CLINICAL REVIEW

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Division / Office	ODEII/DPARP
Reviewer Name(s)	Tracy Kruzick, MD, MPH
Review Completion Date	March 26, 2015
Established Name	Fluticasone furoate/vilanterol
(Proposed) Trade Name	Breo Ellipta
Therapeutic Class	Inhaled corticosteroid/long-acting beta$_2$ agonist
Applicant	GlaxoSmithKline
Formulation(s)	Dry Powder for Inhalation
Dosing Regimen	One inhalation once daily
Indication(s)	Treatment of asthma
Intended Population(s)	Asthma 12 years of age and older

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action from a clinical perspective for fluticasone furoate (FF)/vilanterol (VI) 100/25 and 200/25 mcg inhalation powder is Approval for patients ≥ 18 years of age, and a Complete Response for patients 12 to 17 years of age. Per my review of the risk benefit assessment, the submitted data support approval of both dose strengths for the treatment of asthma in patients 18 years of age and older, but not for patients 12-17 years of age.

1.2 Risk Benefit Assessment

GlaxoSmithKline (GSK) has submitted a supplemental New Drug Application (sNDA) for Breo Ellipta®, a once-daily, fixed-dose, orally-inhaled corticosteroid (ICS) and long-acting-beta-agonist (LABA) combination product for the treatment of asthma in patients 12 years of age and older. Breo Ellipta® contains fluticasone furoate (FF) as the ICS, and vilanterol (VI) as the LABA. The proposed doses are one oral inhalation of FF/VI 100/25 mcg or FF/VI 200/25 mcg once daily.

Fluticasone furoate has already been approved as monotherapy for the treatment of asthma at doses of 100 mcg and 200 mcg once daily (Arnuity Ellipta, NDA 205625). Therefore, the main goal of the combination ICS+LABA program is to demonstrate the added clinical benefit (efficacy) of vilanterol.

In order to frame the risk-benefit assessment, an overview of the efficacy and safety are presented below.

Efficacy

The asthma development program for Breo Ellipta® was designed to demonstrate the efficacy of FF/VI compared to placebo, the contribution of VI to the combination, and the added benefit of the higher dose (200/25) over the lower dose (100/25). The information to support the efficacy of FF/VI for the treatment of asthma is derived primarily from four trials (HZA106827, HZA116863, HZA106829, and HZA106837). In addition, to these four key trials, GSK conducted one trial (HZA113091) in asthma comparing FF/VI to Advair (fluticasone propionate/salmeterol). This trial provides an additional benchmark comparison for FF/VI.

Trial HZA106827 was a 12-week, multinational, randomized, double-blind, placebo-controlled, parallel group trial in patients with persistent asthma that assessed FF/VI 100/25, FF 100, and placebo administered once-daily in the evening. Patients were 12 years of age and older, had a current history of asthma, a pre-bronchodilator percent (%) predicted FEV1 of 40-90% with a post-albuterol/salbutamol reversibility ≥ 12% and 200 mL, and were using a stable dose of ICS or ICS/LABA for at least 12 weeks prior to screening. The co-primary efficacy endpoints were mean change from baseline in trough

FEV1 at 12 weeks and the weighted mean serial FEV1 over 0-24 hours post-dose in the subset of subjects performing serial FEV1 at the end of the double-blind treatment period. The primary treatment comparisons were between FF/VI 100/25 and FF 100, between FF/VI 100/25 and placebo, and between FF 100 and placebo for the co-primary endpoints. Trial HZA106827 included 609 patients in the ITT population, of which 201 patients received the proposed FF/VI 100/25 dose. Once-daily treatment with FF/VI 100/25 and FF 100 demonstrated statistically significant improvements compared with placebo with respect to trough FEV1 and weighted mean FEV1 at Week 12. Compared with placebo, mean treatment differences of 172 mL (FF/VI, $p<0.001$) and 136 mL (FF, $p=0.002$) were observed in trough FEV1. For weighted mean FEV1 (0-24h) (in a subset of subjects) a difference of 302 mL ($p<0.001$) was observed with FF/VI 100/25 and a difference of 186 mL ($p=0.003$) was observed following treatment with FF 100. No statistically significant treatment differences were observed with either endpoint between FF/VI 100/25 relative to FF 100 ($p>0.05$) and so the lung function contribution, as measured by FEV1, of VI to the FF/VI 100/25 combination was not demonstrated in trial HZA106827; however, two subsequent trials did show a contribution of the VI component (HZA116863 and HZA106829).

Trial HZA116863 was a 12-week, multinational, randomized, double-blind, parallel group trial in patients with moderate to severe asthma that assessed FF/VI 200/25, FF/VI 100/25, and FF 100 administered once daily in the evening. Patients were 12 years of age and older, had a current history of asthma, a pre-bronchodilator percent (%) predicted FEV1 of 40-80% with a post-albuterol/salbutamol reversibility ≥ 12% and 200 mL, and were using a stable dose of ICS or ICS/LABA for at least 12 weeks prior to screening. The primary efficacy endpoint was weighted mean serial FEV1 (0-24 hours post-dose). The primary treatment comparison was between FF/VI 100/25 and FF 100. Trial HZA116863 included 1,039 subjects in the ITT population, of which 346 patients received FF/VI 100/25 and 346 patients received FF/VI 200/25. Compared with FF 100 alone, FF/VI significantly improved pulmonary function as measured by weighted mean FEV1 (0-24h), with a treatment difference of 108 mL ($p<0.001$). Trial HZA116863 also provided an opportunity to evaluate the benefit of the higher dose (FF/VI 200/25) over the lower dose (FF/VI 100/25). Comparisons of FF/VI 200/25 to FF/VI 100/25 showed small numerical improvements in lung function (24 mL improvement in weighted mean 0-24 hours FEV1, and 16 mL improvement in trough FEV1), and the change from baseline in the percentage of rescue-free 24 hour periods (0.9% difference favoring FF/VI 200/25). Small improvements also were seen in the percentage of symptom-free 24 hour periods (1.9% difference), morning PEF (3.4 L/min) and evening PEF (2.0 L/min) favoring FF/VI 200/25. Additionally, subjects receiving FF/VI 200/25 were 55% more likely to be well controlled (ACT score ≥20) than those taking FF/VI 100/25.

Trial HZA106829 was a 24-week, multinational, randomized, double-blind, double-dummy, parallel group trial in patients with asthma which assessed FF/VI 200/25, FF 200, and fluticasone propionate (FP) 500 BID. Patient selection criteria and co-primary endpoints were as described for HZA106827. The primary treatment comparison was between FF/VI 200/25 and FF 200. At the end of 24 week treatment period, once daily treatment with FF/VI 200/25 demonstrated statistically significant improvements compared with FF 200 with respect to both co-primary endpoints. Compared with FF 200, treatment differences of 193 mL ($p < 0.001$) and 136 mL ($p=0.048$), were observed for mean change from baseline in trough FEV1 and weighted mean FEV1 (0-24h), respectively.

Trial HZA106837 was a long-term, randomized, double-blind, parallel group, event- driven trial in patients with asthma, which was designed to demonstrate that treatment with FF/VI 100/25 once daily significantly decreased the risk of asthma exacerbations as measured by time to first asthma exacerbation when compared with FF100. Participants were 12 years of age and older and had at least a one year history of asthma, were using FP 200 to 1000 mcg/day (or equivalent) or FP/salmeterol (100/50 BID or 250/50 BID, or equivalent) for at least 12 weeks prior to Visit 1, and had history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or inpatient hospitalization for the treatment of asthma within 12 months prior to Visit 1.

