 15: Primary Analysis of Weighted Mean FEV1 (0-4 hours) (L) at Week 12 (ITT Population 5-17 Years Old)

Treatment Group	n	LS Means	FF/VI vs FF Difference in LS Means (95% CI)	P-value
FF/VI (N = 454)	394	2.08	0.08 [0.04, 0.13]	<0.01
FF (N = 448)	397	2.00		

Source: Statistical Reviewer
CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; FF/VI, fluticasone furoate/vilanterol; ITT: intent-to-treat; LS, least squares; N, total number of subjects; n, number of subjects in the analysis.
The dose of FF/VI was 100/25 mcg once daily for patients aged 12 to 17 years and 50/25 mcg once daily for patients aged 5 to 11 years. The dose of FF was 100 mcg once daily for patients aged 12 to 17 years and 50 mcg once daily for patients aged 5 to 11 years.
Statistical analysis was performed with analysis of covariance (ANCOVA) model with effects due to baseline, region, sex, age and treatment group. The analysis included all available data, regardless of whether the participant remained on-treatment at the time of the assessment. Missing data were assumed to be missing at random (MAR). Baseline FEV1 was measured at Visit 2, Day -5 (Pre-Dose).

The primary analysis included only patients with evaluable data at Week 12 for the primary endpoint (weighted mean FEV1 0-4 HOURS) presented in the table above. The statistical reviewer considers this analysis approach which essentially assumes missing-completely-at-random for missing data not aligned with the Applicant's missing data handling plan with missing-at-random (MAR) assumption and the ITT (5-17 years old) population. The Applicant claimed that the missing data were due to the inherent difficulty in obtaining serial spirometry from this population, particularly the younger children, and due to the patient burden it represented. Refer to Statistical Issues section for the detailed information regarding the missing data and robustness of the primary efficacy analysis results.

A supplementary analysis was conducted to explore an alternative estimand applying a hypothetical strategy for the intercurrent events of discontinuation of randomized treatment and increased use of rescue medication. Using only on-treatment data, the difference in LS means was 0.08 [95% CI: 0.04, 0.13; p-value = <0.01], indicating that the improvement of the FF/VI over FF in the primary endpoint was statistically significant (Table 16).

Table 16: Supplementary Analysis of Weighted Mean FEV1 (0-4 hours) (L) at Week 12 (ITT Population 5-17 Years Old; On-Treatment Data)

Treatment Group	n	LS Means	FF/VI vs FF Difference in LS Means (95% CI)	P-value
FF/VI (N = 454)	393	2.08	0.08 [0.04, 0.13]	<0.01
FF (N = 448)	396	2.00		

Source: Statistical Reviewer
CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; FF/VI, fluticasone furoate/vilanterol; ITT: intent-to-treat; LS, least squares; N, total number of subjects; n, number of subjects in the analysis.
The dose of FF/VI was 100/25 mcg once daily for patients aged 12 to 17 years and 50/25 mcg once daily for patients aged 5 to 11 years. The dose of FF was 100 mcg once daily for patients aged 12 to 17 years and 50 mcg once daily for patients aged 5 to 11 years.

Statistical analysis was performed with analysis of covariance (ANCOVA) model with effects due to baseline, region, sex, age and treatment group. The analysis included only on-treatment data. Missing data were assumed to be missing at random (MAR). Baseline FEV1 was measured at Visit 2, Day -5 (Pre-Dose).

The number of patients in the supplementary analysis (n=393 for FF/VI, n =396 for FF) was similar to the primary analysis (n=394 for FF/VI, n =397 for FF), indicating that not many patients provided data for the primary endpoint after treatment discontinuation and thus deriving almost identical treatment effect estimates between two analyses.

Data Quality and Integrity

Data quality and integrity were assessed by OCS Clinical Services at the beginning of the review process. There were no significant issues with data integrity that prohibited review or required further action.

Efficacy Results – Secondary and other relevant endpoints

All key secondary endpoints shown in Table 17 were analyzed in the ITT population (5-17 years old) under hierarchical type I error control for multiple comparisons. The comparison of FF/VI vs FF for % of Rescue-Free 24-Hour Periods over Weeks 1-12 failed to achieve statistical significance (95% CI: -4.48, 3.79; p=0.87), and no further tests were proceeded. Therefore, results for this endpoint and results for all subsequent endpoints are considered exploratory. There was no meaningful difference in LS mean change between FF/VI vs FF in % of Symptom-Free 24-Hour Periods over Weeks 1-12 (95% CI: -4.20, 4.13; p=0.99), AM FEV1 (L) at Week 12 (95% CI: -0.01, 0.08; p=0.12) or ACQ-5 Score at Week 24 (95% CI: -0.10, 0.09; p=0.91). Although not statistically significant, there was a nominally significant difference of 6.17 in LS mean change from baseline for AM PEF (L/min) over Weeks 1-12 (95% CI: 1.42, 10.94; p=0.01), demonstrating favorable result for FF/VI over FF.

Table 17: Key Secondary Efficacy Endpoints (ITT Population 5-17 Years Old)

			Difference in LS Mean Changes from Baseline (FF/VI vs FF)		
Secondary Endpoint	**Treatment Group**	**n**	**Estimate**	**95% CI**	**P-value**
% of Rescue-Free 24-Hour Periods over Weeks 1-12[1]	FF/VI (N = 454) FF (N = 458)	453 447	-0.35	-4.48, 3.79	0.87
% of Symptom-Free 24-Hour Periods over Weeks 1-12[1]	FF/VI (N = 454) FF (N = 458)	453 447	-0.03	-4.20, 4.13	0.99
AM FEV1 (L) at Week 12[2]	FF/VI (N = 454) FF (N = 458)	417 413	0.04	-0.01, 0.08	0.12
AM PEF (L/min) over Weeks 1-12[1]	FF/VI (N = 454) FF(N = 458)	453 447	6.17	1.42, 10.94	0.01
ACQ-5 Score at Week 24[2]	FF/VI (N = 454)	385	-0.01	-0.10, 0.09	0.91

FF (N = 458) 378

Source: Statistical Reviewer
ACQ, asthma control questionnaire; CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; FF/VI, fluticasone furoate/vilanterol; ITT: intent-to-treat; LS, least squares; N, total number of subjects; n, number of subjects in the analysis; PEF, peak expiratory flow.
The dose of FF/VI was 100/25 mcg once daily for patients aged 12 to 17 years and 50/25 mcg once daily for patients aged 5 to 11 years. The dose of FF was 100 mcg once daily for patients aged 12 to 17 years and 50 mcg once daily for patients aged 5 to 11 years.
A step-down closed testing procedure was applied to the inequality comparison of FF/VI versus FF whereby this comparison was required to be significant at the 0.05 level for the primary endpoint in order to infer on the secondary endpoints, and inference for a test in the pre-defined hierarchy of secondary endpoints was dependent upon statistical significance had been achieved for the previous comparison in the hierarchy of secondary endpoints. If a given statistical test failed to reject the null hypothesis of no treatment difference at the significance level of 0.05, then all tests lower down in the hierarchy were interpreted as descriptive only.
[1] Statistical analyses were performed with ANCOVA models with effects due to baseline, region, sex, age and treatment group. The statistical analyses included all available data, regardless of whether the participant remained on-treatment.
[2] Statistical analyses were performed with MMRM models which allowed for effects due to baseline (FEV1 or ACQ-5 score), region, sex, age, visit and treatment group. The models also contained a visit-by-treatment interaction term and a visit-by-baseline interaction term. For FEV1, the pre-dose measurements from scheduled Visits 4, 5 and 6 (Weeks 4, 8 and 12) were included in the models. For ACQ-5, the scores from scheduled Visits 6 and 9 (Weeks 12 and 24) were included in the models. The statistical analyses included all available data, regardless of whether the participant remained on-treatment.

Asthma exacerbations were reported for 33 participants (7%) in the FF/VI treatment arm and 38 participants (8%) in the FF treatment arm; all required treatment with oral or systemic corticosteroids and 2 participants (<1%) in each treatment arm required hospitalization. Most participants who experiences an asthma exacerbation experienced only one exacerbation during the treatment period, with 2 participants (<1%) in the FF/VI arm and 6 participants (1%) in the FF arm experiencing 2 exacercations during the treatment period. No participants experienced more than 2 exacerbations.

Dose/Dose Response

Dose/Dose response is not applicable to this submission.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

For a PRO endpoint of change from baseline in ACQ-5 at Week 24, refer to Table 17.

Additional Analyses Conducted on the Individual Trial

As discussed above, results from HZA 107116 demonstrated a statistically significant improvement in the weighted FEV1 (0-4 hours) at Week 12 for patients randomized to FF/VI compared to those randomized to FF in the overall population. Since different dose was administered for different age group (FF/VI 50/25 mcg and FF 50 mcg for 5-11 years old; FF/VI 100/25 mcg and FF 100 mcg for 12-17 years old), the statistical reviewer performed the analysis of the primary endpoint for each age group. The results in Table 18 show that the difference in LS mean change from baseline at Week 12 for FF/VI 50/25 mcg compared with FF 50 mcg was 73 mL (95% CI: 28,118) in patients 5 to 11 years of age, and the difference in LS mean change from baseline at Week 12 for FF/VI 100/25 mcg compared with FF 100 mcg was 106 mL (95% CI: -8, 220) in patients 12 to 17 years of age.

Table 18: Primary Efficacy Analysis by Age (5-11 years old and 12-17 years old) - Weighted Mean FEV1 (0-4 hours) (L) at Week 12 On- and Post-Treatment Data (ITT Population 5-17 Years Old)

Age Subgroups	Treatment Group	n	LS Means	FF/VI vs FF Difference in LS Means (95% CI)
5-11 years old	FF/VI 50/25 mcg (N = 289)	286	1.773	0.073 [0.028, 0.118]
	FF 50 mcg (N = 291)	289	1.700	
12-17 years old	FF/VI 100/25 mcg (N = 108)	108	2.902	0.106 [-0.008, 0.220]
	FF 100 mcg(N = 108)	108	2.796	

Source: Statistical Reviewer
CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; FF/VI, fluticasone furoate/vilanterol; ITT: intent-to-treat; LS, least squares; N, total number of subjects; n, number of subjects in the analysis.
Statistical analysis was performed with analysis of covariance (ANCOVA) model with effects due to baseline, region, sex and treatment group. The analysis included all available data, regardless of whether the participant remained on-treatment at the time of the assessment. Missing data were assumed to be missing at random (MAR).

Primary efficacy results from the pre-defined subgroups including age (≤7, 8-11, 12-17), gender, race, ethnicity and geographical region are consistent with the results for the overall population (presented in OB Appendix 15.4).

8.1.3. Integrated Assessment of Effectiveness

The Applicant submitted results from one pivotal clinical trial, HZA 107116. Results from this trial demonstrated a statistically significant improvement in the weighted FEV1 (0-4 hours) at Week 12 for patients randomized to FF/VI compared to those randomized to FF only in the overall population. Subgroup analyses of the primary endpoint in the 5 to 11 and 12 to 17 year old population was consistent with primary analysis. There were no statistically significant differences observed between treatment groups for secondary endpoints, including rescue-free 24-hour periods at 12 weeks, symptom-free 24-hour periods at 12 weeks, change from baseline morning FEV1 at 12 weeks, change from baseline in morning pre-dose PEF at 12 weeks, and change from baseline of ACQ-5 at 24 weeks.

Confirmatory evidence for efficacy of FF/VI in the maintenance treatment of asthma in pediatric patients 5-17 years of age is provided by the previously demonstrated efficacy of FF/VI in the adult population (≥18 years of age), as well as the clinical experience and scientific knowledge of the effectiveness of other drugs in the same pharmacologic class (i.e., ICS/LABA), including in children ≥5 years of age. Additional supportive evidence for approval of FF/VI in the pediatric population 5 to 17 years of age is provided by 9 supporting pediatric studies.

In conclusion, the Applicant has demonstrated substantial evidence of effectiveness for the maintenance treatment of asthma in patients 5 to 17 years of age based on a statistically significant improvement in the weighted mean FEV1 (0 to 4 hours) at Week 12 for patients receiving FF/VI compared to those receiving FF only, combined with confirmatory evidence.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review was performed by the clinical reviewer using JMP Clinical to independently analyze and confirm the safety data in the safety analysis set, defined as all patients receiving any amount of IP and classified by treatment received. Of note, FF (Arnuity Ellipta) is approved for the maintenance treatment of asthma in patients ≥5 years of age, with dosing of 50 mcg one inhalation once daily for patients 5-11 years of age and 100 mcg one inhalation once daily for patients 12-17 years of age, and has an established safety profile. Safety of vilanterol in the pediatric population 5 to 17 years of age has not been previously established. In addition, the dose of vilanterol for the 5-11 and 12-17 years of age subgroups is identical, 25 mcg. Therefore, comparing FF/VI to FF was sufficient to characterize the safety profile of FF/VI given the known safety profile of FF.

8.2.2. Review of the Safety Database

Overall Exposure

Out of 906 randomized patients in HZA107116, 902 were included in the ITT (5 to 17 years old) population based on receiving at least one dose of study treatment. Of note, this safety database consists of pooled data from children 5 to 11 years of age who received FF/VI 50/25 and children 12 to 17 years of age who received FF/VI 100/25. Separate subgroup analyses for safety were performed by age; these analyses were consistent with the pooled population. As such, for this safety review, pooled analyses are presented, unless otherwise specified.

Of the patients in the ITT population (5-17 years of age), 454 patients were in the FF/VI group and 448 patients were in the FF group. Table 19 summarizes exposure to study treatment for each arm. Mean exposure for FF/VI treatment was 164.6 days and for FF was 164.4 days. For both arms, 96% of patients received treatment for ≥141 days, with 43% in the FF/VI arm receiving ≥169 days of treatment.

Table 19. Summary of Exposure to Study Treatment and Study Duration ITT (5-17 years of age)

		FF/VI (N=454)	FF (N=448)
Exposure (days) [a]	n	454	448
	Mean	164.6	164.4
	SD	21.11	20.86
	Median	168.0	168.0
	Min.	14	1
	Max.	213	204
Range of Exposure	≤28 days	2 (<1%)	2 (<1%)
	29-56 days	5 (1%)	5 (1%)
	57-84 days	5 (1%)	2 (<1%)
	85-112 days	3 (<1%)	4 (<1%)
	113-140 days	4 (<1%)	5 (1%)
	141-168 days	241 (53%)	245 (55%)
	≥169 days	194 (43%)	185 (41%)
Post-treatment Study Time (days) [b]	n	433	431
	Mean	8.6	9.0
	SD	7.07	9.30
	Median	8.0	8.0
	Min.	3	0
	Max.	128	118
Total Study Time (days) [c]	n	433	431
	Mean	176.8	176.5
	SD	5.72	6.16
	Median	176.0	176.0
	Min.	159	159
	Max.	221	254

Source: m5.3.5.1, HZA107116 CSR, Section 5.4.5.1, Table 20
Abbreviations: FF= Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; ITT = intent-to-treat; N = Number of participants
Note: The FF/VI group includes participants who received 50/25 mcg or FF/VI 100/25 mcg. Similarly, the FF group includes participants who received FF 50 mcg or FF 100 mcg.
a. Calculated as ([treatment stop date - treatment start date] + 1).
b. Calculated as (study conclusion date - treatment stop date).
c. Calculated as ([study conclusion date - treatment start date] +1).
Source: Applicant's Summary of Clinical Safety, Module 2.7.4, Table 4. Verified by reviewer with JMP Clinical.

Of the patients in the ITT population (5-11 years of age) subgroup who received FF/VI 50/25, 337 patients were in the FF/VI group and 336 patients were in the FF group. Table 20 summarizes exposure to study treatment for each arm. Mean exposure for FF/VI treatment was 165.3 days and for FF was 164.0 days. For both arms, ≥95% of patients received treatment for ≥141 days, with 42% in the FF/VI arm receiving ≥169 days of treatment.