In this trial, the sponsor has defined "severe exacerbation" as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. An adjudication committee determined if serious adverse events were respiratory-related and ensured that all asthma exacerbations were captured as defined in the protocol. Although the definition of severe exacerbation is per consensus guidelines [*Am J Respir Crit Care Med, 180: pp. 58-99, 2009*] the reader will take note later in this review that most exacerbations were defined by use of oral corticosteroids, rather than what might be considered to be the more "severe" components of the definition, specifically inpatient hospitalization or ED visit. As a result, for the purposes of this review, the results will be reported for "asthma exacerbation" when the efficacy of FF/VI is examined, with the qualifier of "severe" omitted.

Once-daily treatment with FF/VI 100/25 demonstrated a statistically significant improvement compared with FF 100 with respect to time to first asthma exacerbation. The hazard ratio for FF/VI 100/25 versus FF 100 was 0.795 (95% CI 0.642, 0.985). This represents a 20% reduction in the risk of asthma exacerbation for subjects treated with FF/VI 100/25 compared with FF100 (p=0.036) in the overall study population. The secondary endpoint of rate of asthma exacerbation also demonstrated a 25% reduction for subjects treated with FF/VI 100/25 compared with FF 100 (p=0.014) in the overall study population.

Trial HZA113091 was a 24-week, randomized, double-blind, double-dummy, parallel group trial in patients with asthma that assessed FF/VI 100/25 versus Advair (FP/salmeterol) 250/50 BID. The primary efficacy endpoint was weighted mean serial FEV1 (0-24h) at 24 weeks. Trial HZA113091 included 806 subjects in the ITT population, of which 403 subjects received FF/VI 100/25. While there was no statistical difference between treatments, Advair numerically outperformed FF/VI at most time points. At the end of treatment, subjects in the FF/VI and Advair groups achieved mean increases from baseline in weighted mean serial FEV1 (0-24h) of 341 and 377 mL, respectively.

Safety

The safety review utilized the same studies as listed above in the efficacy summary, with the addition of HZA106839, a long-term, 52-week, safety study. In general, the safety profile unrelated to serious asthma outcomes of FF/VI is similar to that for other ICS/LABA

products in asthma, and current product labeling contains warning language regarding these risks (i.e. class labeling for ICS effects, LABA effects).

Given the risk of serious asthma outcomes (hospitalizations, intubations, and death) with the use of LABA for asthma, the Agency conducted a meta-analysis of the submitted data to examine the risk of serious asthma outcomes with FF/VI (a detailed discussion of the meta-analysis can be found in the statistical review by Dr. Janelle Charles). In this meta-analysis, there were no asthma-related intubations or deaths. There were a total of 18 asthma-related hospitalizations observed in the 4 trials included in the meta-analysis. There were 10 hospitalizations in the FF/VI group, and 8 in the FF group, which translated to a crude incidence rates of 0.7 per 100 person-years and 0.6 per 100 person-years for FF/VI and FF, respectively. The incidence rate difference was 0.1 per 100 person-years (95% CI -0.5, 0.8). Seventeen of the 18 hospitalization events were noted in Trial 37. As a result, subgroup analysis was conducted for this trial. A numerical imbalance was observed in the < 18 years age group with 4 hospitalizations observed in the FF/VI arm and no hospitalizations observed in the FF arm.

Risk-Benefit Assessment

Given the potential for increased risk for serious asthma-related outcomes in pediatric patients based on both prior evidence and the findings of the meta-analysis described above, we conducted subgroup analyses for lung function (weighted mean serial FEV1 and trough FEV1) in trials HZA106827, HZA116863, and HZA106829. For Trial HZA106837, the subgroup analysis was conducted for time to first exacerbation and rate of exacerbation. Subgroups were examined by age gender, race, and geographical region. While all subgroups were evaluated, pediatric patients were an area of focus, based on the data.

When examining lung function, the number of adolescents 12 to 17 years old in each subgroup was small, treatment effects within subgroups were not statistically significant, and tests for interaction between treatment and age were not statistically significant. However, there was a numerical trend towards a smaller observed treatment effect in the FF/VI treatment group compared to FF alone in younger patients in all three trials for weighted mean serial FEV1 and in two of the three trials for trough FEV1. When considering the typical efficacy of bronchodilators (such as vilanterol), the inability to consistently demonstrate the contribution of a LABA to the combination product in younger patients, even numerically, is of concern.

In trial HZA106837, the adolescent population comprised about 13 to 15% of the total study population. This trial had the largest adolescent subgroup for analysis. When the 12 to 17 year old subgroup is compared to the subgroup ≥ 18 years of age. It is notable that the 20% reduction in risk to time to first exacerbation in the overall population was in the reverse direction and showed a higher risk estimate of time to first exacerbation in patients 12 to 17 years old (HR 1.4 (0.61, 3.21)). This trend was further supported by the analysis of the rate of asthma exacerbations, which similarly showed that the 25% reduction in rate of exacerbations in the overall population was now in the reverse direction and showed a higher risk estimate for patients 12 to 17 years of age (Ratio 1.60; 95% CI (0.70, 3.61)). The numerical trend in the exacerbation data which is in favor of FF over FF/VI is also of concern.

Based on the potential for increased risk of serious asthma-related outcomes both historically and from the Agency's meta-analysis, the higher risk estimate for both time to and rate of exacerbation, and the numerical trends towards a lower treatment effect in pediatric patients with respect to lung function, this reviewer recommends that the risk-benefit assessment does not support approval of Breo Ellipta in patients 12 to 17 years of age. Based on the risk-benefit assessment in the overall population, the data are adequate to support the approval of both strengths of Breo Ellipta in patients ≥ 18 years of age. A joint meeting of the Pulmonary-Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee was held on March 19, 2015. The committee members were in agreement with this risk-benefit assessment; details of the discussion and voting results are included in Section 9.3 of this review.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Recommendations for postmarket risk evaluation and mitigation strategies are currently pending at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

Discussions regarding the necessity and timing for a large LABA-safety trial as a post-marketing requirement are ongoing at the time of this review.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product, Breo Ellipta®, is a fixed-dose, inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination inhalation dry powder inhaler. The combination device contains fluticasone furoate (FF) as the ICS and vilanterol (VI) as the LABA in 2 double foil blister packs. Within the foil packs, for FF/VI 100/25, one strip contains 100 mcg of FF and the second contains 25 mcg of VI, and for FF/VI 200/25, one strip contains 200 mcg of FF and the second contains 25 mcg of VI. Two doses are proposed: 100/25 mcg and 200/25 mcg administered as 1 inhalation once daily.

The sponsor proposes the indication of once-daily treatment of asthma in patients aged 12 years and older.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently Available Therapies for the Maintenance Treatment of Asthma

Class	Generic Name	Brand Name
Inhaled corticosteroids	Fluticasone furoate DPI	Arnuity Ellipta
	Beclomethasone dipropionate HFA	QVAR
	Budesonide DPI/respules	Pulmicort
	Fluticasone propionate HFA, Diskus	Flovent

Table 1. Currently Available Therapies for the Maintenance Treatment of Asthma		
Class	**Generic Name**	**Brand Name**
	Mometasone DPI/HFA	Asmanex
	Ciclesonide HFA	Alvesco
Combination inhaled corticosteroids/long-acting bronchodilator (ICS/LABA)	Budesonide/Formoterol HFA	Symbicort
	Fluticasone/Salmeterol HFA, Diskus	Advair
	Mometasone/Formoterol HFA	Dulera
Immunomodulators	Omalizumab	Xolair (anti-IgE)
Leukotriene modifiers	Montelukast	Singulair
	Zafirlukast	Accolate
	Zileuton	Zyflo
Xanthines	Theophylline	Multiple

2.3 Availability of Proposed Active Ingredient in the United States

Fluticasone furoate was approved on April 27, 2007 as an intranasal formulation for once-daily treatment for topical use in relieving symptoms of seasonal and perennial allergic rhinitis in adults and children (Veramyst®). The approved dose is 110 mcg once daily for patients > 12 years of age and 55 mcg once daily for children 2-11 years of age. FF was next approved in combination with VI, as Breo Ellipta®, on May 10, 2013, as an inhalation product for the once daily treatment of COPD, including both the treatment of airflow obstruction and for reducing exacerbations, at a dose of 100/25 mcg. On August 20, 2014, FF (single ingredient, Arnuity Ellipta®) was approved for the maintenance treatment of asthma at doses of 100 and 200 mcg once daily.

2.4 Important Safety Issues With Consideration to Related Drugs

In patients with asthma, LABA monotherapy has been associated with serious asthma-related adverse events, including an increased risk of hospitalization, intubation, and death. LABA-containing drug products carry a Boxed Warning for these events.
With respect to other safety issues, additional risks highlighted in current ICS/LABA product labeling include:

- Localized infections
- Immunosuppression
- Hypercorticism and adrenal suppression
- Increased systemic corticosteroid and cardiovascular effects with co-administration with strong cytochrome P450 3A4 inhibitors
- Decreases in bone mineral density
- Glaucoma and cataracts
- Cautious use in patients with cardiovascular or central nervous system disorders due to beta-adrenergic stimulation

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division and GSK have had multiple prior interactions to discuss the proposed FF/VI asthma development program. Table 2 below provides a timeline of regulatory interactions relevant to the asthma program. In addition, discussion highlights that are

pertinent to the asthma indication from the interactions regarding the sponsor's COPD program are also depicted, as these were concurrent development programs.

Table 2. Milestone Interactions Between the Agency and the Sponsor

Date	Interaction	Highlights
February 28, 2005	Pre-IND meeting for FF/VI in asthma	• Division agreed that GSK could develop a combination product prior to development of each individual component
July 27, 2005	Clinical Hold	• Full clinical hold due to findings of macrophage accumulation
October 26, 2006	Clinical Hold Release	• Safe-to-proceed
May 12, 2008	Pre-IND meeting for FF/VI in asthma and COPD	• Division reminded GSK that they must show an added benefit for a higher dose of ICS over a lower dose of ICS • Division reminded GSK that for a combination product, each active component must demonstrate a contribution to its claimed effects
March 31, 2009	End of Phase 2 meeting for FF/VI in COPD	• Division noted the need to directly compare daily to twice daily regimens to establish the appropriate dosing frequency
June 17, 2009	End of Phase 2 Meeting for FF/VI in COPD	• Division agreed that QD and BID FF dosing regimens produced similar efficacy results and that FF 50, 100, and 200 mcg were reasonable doses to pursue in the phase 3 COPD program
June 30, 2010	End of phase 2 meeting for FF/VI in asthma	• Division informed GSK that a large safety trial will be required • Division reminded GSK that the clinical program will need to establish fully the efficacy and safety of the monocomponents • Division acknowledged that a VI-only arm is not feasible in asthma given safety concerns so would entertain alternative study design strategies
October 27, 2011	Pre-NDA meeting for FF/VI in asthma	• Division explained to GSK that a head-to-head efficacy comparison of the proposed dose levels will likely be needed to provide adequate justification for both doses
March 16, 2011	End of Phase 2 meeting for FF	• Division noted that the 200 mcg dose would need a numerical dose response in the primary endpoint as well as support from other efficacy measures

Table 2. Milestone Interactions Between the Agency and the Sponsor

Date	Interaction	Highlights
May 7, 2012	Pre-NDA for FF/VI in asthma	• Division expressed concerns that the clinical program failed to provide adequate justification for use of FF/VI combination over FF
May 11, 2012	Type C Pediatric Advice	• Division recommended use of FEV1 as the primary endpoint in children as well as adults
February 11, 2013	Pre-NDA meeting for FF	• Division agreed with carrying forward the 100 and 200 mcg doses for approval as the 50 mcg studies did not replicate • Division noted that the HPA axis data from the FF/VI program is likely acceptable for this application, although this would be a review issue
November 15, 2013	FDA written comments on iPSP for FF/VI	• Division recommended that more than one dosage strength off FF be evaluated in the confirmatory efficacy trials • Division informed GSK that post-dose serial FEV1 data are required to inform the dose selection for vilanterol • Division informed GSK that HPA axis studies are required for 5-11 yo (b) (4) • Division requested a one-year, long-term safety study in 5-11 yo • Division recommended that the studies must take into account adequate representation of the diseased population (i.e. to include more ethnic minorities)
February 10, 2014	Pre-sNDA meeting for FF/VI	• Division discussed that the added benefit of the 200/25 mcg dose over the 100/25 mcg dose would be a review issue • Division noted that a large, long-term LABA safety trial may not be necessary
April 8, 2014	Agreed initial PSP for FF/VI	• PSP agreed upon

EOP2 = end of phase 2, IND = investigational new drug, NDA = new drug application, PSP = pediatric study plan

2.6 Other Relevant Background Information

There is no other relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately indexed and complete to permit review. With the assistance of the statistical review team, two sites were chosen for inspection as they were the largest sites for enrollment and both participated in trial HZA106837 which is of interest as the longest trial conducted. Table 3 illustrates the sites, the lead investigators, and the trials inspected.

Table 3. Sites for OSI Inspection

Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication/Primary endpoint and other endpoints for verification
131966: Alfredo Gazca-Aguilar, MD Avenida,Copérnico 3817 consultorio 14 esquina Sagitario Colonia Arboledas Zapopan, Jalisco México C.P. 45040	HZA106837	74	-Time to first asthma exacerbation
131966	HZA116863	28	-24 hour weighted mean serial FEV1 -Trough FEV1 (powered secondary endpoint
040688: Jeremy Cole, MD IPS Research Company 1111 North Lee, Suite 400 Oklahoma City, OK 73103	HZA106837	16	-Time to first asthma exacerbation
040688	HZA106839	11	-Incidence of asthma exacerbations
040688	HZA106827	36	-Trough FEV1 -0-24 hour weighted mean serial FEV1
040688	HZA106829	48	-Trough FEV1 -0-24 hour weighted mean serial FEV1

The Office of Scientific Investigations found that the study data collected from these clinical sites appeared reliable in support of the requested indication and thus determined that no action was indicated.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each complete study report.

3.3 Financial Disclosures

A financial disclosure template is attached to this review. GSK provided financial disclosure information for trials covered by the Final Rule on Financial Disclosure by Clinical Investigators which included the following studies:

- HZA106851
- HZA106839
- FFA112059
- HZA106827
- HZA106829
- HZA106837
- HZA113091
- HZA113126
- HZA113714
- HZA113719
- HZA114624
- HZA116863

GSK failed to obtain follow-up financial information on 6 investigators: three investigators passed away, and three would either not return contact with the sponsor or refused to provide the follow-up financial disclosure form. The failed reporting from these investigators is unlikely to impact the review of this application as the overall contribution to the totality of data from these investigators would be small.

In study HZA113126, (b) (6) sub investigators at site (b) (6) had been previous employees of GSK, and this site recruited (b) (6)% of the total population in the study. Removal of this site from the study did not change statistical significance for evaluating the Late Asthmatic Response; however, for the Early Asthmatic Response, statistical significance was lost. Given that this was not a confirmatory trial and that the overall number of subjects contributing to the totality of data supporting the application is small, an OSI inspection is not warranted.

Three investigators (listed below with study site number and studies participated in) reported significant payments of other sorts:

(b) (6) HZA106827, HZA106837, HZA106829)
(b) (6); HZA106827)
(b) (6) HZA116863)

Each investigator contributed (b) (6)% of the overall study population so were unlikely to affect the outcome of the results.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The recommendation from the CMC review team is Approval, details of which can be found in the review by Dr. Pramoda Maturu.