Table 20. Summary of Exposure to Study Treatment and Study Duration ITT (5-11 years of age)

		FF/VI (N=337)	FF (N=336)
Exposure (days) [1]	n	337	336
	Mean	165.3	164.0
	SD	20.22	22.98
	Median	168.0	168.0
	Min.	14	1
	Max.	213	204
Range of Exposure	=<28 days	2 (<1%)	2 (<1%)
	29-56 days	3 (<1%)	5 (1%)
	57-84 days	2 (<1%)	1 (<1%)
	85-112 days	2 (<1%)	4 (1%)
	113-140 days	3 (<1%)	3 (<1%)
	141-168 days	183 (54%)	175 (52%)
	>=169 days	142 (42%)	146 (43%)
Post-treatment Study Time (days) [2]	n	325	323
	Mean	8.7	9.2
	SD	7.69	10.38
	Median	8.0	8.0
	Min.	3	1
	Max.	128	118
Total Study Time (days) [3]	n	325	323
	Mean	177.0	176.7
	SD	6.09	6.47
	Median	176.0	176.0
	Min.	159	159
	Max.	221	254

Source: Table 1.50
Abbreviations: FF Fluticasone furoate; FF/VI = Fluticasone furoate/Vilanterol; N = Number of participants
[1] Calculated as ([treatment stop date - treatment start date] + 1).
[2] Calculated as (study conclusion date - treatment stop date).
[3] Calculated as ([study conclusion date - treatment start date] +1).

Source: Applicant's HZA107116 CSR, Table 33. Verified by reviewer with JMP Clinical.

Adequacy of the safety database:

The extent and duration of exposure to both doses of FF/VI is adequate to assess safety for chronic use.

Issues Regarding Data Integrity and Submission Quality

A Core Data Fitness assessment was conducted through the FDA Office of Computational Science and identified no significant issues with submission quality or data integrity.

Categorization of Adverse Events

The Applicant used definitions of adverse events (AEs) and serious adverse events (SAEs) consistent with the requirements outlined in 21 Code of Federal Regulations 312.32. AEs were collected from the start of study intervention until the follow-up contact.

Routine Clinical Tests

Routine clinical tests were assessed per the schedule outlined in

Figure 4.

8.2.3. Safety Results

Deaths

No deaths occurred during the study.

Serious Adverse Events

In both groups, at least 1 SAE was reported for 5 (1%) patients in each group, with asthma being most common. Overall, SAEs were balanced across arms, and no new safety signals were identified from these data. No drug-related SAE was reported in either treatment group. Details of SAEs are presented in Table 21.

Table 21. On-Treatment Serious Adverse Events (ITT 5-17 years of age)

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

Source: Adapted from Applicant's CSR Table 3.9. Verified by reviewer with JMP Clinical.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 22 presents data on adverse events leading to study drug discontinuation or study withdrawal. For the overall population, 3 patients (<1%) in the FF/VI arm and 1 patient (<1%) in

the FF arm, at least 1 AE led to permanent discontinuation from study intervention or to premature withdrawal from the study. Of note, dysphonia is a known adverse event with ICS use.

Table 22. Adverse Events Leading to Permanent Discontinuation of Study Drug or Withdrawal from Study (ITT 5-17 years of age)

System Organ Class **Preferred Term**	**FF/VI** **(N=454)**	**FF** **(N=448)**
Gastrointestinal disorders		
Intestinal obstruction	1 (<1%)	0
Nervous system		
Lethargy	1 (<1%)	0
Psychiatric disorders		
Insomnia	1 (<1%)	0
Respiratory, thoracic and mediastinal disorders		
Dysphonia	0	1 (<1%)

Source: Adapted from Applicant's CSR Table 3.8. Verified by reviewer with JMP Clinical.

Treatment Emergent Adverse Events and Adverse Reactions

Table 23 summarizes treatment-emergent adverse events occurring with an incidence >1%. In the 5-17 years of age ITT population, 181 (40%) patients in the FF/VI arm and 163 (36%) patients in the FF arm experienced at least 1 TEAE. In the FF/VI group, the most commonly reported AEs were nasopharyngitis in 49 patients (11%), upper respiratory tract infection in 32 patients (7%), allergic rhinitis in 19 patients (4%), headache in 14 patients (3%), rhinitis in 15 patients (3%), and viral upper respiratory tract infection in 13 patients (3%). In the FF group, the most commonly reported AEs were nasopharyngitis in 34 patients (8%), upper respiratory tract infection in 26 patients (6%), allergic rhinitis in 6 patients (1%), headache in 9 patients (2%), rhinitis in 6 patients (1%), and viral upper respiratory tract infection in 2 patients (<1%). Of note, in the CSR, the Sponsor reports the incidence of nasopharyngitis in the FF/VI group to be 10%, which is slightly different from this reviewer's analysis. Given that the incidence is similar, this minor discrepancy does not impact the overall safety conclusions.

Table 23. On-Treatment Adverse Events with Incidence >1% (ITT 5-17 years of age)

System Organ Class **Preferred Term**	**FF/VI** **(N=454)**	**FF** **(N=448)**
Infections and infestations		
Nasopharyngitis	49 (11%)	34 (8%)
Upper respiratory tract infection	32 (7%)	26 (6%)
Rhinitis	15 (3%)	6 (1%)
Pharyngitis	9 (2%)	6 (1%)
Viral upper respiratory tract infection	13 (3%)	2 (<1%)
Bronchitis	6 (1%)	8 (2%)
COVID-19	8 (2%)	5 (1%)

Influenza	4 (<1%)	5 (1%)
Respiratory, thoracic and mediastinal disorders		
Rhinitis allergic	19 (4%)	6 (1%)
Rhinorrhea	3 (<1%)	8 (2%)
Asthma	4 (<1%)	5 (1%)
Nervous system disorders		
Headache	14 (3%)	9 (2%)

Source: Adapted from Applicant's CSR Table 3.2. Verified by reviewer with JMP Clinical.

Laboratory Findings

No clinically meaningful effects on chemistry parameters were noted, including fasting glucose.

Vital Signs

No clinically meaningful effects on vital signs were noted.

Electrocardiograms (ECGs)

ECG recordings were taken at Screening and at Visit 9 (Week 24). Changes in ECG parameters from baseline were similar between both treatment groups as demonstrated in Table 24.

Table 24. Summary of Change from Baseline in ECG Values (ITT 5-17 years of age)

	FF/VI (N = 454)	**FF (N=448)**
QTc (F) (ms)		
Mean, Visit 9 (Week 24)	-2.4	0.7
Mean, Maximum post-baseline	-2.2	1.1
QTc (B) (ms)		
Mean, Visit 9 (Week 24)	-4.4	-0.9
Mean, Maximum post-baseline	-4.1	-0.3
RR interval (ms)		
Mean, Visit 9 (Week 24)	23.7	18.7
Mean, Maximum post-baseline	24.9	19.1
PR interval (ms)		
Mean, Visit 9 (Week 24)	1.1	1.7
Mean, Maximum post-baseline	1.3	1.8
QRS duration (ms)		
Mean, Visit 9 (Week 24)	1.6	1.0
Mean, Maximum post-baseline	1.7	0.9

Source: Adapted from Applicant's CSR Table 3.23. Verified by reviewer with JMP Clinical.

QT

1 patient in each group had prolonged QT intervals. Prolonged QT intervals were considered by the investigator to be related to the study drug. All AEs of prolonged QT interval were mild in intensity. The AEs of prolonged QT intervals were resolving at the end of the study.

Immunogenicity

Not applicable.

8.2.4. Analysis of Submission-Specific Safety Issues

Adverse Events of Special Interest

Adverse Events of Special Interest were defined based on known safety profiles and mechanisms of action of ICS and LABAs as classes, including hypersensitivity reactions, lower respiratory tract infections, asthma, bone fractures, cardiovascular effects, and local corticosteroid effects. Slightly more patients in the FF/VI group (44 patients, 10%) experienced at least 1 Adverse Event of Special Interest (AESI) than in the FF group (37 patients, 8%). As presented in Table 25, the majority of AESIs were similar in type and frequency in both treatment groups, except for hypersensitivity events and glucose events, which were reported in more patients in the FF/VI group. Of the hypersensitivity events, allergic rhinitis was the most commonly reported for 19 patients (4%) in the FF/VI group and for 6 patients (1%) in the FF group. Effects on glucose were reported for 3 patients (<1%) in the FF/VI group and none in the FF group.

Table 25. Adverse Events of Special Interest

AESI Term Preferred Term	FF/VI (N=454)	FF (N=448)
Hypersensitivity		
Rhinitis allergic	19 (4%)	6 (1%)
Conjunctivitis allergic	2 (<1%)	2 (<1%)
Eczema	1 (<1%)	1 (<1%)
Urticaria	1 (<1%)	1 (<1%)
Angioedema	1 (<1%)	0
Dermatitis allergic	0	1 (<1%)
Dermatitis atopic	1 (<1%)	0
Multiple allergies	0	1 (<1%)
Lower respiratory tract infection excluding infective pneumonia		
Bronchitis	6 (1%)	8 (2%)
Lower respiratory tract infection	2 (<1%)	0
Tracheitis	1 (<1%)	0

Asthma/bronchospasm		
Asthma	4 (<1%)	5 (1%)
Decreased bone mineral density and associated fractures		
Radius fracture	2 (<1%)	0
Clavicle fracture	0	1 (<1%)
Foot fracture	1 (<1%)	0
Wrist fracture	1 (<1%)	0
Local steroid effects		
Dysphonia	1 (<1%)	2 (<1%)
Oropharyngeal pain	1 (<1%)	2 (<1%)
Oral candidiasis	1 (<1%)	1 (<1%)
Stomatitis	1 (<1%)	0
Infective pneumonia		
Pneumonia	1 (<1%)	3 (<1%)
Pneumonia mycoplasma	0	1 (<1%)
Cardiovascular effects		
QT prolonged	1 (<1%)	1 (<1%)
PR prolongation	0	1 (<1%)
Extrasystoles	0	1 (<1%)
Effects on glucose		
Blood glucose increased	1 (<1%)	0
Hyperglycemia	1 (<1%)	0
Weight decreased	1 (<1%)	0

Source: Adapted from Applicant's CSR Table 3.13. Verified by reviewer with JMP Clinical.

8.2.5. Safety Analyses by Demographic Subgroups

Adverse events were balanced between the FF/VI and FF treatment arms when analyzed by the following subgroups:

- Age: ≤7 years, 8-11 years, and 12-17 years of age
- Gender: Female, male
- Race and ethnicity: African American, Asian, White, Mixed race, Hispanic or Latino, Not Hispanic or Latino

There were no imbalances in adverse events in subgroup analyses that inform labeling. Safety analyses for these subgroups were consistent with the overall population.

8.2.6. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not applicable

Human Reproduction and Pregnancy

No pregnancy was reported in this study.

Pediatrics and Assessment of Effects on Growth

The Applicant collected height measurements on all patients at screening. Given that follow-up height measurements were not collected at the end of the treatment period, as well as the short duration of the trial, no conclusions about the effects of FF/VI on growth can be drawn.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdose or drug abuse potential is anticipated with the use of FF/VI.

8.2.7. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Office of Pharmacovigilance and Epidemiology conducted a pediatric postmarketing pharmacovigilance review for FF/VI, covering the time period from May 10, 2013 to September 29, 2022. There were no safety signals, no increased severity or frequency of labeled adverse events, and no pediatric deaths that could be attributed to FF/VI.

Expectations on Safety in the Postmarket Setting

We do not anticipate that the post-marketing experience will vary significantly from clinical experience to date observed during Study HZA107116 or from the safety experience from other members of the ICS and LABA classes.

8.2.8. Integrated Assessment of Safety

The safety data submitted with this application were sufficient to support a new indication for asthma in pediatric patients 5 to 17 years of age. The safety assessment included an evaluation of deaths, SAEs, all AEs, dropouts, laboratory findings, vital signs, ECGs, exacerbations, and hospitalizations. No new safety signals were revealed in this application. There were no large imbalances identified between treatment arms.

8.3. Statistical Issues

- Robustness of Primary Efficacy Data

There were 902 patients in the ITT population and 791 contributed to the primary analyses. Of the 111 patients who did not contribute to this analysis, a breakdown of the reasons is given in Table 26.

With respect to the missing data for the primary efficacy analysis, the majority of the cases (76%) was because of patients who were still in the study and attended the Week 12 visit, but were unable to provide sufficient serial spirometry. The Applicant noted that the reason for not collecting it was due to the inherent difficulty in obtaining serial spirometry from this population, particularly in younger children, and due to the patient burden it represented, which was not unexpected in this population.

Table 26: Distribution of Missing Data in Primary Analysis

	FF/VI (N = 454)	**FF (N = 448)**	**Total (N = 902)**
Participants not contributing to primary analysis	**60**	**51**	**111**
Missing covariates	5 (8%)	2 (4%)	7 (6%)
All covariates present, but withdrawn prior to Visit 6 (Week 12)	11 (18%)	9 (18%)	20 (18%)
All covariates present, attended Visit 6 (Week 12) but did not provide sufficient serial spirometry	44 (73%)	40 (78%)	84 (76%)

Source: Adapted from the Applicant's Response to FDA Information Request Received February 13, 2023, p1

A planned sensitivity analysis was performed by the Applicant to evaluate the impact of missing data and to examine the robustness of the primary analysis to departures from the assumption that missing data are missing-at-random (MAR). Implementation of the jump to reference (J2R) method assumed that for participants in the FF/VI group with missing data, their imputed mean response was that of the FF group. In this sensitivity analysis for FF/VI vs FF, the treatment effect remained statistically significant [95% CI: 0.03, 0.12; p-value = <0.01] (Table 27).

Table 27: Missing Data Sensitivity Analysis (J2R) of Weighted Mean FEV1 (0-4 hours) (L) at Week 12 (ITT Population 5-17 Years Old)

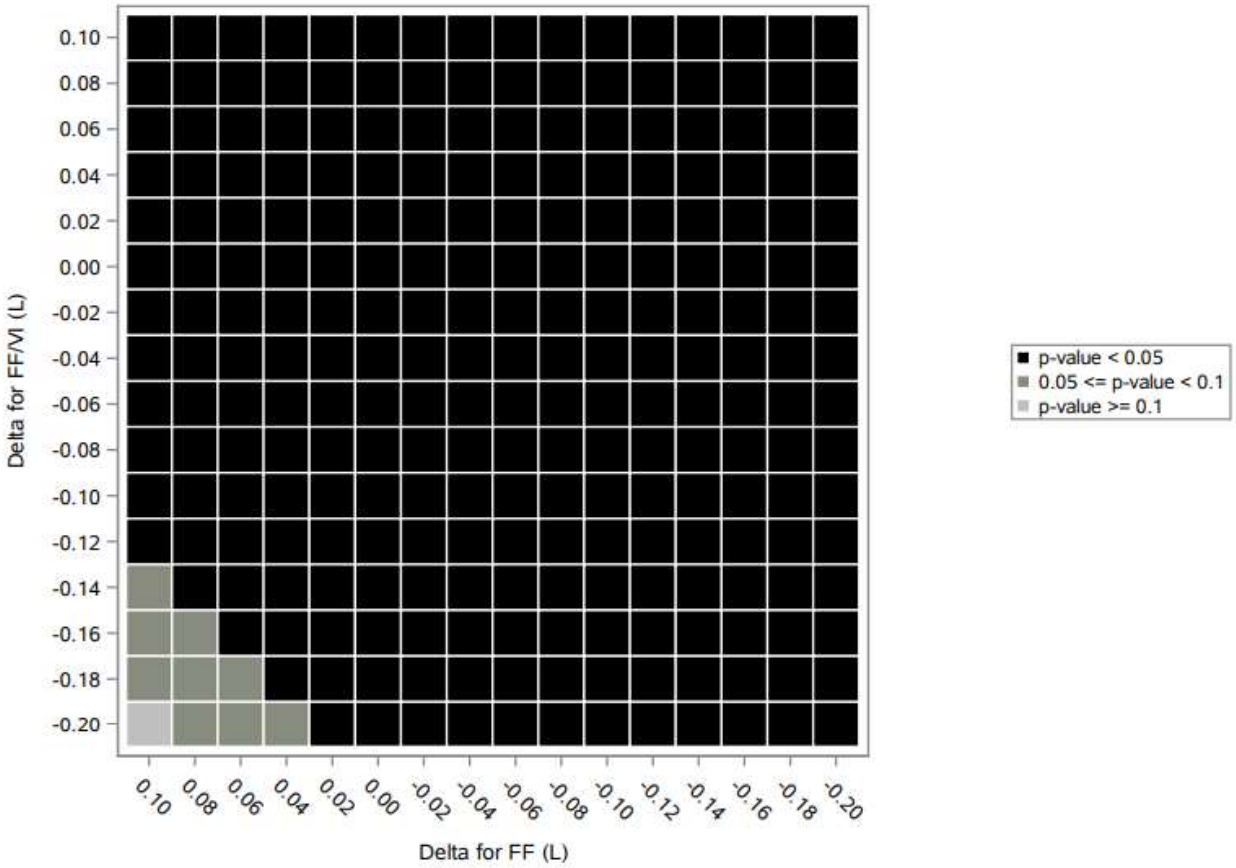
			FF/VI vs FF	
Treatment Group	**n**	**LS Means**	**Difference in LS Means (95% CI)**	**P-value**
FF/VI (N = 454)	449	2.04	0.07 [0.03, 0.12]	<0.01
FF (N = 448)	446	1.97		

Source: Statistical Reviewer
FEV, forced expiratory volume in 1 second; FF, fluticasone furoate; FF/VI, fluticasone furoate/vilanterol; J2R, jump-to-reference; ITT: intent-to-treat; LS, least squares; N, total number of subjects; n, number of subjects in the analysis.
Statistical analysis was performed with analysis of covariance (ANCOVA) model with effects due to baseline, region, sex, age and treatment group. The analysis included all available data, regardless of whether the participant remained on-treatment at the time of the assessment. Missing data were assumed to be missing at random (MAR). Baseline FEV1 was measured at Visit 2, Day -5 (Pre-Dose).