The product is a plastic inhaler with a light grey body, a pale blue mouthpiece cover, and a dose counter, packed in a foil tray which contains a desiccant packet. The inhaler contains two strips of either 30 or 14 regularly distributed blisters, each containing a white powder. One blister strip contains a white powder mix either of 100 mcg or 200 mcg of micronized FF with 12. (b) (4) mg lactose monohydrate as (b) (4) The second blister strip contains a white powder mix of 40 mcg of micronized VI trifenatate with 125 mcg magnesium stearate as (b) (4) and 12 (b) (4) mg lactose monohydrate as (b) (4)

4.2 Clinical Microbiology

An approval of the original NDA 204,275 was recommended from the product quality microbiology team. Additional details from the microbiology review are found in Dr. Stephen Langille's microbiology review dated November 27, 2012.

4.3 Preclinical Pharmacology/Toxicology

The preliminary recommendation from the preclinical review is Approval; however, final recommendations are pending at the time of this review. Details of the preclinical pharmacology/toxicology information can be found in the nonclinical review by Dr. Luqi Pei.

Fluticasone furoate
All FF nonclinical data were previously submitted to and reviewed in NDA 22-051 (Veramyst)®, NDA 205625 (Arnuity Ellipta)®, and this original NDA. Per the nonclinical review, FF possesses a toxicity profile typical of inhaled corticosteroids and the drug is non-genotoxic, non-carcinogenic and non-teratogenic.

Vilanterol and FF/VI combination
All vilanterol data were previously reviewed as part of this original NDA. Per the nonclinical review, all findings were typical of beta-agonists.

FF and VI in combination
All FF/VI combination data were reviewed as part of this original NDA. The nonclinical review did not find any significant toxicological interactions between inhaled VI and FF.

FF/VI has been given a pregnancy C category rating which is consistent with other approved ICS/LABA products.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Fluticasone furoate is an inhaled corticosteroid that acts as an anti-inflammatory. Corticosteroids have been shown to have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. The use of ICS in asthma is considered the most effective treatment for maintenance control. Vilanterol (VI) acts by binding and activating beta-2-adrenergic receptors in the lungs, predominantly in bronchial smooth muscle, to promote bronchodilation.

4.4.2 Pharmacodynamics

4.4.2.1 Vilanterol Dose Ranging

Vilanterol dose-ranging trials were reviewed as part of the original NDA application. Dose selection for VI in asthma was primarily based on 2 trials: B2C109575 (asthma dose-ranging trial) and HZA113310 (asthma dose-regimen trial). Two other trials, B2C112060 and B2C111401 are briefly described here as they provide data on VI doses versus placebo.

Based on the results of these trials, the selection of once-daily VI 25 mcg for confirmation in phase 3 trials was reasonable.

Trial B2C109575: VI Dose-Ranging

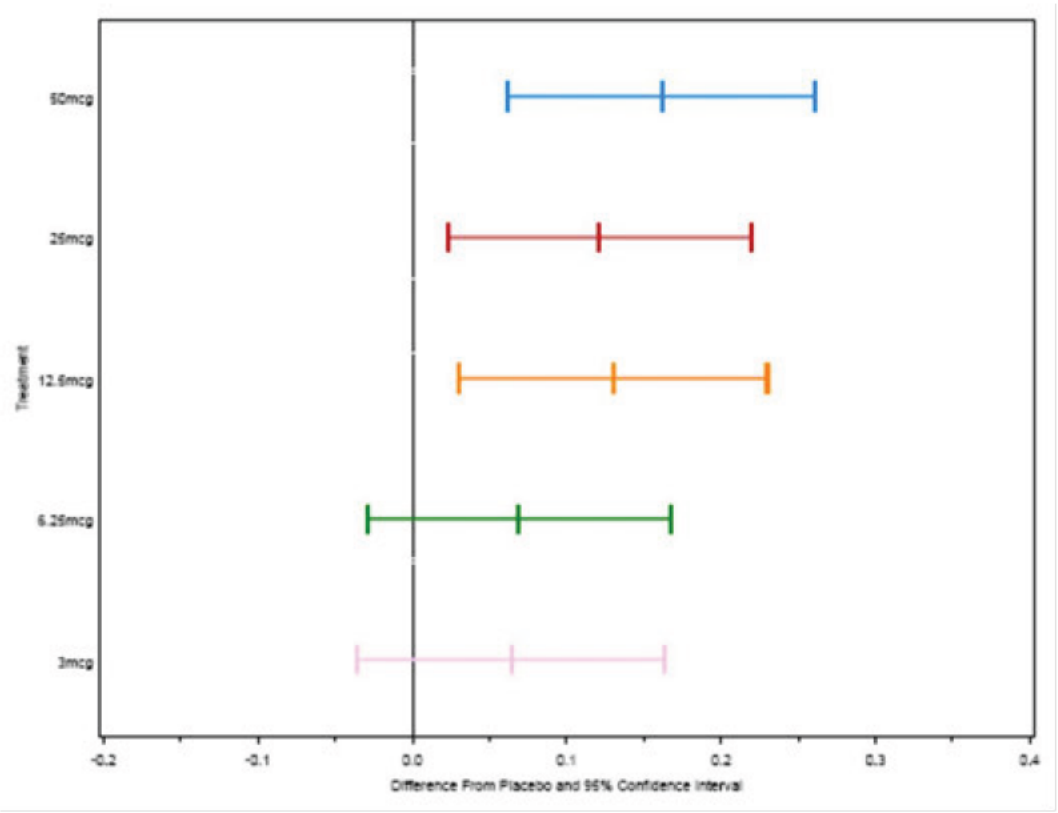
Trial B2C109575 evaluated the efficacy and safety of five doses of VI (3, 6.25, 12.5, 25, and 50 mcg) administered once-daily compared with placebo in subjects ≥ 12 years of age with persistent asthma uncontrolled on ICS alone. The primary efficacy endpoint was the mean change from baseline trough FEV1 at the end of 28 days of treatment. As can be seen in Table 4, the 12.5, 25, and 50 mcg doses provided statistically significant benefit compared to placebo. The FEV1 time curve was suggestive of a dose-dependent effect, although the benefit of higher doses appeared to dissipate towards the end of dosing, and a lower treatment effect for 12.5 mcg versus 25 mcg was seen at earlier time points as depicted in Figure 1. However, clinical symptom endpoints were greater for the 25 mcg dose compared to the 12.5 mcg dose. Subsequently, this trial supported carrying forth the 25 mcg dose.