In addition, a planned tipping point analysis was conducted by the Applicant under a range of missing data assumptions to determine how extreme these assumptions need to be for the conclusion of the primary analysis to change. The initial tipping point analysis included a two-way tipping point analysis based on the deltas (ranging from -0.12 L to 0 L, in 0.02 L increments)

added to both the FF/VI and FF treatment groups, in which no delta values between -0.12 L and 0 L produced a tipping point (results not shown). However, to further explore the plausibility of missing data assumptions under which the conclusions change, the Applicant conducted a tipping point analysis on a broader range of deltas (-0.20 L to 0.10 L, in 0.02 L increments). In the tipping point analysis for FF/VI vs FF, the treatment effect remained statistically significant ($p < 0.05$) under most scenarios after multiple missing data imputations, except under few implausible extreme shifting scenarios (where $p > 0.05$) (Figure 6). For example, the treatment difference between FF/VI and FF would not be statistically significant, if the delta of -0.14 L was added to the missing data in FF/VI group, and the delta of 0.10 L was added to the missing data in FF group. Such a scenario is considered clinically implausible.

Figure 6: Summary of P-values from Tipping Point Analysis for Weighted Mean FEV1 (0-4 hours) (L) at Week 12



Source: Applicant's Response (efficacy-figures) to FDA Information Request Received February 13, 2023

The missing data sensitivity analyses above support treatment effect on the primary endpoint. Therefore, the results of primary efficacy are considered reasonably robust against the underyling missing data assumption.

- Sensitivity Analysis Excluding Sites with Data Concerns

There were 3 sites (Site 235742 (USA), Site 234175 (Poland), Site 233822 (Mexico)) closed prematurely due to suspected non-compliance with ICH GCP. These sites screened a total of 80 participants (3.33% of 2402 total participants screened) and randomized 30 participants (3.30% of 908 total participants randomized). All data for these three sites in the ITT populations were included in all safety and efficacy summaries and analyses planned in the RAP. In addition, the Applicant performed a sensitivity analysis for the primary endpoint exlcuding the data for all participants from these three sites, and found no change in the primary efficacy results (Table 28). Therefore, the statistical reviewer does not believe that the suspected non-compliance with ICH GCP affects the primary efficacy conclusions.

Table 28: Sensitivity Analysis of Weighted Mean FEV1 (0-4 hours) (L) at Week 12 On- and Post-Treatment Data - (ITT Population 5-17 Years Old) Excluding Sites with Data Concerns

			FF/VI vs FF	
Treatment Group	**n**	**LS Means**	**Difference in LS Means (95% CI)**	**P-value**
FF/VI (N = 454)	380	2.06	0.08 [0.03, 0.13]	<0.01
FF (N = 448)	387	1.98		

Source: Adapted from Clinical Study Report Table 2.79, p.636

8.4. Conclusions and Recommendations

The data submitted by the Applicant demonstrated substantial evidence of effectiveness and safety for FF/VI for the treatment of asthma in pediatric patients 5 to 17 years of age. The recommended regulatory action for this population and proposed dosing regimen is **Approval**.

Study HZA107116 was the pivotal trial submitted with this application. HZA107116 was a phase 3, randomized, double-blind, parallel-group, multicenter trial evaluating the safety and efficacy of once daily FF/VI inhalation powder compared to once daily FF inhalation powder in the treatment of asthma in patients 5 to 17 years old currently uncontrolled on inhaled corticosteroids. The trial was conducted over a total duration of approximately 29 weeks: 4-week run-in period, followed by a 24-week double-blind treatment period and a 1-week follow-up period. Patients were stratified by age (5 to 11 years old; and 12 to 17 years old) and randomized in a 1:1 ratio, as follows:

- Patients 5 to 11 years old:
  - FF 50 μg once daily in the morning
  - FF/VI 50/25 μg once daily in the morning
- Patients 12 to 17 years old:
  - FF 100 μg once daily in the morning
  - FF/VI 100/25 μg once daily in the morning

The primary endpoint was weighted mean FEV1 (0 to 4 hours) at Week 12. Primary endpoint

analysis demonstrated a statistically significant treatment difference of 0.083L between treatment groups, in favor of FF/VI. No statistically significant treatment differences were seen in any of the secondary endpoints, including rescue-free 24-hour periods, symptom-free 24-hour periods, morning FEV1, morning PEF, ACQ-5, evening PEF, and exacerbations.

Confirmatory evidence of efficacy of is provided by the previously demonstrated efficacy of FF/VI in the adult population (≥18 years of age), as well as the clinical experience and scientific knowledge of the effectiveness of other drugs in the same pharmacologic class (i.e., ICS/LABA), including in children ≥5 years of age. Together, the single adequate and well-controlled trial (HZA107116) and confirmatory evidence provide substantial evidence of efficacy to support approval of this product at the proposed doses in the 5 to 17-year-old population for the maintenance treatment of asthma.

No new safety signals were revealed in this application. The incidence of AEs was generally balanced between treatment arms.

The Applicant has submitted sufficient data to support a favorable benefit-risk assessment. Approval of this supplement provides patients 5 to 17 years of age with an option for once daily dosing of an ICS/LABA fixed-dose combination product.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not necessary for this supplemental NDA.

10 Pediatrics

FF/VI was approved on April 30, 2015 for the maintenance treat of asthma in adult patients aged 18 years and older. While clinical trial data used to support that action included patients 12 years of age and older, FF/VI was not approved in the 12 to 17 year old population due, in part, to concerns that there were a higher number of asthma-related hospitalizations in FF/VI treatment patients compared to FF treated patients in this age group. In addition, the bronchodilation and exacerbation benefits were also less consistent in this age group compared to adults. This issue was discussed at an Advisory Committee held on March 19, 2015 where the majority voted that the were not adequate data to support the approval in the 12-17 year old age group (1 for approval, 19 against approval).

At the time of Approval in the adult population for asthma, 3 PREA PMRs were issued (PMRs 2904-1, 2904-2, and 2904-3) to study FF/VI in pediatric patients 5-11 years of age (Section 3.1). After further discussion between the Applicant and the FDA regarding the Applicant's plans for studying adolescents 12-17 years of age, a new protocol for study HZA107116 that included pediatric patients 5-17 years of age was submitted. As a result, the original 3 PMRs were released and a new PMR was issued. The new PMR (2904-4) was as follows:

> Conduct a randomized, double-blind, parallel-group study to evaluate the efficacy and long-term safety of fluticasone furoate/vilanterol (FF/VI) and fluticasone furoate (FF) in children 5 to less than 18 years of age.

Subsequent to the issuing PMR 2904-4, the Applicant submitted a proposed pediatric study request (PPSR) that proposed a study consistent with PMR 2904-4.

The Agency issued a pediatric written request (WR) on December 20, 2017.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

12 Risk Evaluation and Mitigation Strategies (REMS)

No REMS is proposed.

13 Postmarketing Requirements and Commitment

No postmarketing requirement or commitment is proposed.