Table 4. Trial B2C109575: VI-Dose Ranging

	Placebo N = 95	VI 3 N = 98	VI 6.25 N = 99	VI 12.5 N = 97	VI 25 N = 99	VI 50 N = 100
LS Mean (L)	2.388	2.452	2.458	2.518	2.509	2.55
Change from placebo (L)		0.064	0.069	0.13	0.121	0.162

Table 4. Trial B2C109575: VI-Dose Ranging						
	Placebo N = 95	VI 3 N = 98	VI 6.25 N = 99	VI 12.5 N = 97	VI 25 N = 99	VI 50 N = 100
p-value		0.208	0.169	0.011	0.016	0.001
Source: CSR B2C109575 Table 12						

Figure 1. Trial B2C109575: Vilanterol Dose Ranging Adjusted treatment differences of change from baseline in trough FEV1 (LOCF) at Day 28



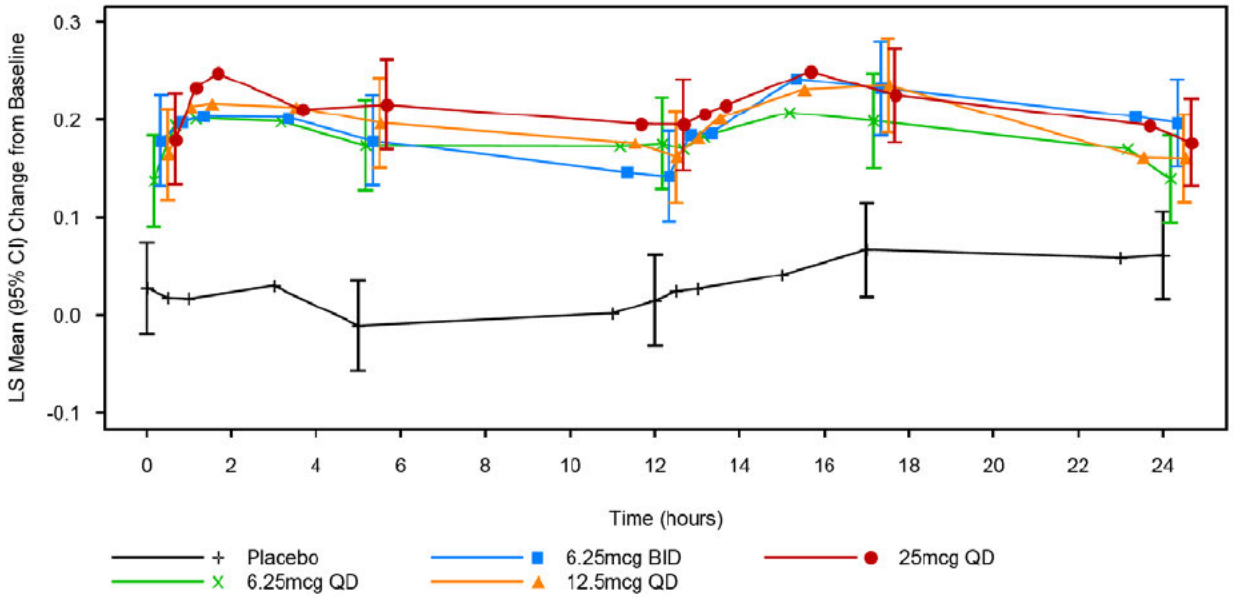
Source: CSR B2C109575 Figure 7.1

Trial HZA113310: VI Dose-Regimen Trial

The once-daily versus twice-daily dosing regimen was evaluated in Trial HZA113310, a randomized, double-blind, placebo-controlled, five-period, crossover trial in 75 adult patients with persistent asthma. This trial did not directly compare the nominal dose ultimately selected for Phase 3 trials, VI 25 mcg QD, to its divided dose counterpart, VI 12.5 mcg BID. However, a comparison of the serial FEV1 profiles for VI 12.5 mcg QPM and VI 6.25 mcg BID supports that BID dosing is not superior to QPM dosing (Table 5 and Figure 2). The shape of the serial FEV1 profile also indicates that an excessively high dose of VI was not selected in order to achieve an effect with once- daily dosing.

Table 5. Trial HZA113310: VI Dose-Regimen Trial				
	6.25 QD N = 73	6.25 BID N = 74	12.5 QD N = 73	25 QD N = 73
Trough FEV1: day 7 change from baseline				
LS mean change from placebo (L)	0.094	0.140	0.102	0.125
P value	<0.001	<0.001	<0.001	<0.001
Weighted mean FEV1 (0-24h): day 7 change from baseline				
LS mean change from placebo (L)	0.153	0.166	0.168	0.185
P value	<0.001	<0.001	<0.001	<0.001
Source: CSR HZA113310 Tables 13 and 14 QD = once daily, BID = twice daily				

Figure 2. Trial HZA113310: Day 7 Mean Change from Baseline in FEV1



Source CSR HZA113310 Figure 6.12

Trial B2C112060: VI Efficacy and Safety Trial/Comparison to Salmeterol

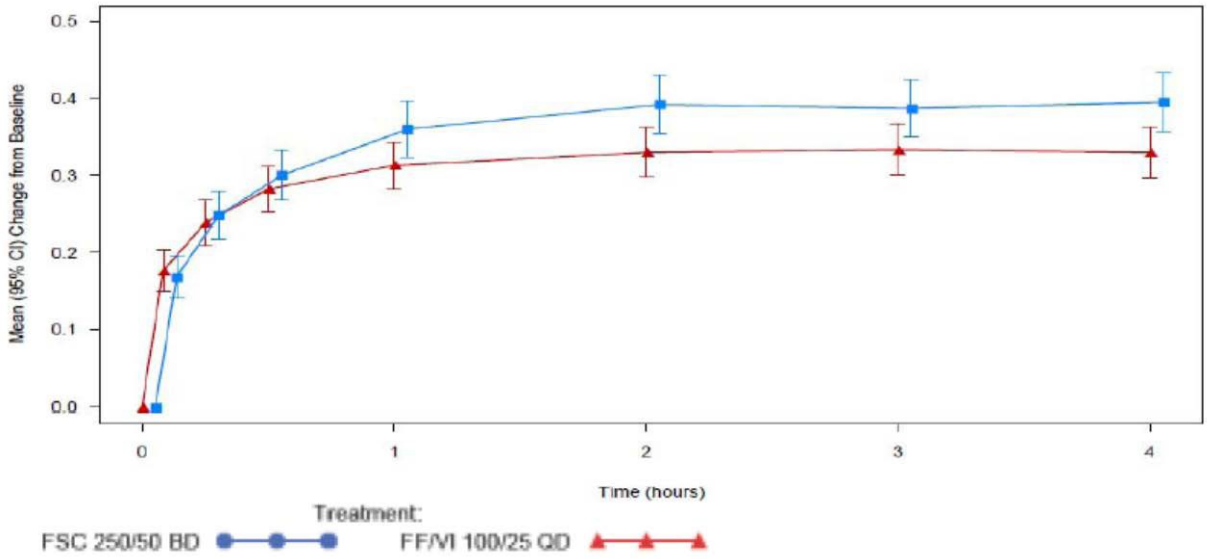
Trial B2C112060 provided a benchmark comparison for VI 25 mcg QD to another LABA, salmeterol 50 mcg BID. This was a 12-week, randomized, double-blind, double-dummy, placebo-controlled, parallel group trial in 347 adult and adolescent patients with persistent asthma uncontrolled on ICS. While patients treated with VI 25 mcg QD demonstrated a higher weighted mean 0-24 hour FEV1 (L) LS mean treatment increase from baseline compared to salmeterol 50 mcg BID (359 versus 283 ml), neither treatment group was statistically different from placebo. GSK has attributed this outcome to the

unexpectedly large increase in FEV1 observed in the placebo group (289 ml). Similar results were observed between the ITT and per-protocol analyses. Given the lack of a significant effect for salmeterol compared to placebo, the sensitivity of the assay is in question, making the results of Trial 2060 less straightforward.

The FF/VI program included other trials with an active comparator to help benchmark the bronchodilatory effects of VI. For example, trial HZA113091 was a 24-week, randomized, double-blind, double-dummy, parallel group trial in 806 adults with asthma comparing FF/VI 100/25 to Advair 250/50 (fluticasone propionate/salmeterol).
Although these trials did not include VI or salmeterol alone, review of the FEV1(0-4h) time curve after the first dose is informative. Neither the FF nor FP ICS component would be expected to have such an acute effect on FEV1, so these initial FEV1 time-curves can be viewed as a comparison of the two LABA components, VI 25 and salmeterol 50.

As can be seen in below, the effect of VI 25 in the first 4 hours after dosing is less than or approximates the effect of salmeterol. These results indicate that the selection of the VI 25 dose is conservative. Further discussion of the trial design and main results from these trials, including the 24-hour serial FEV1 profile at Day 84, are discussed in detail below in Section 6.