14 Deputy Division Director for Safety Comments (designated signatory authority)

GlaxoSmithKline (GSK) has submitted a supplemental new drug application (sNDA) for the fixed dose combination of fluticasone furoate (FF) and vilanterol (VI) dry powder for inhalation to extend the asthma indication to include patients aged 5 to 17 years. FF/VI is currently approved for the maintenance treatment of asthma in patients 18 years and older. This indication was approved on April 30, 2015. While clinical trial data used to support that action included patients 12 years of age and older, FF/VI was not approved in the 12 to 17 year old population due to potential concerns, in particular, there were a higher number of asthma related hospitalizations in FF/VI treatment patients compare to FF treated patients in this age group. In addition, the benefit in terms of bronchodilation and exacerbation was also less consistent in this age group compared to adults. This issue was discussed at an Advisory Committee held on March 19, 2015 where the majority voted that the were not adequate data to support the approval in the 12-17 year old age group.

At the time of Approval in the adult population for asthma, 3 PREA PMRs were issued (PMRs 2904-1, 2904-2, and 2904-3). After further discussion between the Applicant and the FDA, these 3 PMRs were released and another PMR issued (2904-4). The PMR was as follows:

> Conduct a randomized, double-blind, parallel-group study to evaluate the efficacy and long-term safety of fluticasone furoate/vilanterol (FF/VI) and fluticasone furoate (FF) in children 5 to less than 18 years of age.

Subsequent to the issuing PMR 2904-4, the Applicant submitted a proposed pediatric study request (PPSR) which proposed a study consistent with PMR 2904-4. The Agency then issued a pediatric written request (WR) on 12/20/2017.

In this sNDA submission, the Applicant has submitted the results of trial HZA107116, which was conducted to fulfill both PMR 2904-4 and the WR, to support the expansion of the age range for the asthma indication to include 5-17 years olds at the following doses:

- 50/25 mcg once daily for patients 5 to 11 years old;
- 100/25 mcg once daily for patients 12 to 17 years old.

Trial HZA107116 was a randomized, double-blind, parallel-group study evaluating the efficacy and safety of once daily FF/VI inhalation powder compared to once daily FF inhalation powder in the treatment of asthma in patients 5 to 17 years old currently uncontrolled on ICS. FF/VI doses included were as above, and FF doses were 100 and 50 mcg once daily for patients 5-11 and 12-17 years of age, respectively. This trial included a total of 902 patients, of which 454 received FF/VI (5 to 11 years old n=337; 12-17 year old = 117), and 448 received FF (5 to11 years old n=336; 12 to 17 years old n=112). For the primary endpoint FEV1 (0 to 4 hours) at Week 12 across the study population, the results were statistically significant for when comparing FF/VI to FF treatment patients [83mL (95%CI 37, 129)]. Subgroups analyses of the 5 to 11 and 12 to 17 year old age group was consistent with the overall population. These

spirometric data support the efficacy of FF/VI in terms of bronchodilation. For the secondary endpoints, which included rescue-free 24-hour periods, symptom-free 24-hour periods, AM FEV1, AM PEF, and ACQ-5, results were not statistically significant and did not provide additional support for efficacy. With regard to the secondary endpoint of asthma exacerbations, events occurred with similar frequency between FF/VI and FF groups (7% and 8%, respectively). For exacerbations associated hospitalization or emergency rooms (ER) visits, events were uncommon and numerically similar between groups (<1% in each group). Overall, primary endpoint data from HZA107116 in conjunction with the previously demonstrated efficacy in the adult population and the clinical experience and scientific knowledge of the effectiveness of other drugs in the same pharmacologic class (i.e., ICS/LABA) provide sufficient support for the efficacy of this product at the proposed doses in the 5 to 17 year old population for the maintenance treatment of asthma.

Regarding safety, the Trial HZA107116 was adequate for evaluation of safety in the 5 to 17 year old population. The overall safety profile based on results of this trial was consistent with that observed in the adult population and other medications in this class. In addition, while exacerbation was considered an efficacy related endpoint, it is worth noting that asthma exacerbations and exacerbations associated with hospitalizations and/or ER visit were similar between FF/VI and FF treatment groups, which is reassuring given the concerns raised during the initial approval for the asthma indication for the adult population. No new safety concerns were identified.

Overall, the benefit-risk of this product in this 5 to 17 year old age group is favorable. The Division and the Applicant have agreed upon the final labeling language. I have reviewed the recommendations of all disciplines. The submitted clinical program is adequate to support the safety and efficacy of FF/VI for the maintenance treatment of asthma at the doses proposed in the 5 to 11 and 12 to 17 year old age groups. PMR 2904-4 is fulfilled and conditions of the WR were satisfied. The action for this application will be ***Approval.***

15 Appendices

15.1. References

None.

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): HZA107116

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 501		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 5		
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: 5 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation

		from Applicant)

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

Applicant's Population Pharmacokinetic Analysis:

15.3.1. Data

The Sponsor adopted a population pharmacokinetics approach to characterize the PK profile of vilanterol (VI) in children aged 5 – 11 years old. The need for a popPK analysis was raised due to sparse PK sampling (only pre-dose and 10 – 15 minutes post-dose samples were collected) and most samples with BLQ (LLQ = 10 pg/mL) in the phase 2b dose-ranging study (HZA106853). This study evaluated repeat doses of VI 6.25 mcg, 12.5 mcg, and 25 mcg for 4 weeks in children 5 – 11 years old. The percentage of samples with BLQ for each dose level of HZA106853 at visit 5 (end of treatment period at week 4) are provided in Table 29.

Table 29. Percentage of Samples Analyzed Below the Lower Limit of Quantification (Study HZA106853, PK Population)

Planned Relative Time	VI 6.25 OD N=92	VI 12.5 OD N=95	VI 25 OD N=90
Pre-dose	82/90 (91%)	88/94 (94%)	67/90 (74%)
10-15 min post-dose	42/88 (48%)	27/90 (30%)	17/85 (20%)

Source: Table 5, Module 2.7.2 Summary of Clinical Pharmacology (confirmed by the reviewer based on data from adpc.xpt of HZA106853; LLQ = 10 pg/mL

As a considerable number of samples were below limit of quantitation for lower doses, only plasma concentration data from VI 25 mcg of HZA106853 along with data pooled from HZA112776 and 112777 was included in popPK dataset. HZA112776 evaluated the PK of VI following VI 25 mcg once daily for 7-days and HZA112777 evaluated the PK of FF or VI following FF 100 mcg or FF/VI 100/25 mcg once daily for 14 days. The samples from all three studies were analyzed for VI plasma concentrations using similar methodology with the same lower limit of quantification (LLQ) of 10 pg/mL.

The popPK dataset includes a total of 142 subjects from 3 studies with a total of 508 sample records of which 39.4% were reported as not quantifiable (<LLQ). Note that there were 8 records commented out using R-script for exclusion from the analysis because the concentration at 24 hours was notably higher than that for those in the first hour post-dose. The demographic characteristics of popPK dataset are summarized below in Table 30.

Table 30. Summary of Demographic Characteristics (Pop PK Dataset)

Demographics	
Age in years, mean [range]	8 [5–11]
Sex, n (%)	
Female:	57 (40.1)
Male:	85 (59.9)
Body mass index in kg/m², mean [range]	18.5 [13.0-42.5]
Height in cm, mean [range]	130.7 [108-156]
Weight in kg, mean [range]	32.3 [17.3-72.7]
Ethnicity, n (%)	
Hispanic or Latino:	71 (50)
Not Hispanic or Latino:	71 (50)
Race, n (%)	
White – White/Caucasian/European heritage	93 (65.5)
African American/African heritage	10 (7.0)
Asian – Japanese heritage	5 (3.5)
Asian –South East Asian heritage	1 (<1)
American Indian/Native Alaskan	8 (5.6)
White – Arabic/North African	2 (1.4)
Other	23 (16.2)

Source: module 5.3.3.5, hza106853-poppk report

15.3.2. PopPK Model

As a consequence of the large extent of non-quantifiable data in the dataset it was necessary to use methodology that maximized the likelihood for all the data, treating those data below the LLQ as censored. The data were analyzed using the methodology referred to as M3 and requires the use of the F_FLAG option and PHI function available in NONMEM v7.

The Applicant previously developed a three-compartment (3-cmt) base model with zero-order absorption to characterize VI PK profile in adult/adolescents with asthma. However, due to the limited data in the current popPK dataset, 3-cmt model is not possible. Therefore, the Applicant considered a 2-cmt base model with zero order absorption and first order elimination with an additive error model.