Figure 3. Trial HZA 113091: Raw mean change from baseline in FEV1 (0-4h) at Day 1



Source: Module 5.3.5, Complete Study Report Figure 3

Trial B2C111401: Single Dose Dose-Ranging Trial

Although not submitted as part of this sNDA application, Trial B2C11401 was reviewed as part of the original application. It is reviewed here as it provides information on VI 6.25 and 25 mcg versus placebo. The trial was a single-dose, double-blind, randomized, placebo controlled, five–way cross-over trial evaluating three doses of a previous formulation of VI and three doses (6.25, 25, and 100 mcg) of the to-be-marketed VI versus placebo. The primary endpoint was trough FEV1. VI 25 and 100 mcg, but not 6.25 mcg, showed statistical significance compared to placebo. The 6.25 mcg dose provided a

0.13 L improvement over placebo (p = 0.0067), the 25 mcg dose a 0.22 L improvement over placebo (p < 0.0001), and the 100 mcg group a 0.23 L improvement over placebo (p < 0.0001). As there was no significant separation between the 25 and 100 mcg doses, it is appropriate that the 25 mcg dose was bought forth for registration.

Trial HZA114624: FF/VI Dose Regimen Trial

Another trial, HZA114624, examined FF/VI 100/25 mcg QAM versus QPM dosing and found that there was no difference between the two dosing regimens (data not shown).

4.4.2.2 Fluticasone Furoate Dose Ranging

All dose ranging trials were reviewed as part of this original NDA by Dr. Sofia Chaudhury and by this reviewer as part of NDA 205625 (Arnuity Ellipta®). Dose selection was studied in three primary trials, FFA 109687, 109685, and 109684. Once versus twice daily dosing was studied in trial FFA112202 and FFA106783. Morning versus evening dosing was examined in FFA20001 and FFA106783.

Based on these trials, appropriate doses of 50, 100, and 200 mcg dosed once-daily were carried into Phase 3 development.

Trial FFA109687: FF Dose-Selection Trial

Trial FFA109687 was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, dose-ranging trial evaluating four doses of FF (25, 50, 100, and 200 mcg) once daily, FP (fluticasone propionate) 100 mcg twice-daily, and placebo. A total of 601 adult and adolescent patients with persistent asthma, uncontrolled on non-ICS maintenance therapy, received treatment for eight weeks. The primary endpoint was a change from baseline in trough FEV1 at Week 8. All doses except the 25 mcg dose demonstrated a statistically significant benefit over placebo.

Trial FFA109685: FF Dose-Selection Trial

Trial FFA109685 was similarly designed to FFA109687; however 109685 evaluated higher doses of FF (100, 200, 300, and 400 mcg). Subsequently, the FP comparator arm was 250 mcg BID, and the patient population was controlled on low-dose ICS. A total of 615 patients uncontrolled on low-dose ICS were randomized, and the primary endpoint was change in baseline FEV1 at week 8. All doses showed a statistically significant benefit over placebo, however there was little dose response for doses above FF 200 mcg (see

Figure 4).

Trial FFA109684: FF Dose-Selection Trial

Trial FFA109684 was similarly designed and evaluated even higher dosage strengths of FF (200, 400, 600 and 800 mcg). Subsequently, the FP comparator was 500 mcg BID. A total of 622 subjects with asthma uncontrolled on medium-dose ICS were randomized; the patient population was more severe, being uncontrolled on medium-dose ICS. A total of 622 subjects were randomized, and the primary endpoint was change in baseline FEV1 at week 8. All doses showed a statistically significant benefit over placebo as shown in Table 6.

Table 6. Results of FF Dose-Ranging Trials

		FF once daily								FP twice daily		
	PBO	25	50	100	200	300	400	600	800	100	250	500
Week 8 Change from Baseline Trough FEV1												
Trial 109687												
N	93	94	97	109	94					101		
LS[1]		0.101	0.129	0.204	0.23					0.106		
P value		0.095	0.033	<0.001	<0.001					0.074		
Trial 109685												
N	106			102	101	102			97		99	
LS[1]				0.207	0.238	0.293			0.279		0.225	
P value				< 0.001	< 0.001	< 0.001			< 0.001		< 0.001	
Trial 109684												
N	103				98		101	107	102			107
LS†					0.275		0.272	0.264	0.225			0.198
P value					<0.001		<0.001	<0.001	<0.001			<0.001

† LS Mean Change from placebo (L)
Source: CSR 109687 Table 11,109685 Table 11, 109684 Table11
FP = fluticasone propionate, PBO = placebo

A dose effect was seen; however, benefit did not increase with doses over 200 mcg as shown in

Figure 4.

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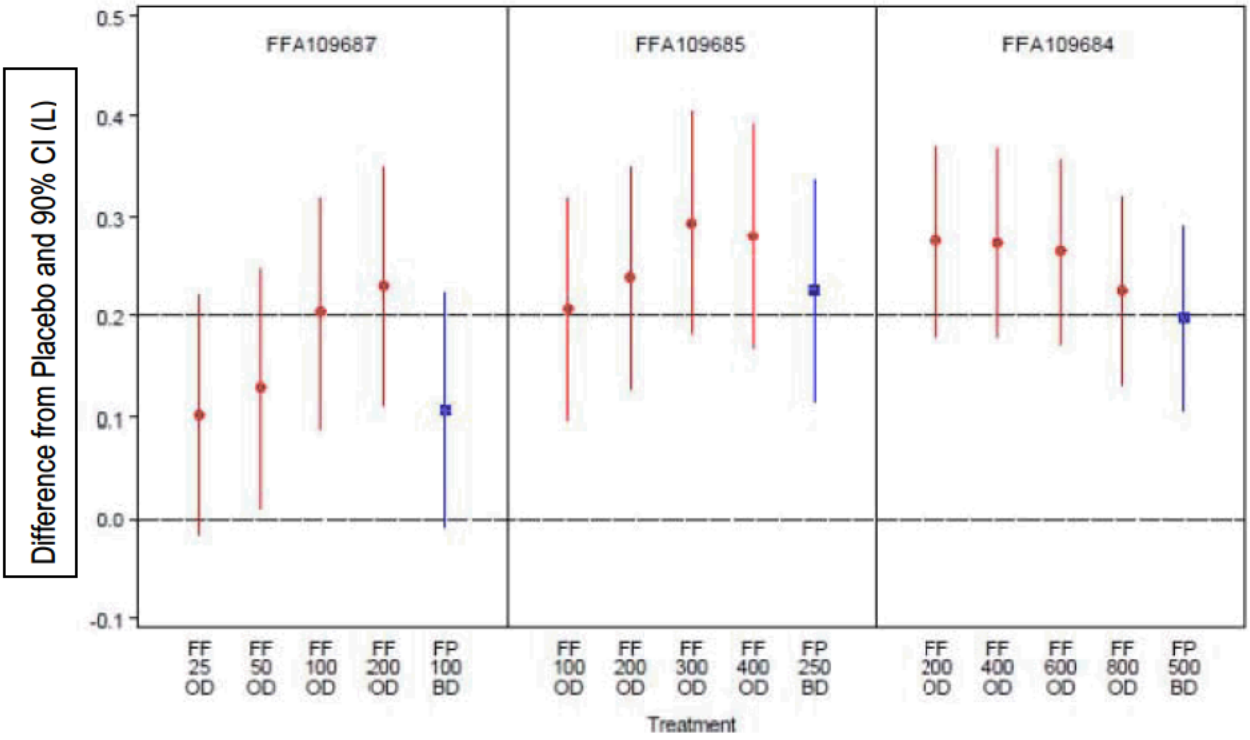
Figure 4. FF Dose-Ranging Trials