After establishing the structural base model, potential covariate-parameter relationships were explored graphically using the individual inter-individual variabilities (ETAs) from the base model. None of the covariates assessed (age, race, ethnicity, sex, body weight, body mass index) apparently impacted the estimate of inter-individual variabilities (ETAs) of CL/F, V1/F, Q/F, V2/F or D1. Furthermore, age and body weight were evaluated as potential covariates on CL/F, V1/F, and V2/F, but did not show significant covariates to affect these parameter estimates.

15.3.3. **Model Results**

The reviewer ran the model and found the similar parameter estimates including their %RSE as reported by the Applicant. In addition, covariate model analysis did not demonstrate the significant impact of above-mentioned covariates on the PK parameter estimates as indicated by no significant decrease in objective function values. The parameter estimates are compiled in the table below:

Table 31. Base VI Pharmacokinetic Model; Log-transformed and Untransformed Parameter Estimates

Parameter	Ln Estimate [95% CI]	Estimate [95% CI]
CL/F [L/h]	5.72 [5.67, 5.77]	305 [290, 321]
V1/F [L]	8.59 [8.40, 8.78]	5378 [4447, 7115]
Q/F [L/h]	8.74 [8.54, 8.94]	6248 [5115, 7631]
V2 /F [L]	12.5 [11.6, 13.4]	268337 [109098, 660003]]
D1 [h]	-3.44 [-4.63, -2.25]	0.0321 [0.0098, 0.1054]

CL/F=inhaled clearance; V1/F = volume of central compartment; Q/F= intercompartmental clearance; V2/F= volume of peripheral compartment, D1=input duration, CI=Confidence Interval
Source: module 5.3.3.5, hza106853-poppk report ,Table 3.

After excluding BLQ data points, Goodness of fit (GOF) plots (Figure 7) were constructed. GOF plots indicate that there is a good agreement between the observed and individual predicted or population predicted data. A little under-prediction was noted at 24 hours based on CWRES (conditional weighted residuals) vs time after dose plot. The validity of this model is confirmed by VPC plots (Figure 8). The VPC plot showed that majority of the data is captured in the prediction interval encompassing 95% of the population as indicated by the 2.5th and 97.5th percentile boundary, indicating that the model was reasonable for this asthma dataset.

Figure 7. Goodness of Fit Plots – Base Model (Reviewer's Analysis)

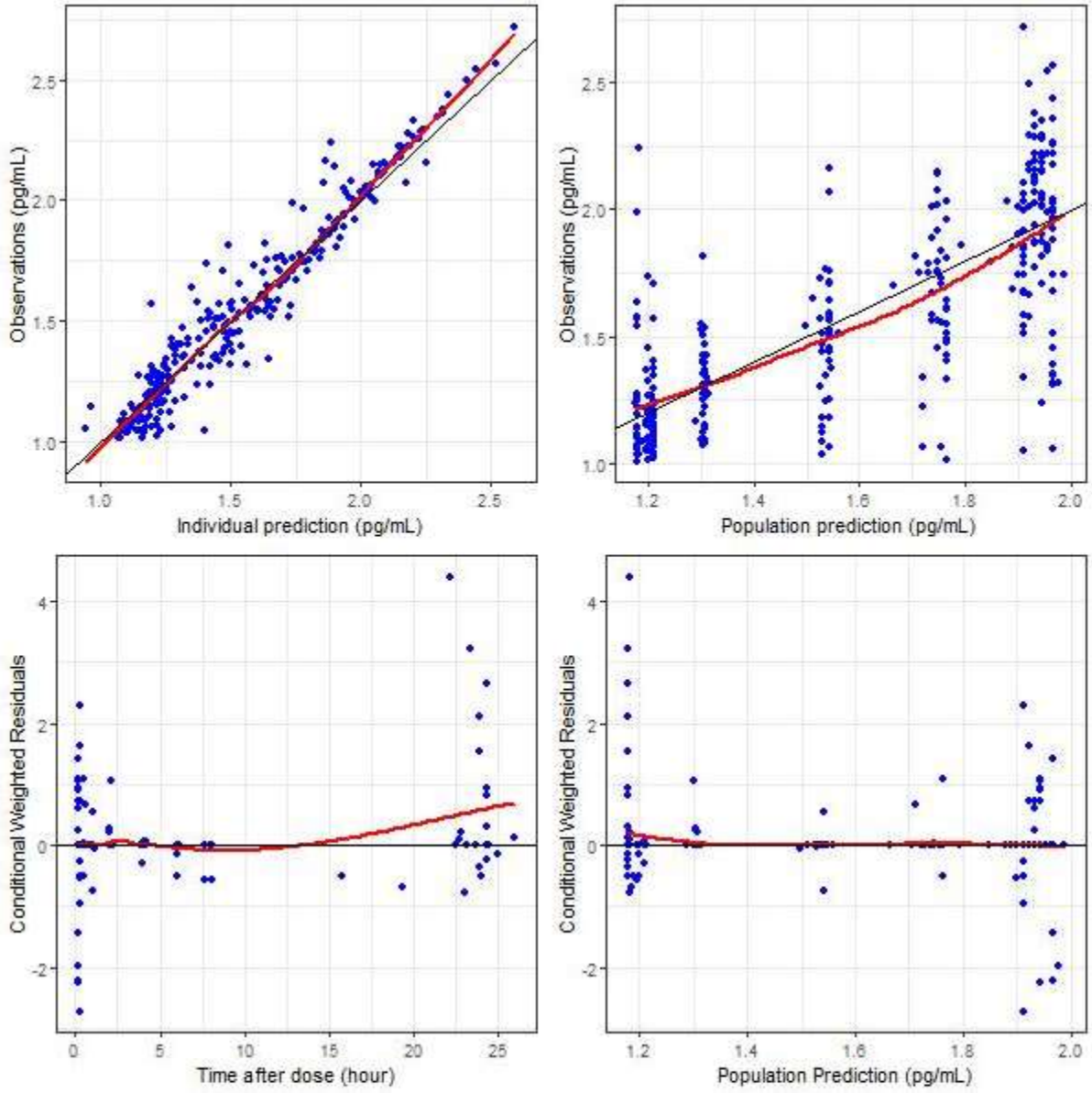
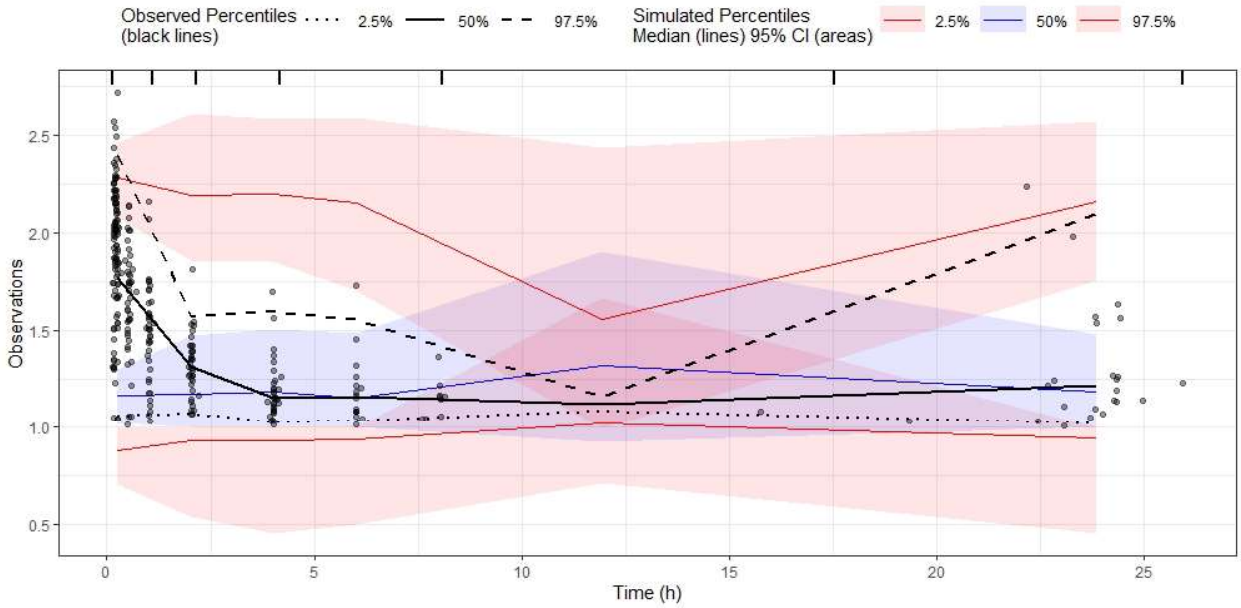
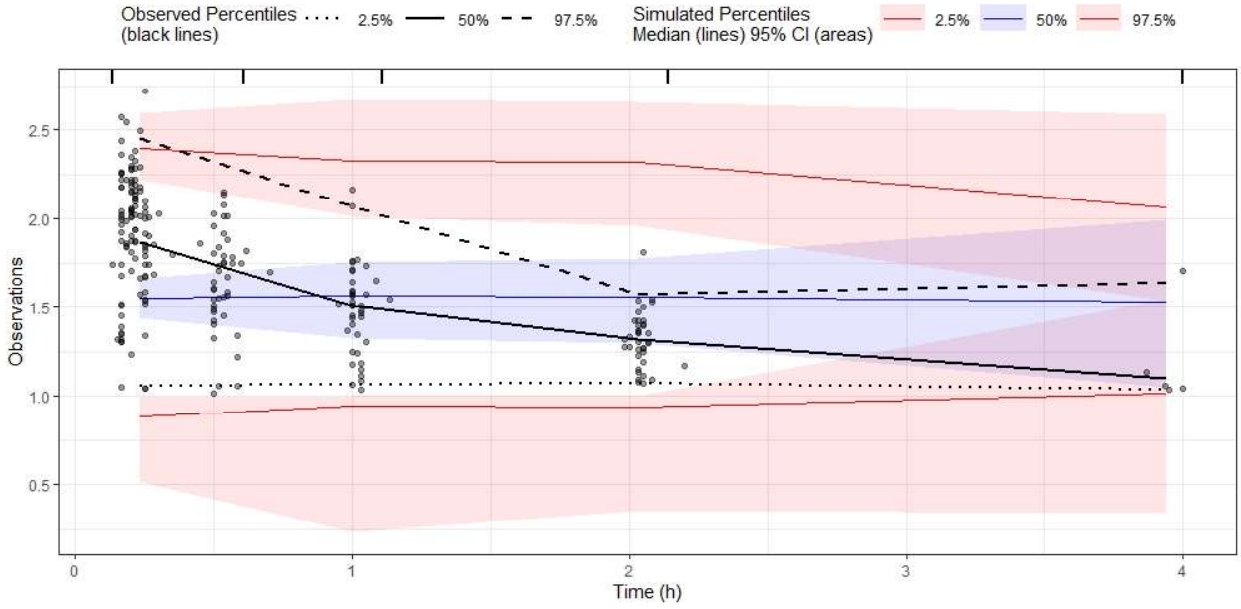