Source: Clinical Overview, Figure 1

Trial FFA112202: FF Dose-Regimen Trial

Trial FFA112202 was a multicenter, randomized, double-blind, cross-over trial evaluating the non-inferiority of once daily versus twice daily dosing of FF 100 mcg in 190 adult and adolescent patients 12 years of age and older. Additional treatment arms included FP 200 mcg in the evening, FP 100 mcg twice daily, and placebo. Subjects entered a 2 week run-in period followed by randomization to 1 of 12 sequences: 6 cross-over sequences including FF 200 daily, FF 100 twice daily, and placebo OR FP 200 once daily, FP 100 twice daily, and placebo. Each treatment period was separated by a 14-day washout period. The primary efficacy endpoint was trough FEV1 at the end of each 28-day treatment period. A similar treatment effect was noted for the once daily dosing and the twice daily dosing (p=0.641); these results are shown in Table 7. Thus, the doses of 50, 100, and 200 mcg once daily were carried forward into phase 3 development. (b) (4)

Table 7. Trial FFA112202: FF Dose-Regimen Trial

	FF 200 QD N=140	FF 100 BID N = 142	FP 200 QD N = 42	FP 100 BID N = 43
Trough FEV1: LS mean change from baseline at Day 28				
LS mean change from placebo (L)	0.108	0.098	0.087	0.132
P value	<0.001	<0.001	<0.001	<0.001
LS mean change from FF 100 BID (L)	0.011			

Table 7. Trial FFA112202: FF Dose-Regimen Trial				
	FF 200 QD N=140	FF 100 BID N = 142	FP 200 QD N = 42	FP 100 BID N = 43
P value	0.641			
Source: CSR FFA112202 Table 12 BID = twice a day, FP = fluticasone propionate, QD = once a day				

Trial FFA20001: FF Dose-Regimen Trial

Trial FFA20001 was a Phase 2 randomized, double-blind, double-dummy, placebo-controlled, parallel-group, multi-center study which examined morning versus evening dosing of FF 100 mcg. 545 subjects were randomized to FF 100 QAM, FF 100 QPM, FF 250 QPM, or placebo for 28 days. The primary endpoint was mean change from baseline in daily trough PEF. The study found no difference between the two dosing regimens (data not shown).

Trial FFA106783: FF Dose-Regimen Trial

Trial FFA106783 was a Phase 2 multi-center, randomized, double-blind, parallel group, placebo-controlled study which examined both once versus twice daily dosing as well as morning versus evening dosing (FF 200 mcg BID, FF 400 mcg QAM, 400 mcg QPM, FF 200 mcg QAM, and placebo.) There was no difference between morning and evening dosing. Once daily PM dosing was similar to twice daily dosing, and although once-daily AM dosing had a smaller difference in trough FEV1 versus placebo than the twice daily dosing, the difference was still highly statistically significant ($p < 0.001$), thus supporting once daily dosing (data not shown).

Reviewer's Comment: The sponsor has provided sufficient evidence for the chosen FF dose and dosing regimen brought forth for registration.

4.4.3 Pharmacokinetics

The preliminary assessment of the clinical pharmacology review is for Approval; however, final recommendations are pending at the time of this review. For further details, see clinical pharmacology review by Dr. Jianmeng Chen.

Compared with healthy subjects FF Cmax and AUC(0-24) following FF/VI 200/25 was 18% and 7% lower, respectively, in subjects with asthma. Compared with healthy subjects VI Cmax and AUC(0-24) was 62% and 21% lower in subjects with asthma. Similar differences were also observed following FF/VI 100/25.

VI clearance is decreased by 27% in patients > 65 years of age resulting in a higher $AUC_{(0-24)}$ in these patients. There was no difference in systemic exposure to either FF or VI in adolescent (12-17 years) subjects with asthma compared with adult (≥18 years) subjects with asthma. No difference in exposure for patients > 65 years of age is seen for FF in subjects with COPD. There was no influence of gender on PK for either FF or VI. However, systemic exposure of FF for East Asian, Japanese and South Asian patients are, on average, 23%-49% higher compared to white Caucasians; there was no effect of race on the pharmacokinetics of VI in subjects with COPD.

In subjects with mild, moderate or severe hepatic impairment, repeat administration of FF/VI resulted in greater FF systemic exposure (up to three-fold) and a reduction in serum cortisol by 34% compared with healthy subjects. There was no effect of hepatic impairment on VI systemic exposure. Caution should be taken when used in those with hepatic impairment, but no dose adjustments are recommended.

Co-administration with ketoconazole results in a modest increase in mean FF and VI $AUC_{(0-24)}$ and C_{max} (FF 36% and 33%; VI 65% and 22%); however no dose adjustment is recommended for FF/VI when co-administered with ketoconazole.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The dose ranging studies for the individual components FF and VI have been reviewed as part of the Breo COPD and Arnuity asthma programs, and their results are summarized in Section 4.

The FF dose-ranging and regimen trials are summarized in Table 8. The VI dose-ranging and regimen trials are summarized in Table 9.

Table 8. Fluticasone Furoate Dose-Ranging Trials

Trial (Dates)	Design	Population (n randomized)	Treatment arms	N (ITT)	Primary Endpoint	Sites (Countries)
Fluticasone furoate – Dose-ranging studies						
FFA 109684 *(12/07-9/08)*	R, PC, DB, PG 8 weeks	Asthma (622) Uncontrolled on med dose ICS	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	99 101 107 102 110 103	Trough FEV1	*94 (US, Canada, Mexico, Europe, Australia, S. Africa, Thailand)*
FFA 109685 *(12/07-11/08)*	R, PC, DB, PG 8 weeks	Asthma (615) Uncontrolled on ow dose ICS	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo BID	105 101 103 99 100 107	Trough FEV1	*98 (US, Canada, Mexico, Europe Korea, Philippine, S. Africa)*
FFA 109687 *(9/11-10/12)*	R, PC, DB, PG 8 weeks	Asthma (598) Uncontrolled without ICS	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo BID	97 100 110 95 110 94	Trough FEV1	*107 (US, Canada, Mexico, Korea, Europe, Peru, Philippines)*

Table 8. Fluticasone Furoate Dose-Ranging Trials

Trial (Dates)	Design	Population (n randomized)	Treatment arms	N (ITT)	Primary Endpoint	Sites (Countries)
Fluticasone furoate – Dose-regimen study						
FFA 112202 *(10/08-3/09)*	R, DB, PC, XO 4 weeks	Asthma (190) Uncontrolled without ICS	FF 200 QD PM FF 100 BID FP 200 QD PM FP 100 BID Placebo	140 142 42 43 187	Trough FEV1	*16 (US)*

Source: Module 5.2, Tabular listing of all studies and individual CSR
R = randomized, DB = double-blind, PC = placebo controlled, PG=parallel group, XO=cross-over; N=North, S=South, US=United States

Table 9. Vilanterol Dose-Ranging Trials

Study	Design	Population (n randomized)	Treatment	N (ITT)	Primary Endpoint	Sites (Countries)
B2C 109575 *(12/07-9/08)*	R, PC, DB, PG 4 weeks	Asthma FEV1 40-90%	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD Placebo QD	101 101 101 101 101 102	Trough FEV1	*88 (US, Canada, Europe, S. America, Korea, Philippines, Thailand, S. Africa)*
Vilanterol -- Dose Regimen Study						
HZA 113310 *(4/08-10/08)*	R, PC, DB, XO 1 week	Asthma FEV1 40-85%	VI 6.25 QD VI 6.25 BID VI 12.5 QD VI 25 QD Placebo QD	75	Trough FEV1 Serial FEV1	*9 (US)*
Comparison to Salmeterol						
B2C 112060 *(9/10-8/11)*	R, DB, DD, PC, PG 12 weeks	Asthma (347) FEV1 40 -90%	VI 25 QD Sal 50 BID Placebo	115 116 116	0-24 hour weighted mean serial FEV1	*34 (Europe, S. America, US)*

Sources: Module 5.2, Tabular listing of all studies, individual CSRs
FF = fluticasone furoate, VI=vilanterol, GW64244=(b) (4) of vilanterol (earlier formulation), R = randomized, PC =placebo controlled, DB = double blind, PG = parallel group, XO = cross over, SD = single dose, S.=South

The information to support the efficacy/safety of FF/VI for the treatment of asthma is derived primarily from four trials (HZA106827, HZA116863, HZA106829, and HZA106837). In addition to these four key trials, GSK conducted one trial (HZA113091) in asthma comparing FF/VI to Advair (fluticasone propionate/salmeterol). This trial provides an additional benchmark comparison for FF/VI. Trial HZA106839 is also included in the review as a long-term safety trial. Table 10 summarizes the efficacy trials.