Figure 8. Visual Predictive Check – Final Model: a) Up to 25 hours; b) Up to 4 hours

a.



b.



Individual AUC0-24h values, derived from individual post-hoc estimates of CL/F and Cmax values obtained from simulation are summarized for subjects from study HZA106853 in Table 32. The reviewer's independent analysis provides similar results as well.

Table 32. Model Predicted VI Cmax and AUC0-24h (Geometric Mean [95% CI]) following administration of VI 25 mcg (as VI or FF/VI) in Pediatric Subjects with Asthma (HZA106853**)**

Parameter (Units)	N	GM	Lower 95% CI	Upper 95% CI
Cmax (pg/mL)	90	100.6	30.2	363.1
AUC0-24 (pg.h/mL)	90	83	74.8	92.7

Source: Table 4, popPK report of HZA106853

15.3.4. **Discussion and Conclusion**

The primary objective of this popPK analysis was to characterize the population PK of VI and define influential covariates following VI administered once daily to pediatric subjects with asthma. One Phase IIb (HZA106853) and two Phase IIa (HZA112776 and HZA112777) studies were included in the analysis.

The VI concentration-time data was described by a two-compartment linear model with zero order absorption and first order elimination with an additive error model. The high estimate for V2/F was not physiological but attempts to model the data fixing this to adult estimates resulted in a biased model. None of the demographic covariates evaluated (age, weight, BMI, sex, ethnicity, and race) were shown to be significant on VI pharmacokinetic parameters.

The average VI AUC0-24h and Cmax for pediatric subjects with asthma in study HZA106853 were similar to those estimated using non-compartmental analysis methods for pediatric subjects in the Phase IIa studies following administration of VI alone or in combination (refer to clin pharm review for details).

15.4 OB Appendices (Subgroup Analyses for Weighted Mean FEV1 (0-4hours) (L) at Week 12 On- and Post-Treatment Data)

Subgroup analyses of the primary efficacy endpoint (weighted mean FEV1 at Week 12) to assess the consistency of treatment effect for the combined FF/VI arm (100/25 mcg and 50/25 mcg) versus combined FF arm (100 mcg and 50 mcg) across subgroups were conducted in Study HZA107116. Analysis of subgroups including age, gender, race, ethnicity and geographical region revealed no notable differences in the impact of the treatment effect nor changed the overall assessment of effectiveness. As depicted in Table 33, analysis of the primary endpoint generally favored FF/VI within all subgroups.

Table 33: Subgroup Analyses - Weighted Mean FEV1 (0-4 hours) (L) at Week 12 On- and Post-Treatment Data (ITT Population 5-17 Years Old)

	Subgroups	Treatment Group	n	LS Means	FF/VI vs FF Difference in LS Means (95% CI)
Age	≤7 years old	FF/VI (N = 102)	81	1.296	0.008 [-0.061, 0.078]
		FF (N = 100)	83	1.287	
	8-11 years old	FF/VI (N = 235)	208	1.961	0.105 [0.048, 0.162]
		FF (N = 236)	208	1.857	
	12-17 years old	FF/VI (N = 117)	108	2.902	0.106 [-0.008, 0.220]
		FF (N = 112)	108	2.796	
Gender	Female	FF/VI (N = 165)	146	2.000	0.113 [0.042, 0.184]
		FF (N = 191)	167	1.887	
	Male	FF/VI (N = 289)	251	2.137	0.068 [0.008, 0.128]
		FF (N = 257)	232	2.069	
Race	African American	FF/VI (N = 34)	26	1.968	0.097 [-0.029, 0.223]
		FF (N = 40)	36	1.871	
	American Indian	FF/VI (N = 22)	19	1.877	0.126 [-0.064, 0.316]
		FF (N = 29)	26	1.751	
	Asian	FF/VI (N = 32)	27	1.930	-0.099 [-0.339, 0.140]
		FF (N = 26)	24	2.029	
	White	FF/VI (N = 335)	294	2.154	0.086 [0.030, 0.142]
		FF (N = 320)	283	2.069	
	Mixed Race	FF/VI (N = 31)	31	1.735	0.034 [-0.083, 0.150]
		FF (N = 33)	30	1.701	
Ethnicity	Hispanic or Latino	FF/VI (N = 120)	106	1.982	0.085 [-0.001, 0.170]
		FF (N = 131)	115	1.897	
	Not Hispanic or Latino	FF/VI (N = 334)	291	2.118	0.080 [0.026, 0.135]
		FF (N = 317)	284	2.038	
Geographical Region	US	FF/VI (N = 42)	39	2.158	0.095 [-0.024, 0.213]
		FF (N = 58)	50	2.063	
	Non-US	FF/VI (N = 412)	358	2.071	0.079 [0.027, 0.131]
		FF (N = 390)	349	1.992	

Source: Statistical Reviewer
CI, confidence interval; FEV1, forced expiratory volume in 1 second; FF, fluticasone furoate; FF/VI, fluticasone furoate/vilanterol; ITT: intent-to-treat; LS, least squares; N, total number of subjects; n, number of subjects in the analysis.
The dose of FF/VI was 100/25 mcg once daily for patients aged 12 to 17 years and 50/25 mcg once daily for patients aged 5 to 11 years. The dose of FF was 100 mcg once daily for patients aged 12 to 17 years and 50 mcg once daily for patients aged 5 to 11 years.
Statistical analysis was performed with analysis of covariance (ANCOVA) model with effects due to baseline, region, sex, age and treatment group. The analysis included all available data, regardless of whether the participant remained on-treatment at the time of the assessment. Missing data were assumed to be missing at random (MAR).

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