The protocols for the efficacy/safety trials are reviewed in Section 5. The results of the efficacy trials and the active comparator trials are reviewed in Section 6. The general safety and long-term safety trials are reviewed in Section 7.

Table 10. Clinical Development Program

Study (*Dates*)	Design	Treatment	N	Population	Duration (weeks)	Primary Endpoint(s)	Sites *Countries (n)*
Efficacy and Safety Trials							
HZA 106827 (8/10-10/11)	MC, R, DB, PG, PC	FF/VI 100/25 QD FF 100 QD Placebo QD	201 205 203	Asthma FEV1 40-90%	12	Trough FEV1 0-24 hour weighted mean serial FEV1	*US (196), Poland (124), Romania (89), Ukraine (83), Germany (67), Japan (50)*
HZA 116863 *(9/12-10/13)*	R, DB, PG	FF/VI 100/25 QD FF/VI 200/25 QD FF 100 QD	346 346 347	Asthma FEV1 40-80%	12	0-24 hour weighted mean serial FEV1 Trough FEV1 (powered secondary endpoint)	*US (31), Russia (20), Argentina (13), Germany (12), Romania (12), Ukraine (11), Chile (7), Netherlands (7), Poland (6), Mexico (3), Sweden (3)*
HZA 106829 *(6/10-10/11)*	MC, R, DB, PG, AC	FF/VI 200/25 QD FF 200 QD FP 500 BID	197 194 195	Asthma FEV1 40-90%	24	Trough FEV1 0-24 hour weighted mean serial FEV1	*Russia (163), US (143), Romania (117), Germany (66), Poland (61), Japan (36)*
HZA 106837 *(2/10-9/11)*	R, DB, PG	FF/VI 100/25 QD FF 100 QD	1009 1010	Asthma FEV1 $\geq$ 50%	Up to 76 weeks	Time to first asthma exacerbation	*US (373), Russia (300), Mexico (233), Ukraine (231), German (179), Argentina (159), Poland (156), Philippines (154), Romania (153), Japan (62), Australia (19)*
Long-Term Safety Trial							
HZA 106839 *(10/09-5/11)*	R, DB, DD, AC, PG	FF/VI 100/25 QD FF/VI 200/25 QD FP 500 BID	201 202 100	Asthma FEV1 $\geq$ 50%	52	Safety	*US (17), Germany (14), Ukraine (10), Thailand (4)*
Active Comparator Trial							

Table 10. Clinical Development Program

Study (*Dates*)	Design	Treatment	N	Population	Duration (weeks)	Primary Endpoint(s)	Sites *Countries (n)*
HZA 113091 *(6/10-7/11)*	MC, R, DB, DD, PG	FF/VI 100/25 QD FP/salmeterol 250/50 BID	403 403	Asthmatics FEV1 40-85%	24	0-24 hour weighted mean serial FEV1 Trough FEV1	*US (26), Argentina (10),Chile (7), S. Korea (7), Netherlands (7), Philippines (7)*

Source: Module 5.2, Tabular listing of all studies, individual CSR; FP=Fluticasone propionate, R=randomized, PC =placebo controlled, DB =double blind, PG = parallel group, PC=placebo controlled, AC=active controlled

The pooled safety database consists of 18 completed parallel-group phase 2 and 3 studies conducted with the Ellipta inhaler. Not all of these studies included an FF/VI arm as seen in the table below.

Table 11. Pooled Safety Database

		FF (mcg) once a day								FF/VI (mcg) once a day		VI
	Placebo	**25**	**50**	**100**	**200**	**300**	**400**	**600**	**800**	**100/25**	**200/25**	**25**
All studies[1]	858	97	338	1663	608	103	200	107	102	2369	956	218
4 week												
B2C109575 (VI Asthma Dose Ranging)												103
6 week												
HZA106851 (HPA axis)	56									56	56	
8 week												
FFA109687 (FF Dose Ranging)	94	97	100	110	95				102			
FFA109685 (FF Dose Ranging)	107			105	101	103	99					
FFA109684 (FF Dose Ranging)	103				99		101	107				

Table 11. Pooled Safety Database

		FF (mcg) once a day								FF/VI (mcg) once a day		VI
	Placebo	25	50	100	200	300	400	600	800	100/25	200/25	25
All studies[1]	858	97	338	1663	608	103	200	107	102	2369	956	218
12 week												
FFA115283 (FF 50 mcg Trial)	121		121									
HZA106827 (FF/VI Confirmatory Trial)	203			205						201		
HZA113719 (FF 100/25 v P; Asian)	154									153		
HZA116863 (FF/VI Confirmatory Trial)				347						346	346	
HZA113714 (FF/VI 200/25 v FP 500; Asian)											155	
B2C112060 (VI v salmeterol)	118											115
24 week												
FFA115285 (FF 50 mcg Trial)	115		117									
FFA114496 (FF Confirmatory Trial)				119	119							
FFA112059 (FF Confirmatory Trial)	115			114								
HZA106829 (FF/VI Confirmatory Trial)					194						197	
HZA113091 (FF/VI 100/25 v Advair 250)										403		
52 weeks												
HZA106839 (Long-term safety)										201	202	
Up to 76 weeks												
HZA106837 (Long-term safety)				1010						1009		

Source: Tabular Listing of Studies

5.2 Review Strategy

This clinical review will focus on those studies which are clinically relevant to demonstration of the efficacy and safety of FF/VI 100/25 mcg and 200/25 mcg. The dose-ranging studies have been previously reviewed in detail as part of this original NDA application for COPD and as part of the FF application for asthma (NDA 205625), and are summarized in Section 4.4.2.

The protocols of the confirmatory trials, additional safety trials, and the comparator trial are described in Section 5.3. The efficacy and safety results are reviewed in Section 6 and Section 7, respectively. Any supportive efficacy and safety data generated from other trials are reviewed in the applicable efficacy or safety section.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Confirmatory Trials

5.3.1.1 Trial HZA106827

Administrative Information:

- Study Title: A randomized, double-blind, placebo-controlled (with rescue medication), parallel group multi-center study of fluticasone furoate/GW642444 inhalation powder and fluticasone furoate Inhalation powder alone in the treatment of persistent asthma in adults and adolescents
- Study Dates: 8/20/2010-10/19/2011
- Study Sites: US (196), Poland (124), Romania (89), Ukraine (83), Germany (67), Japan (50)
- Study Report Date: April 2012

Objectives/Rationale

Primary:

- To compare the efficacy and safety of FF/VI inhalation powder 100/25 mcg and FF 100 mcg both administered once-daily in the evening in adolescent and adult subjects, 12 years of age and older, with persistent bronchial asthma over a 12-week treatment period

Study Design and Conduct

Overview:
This was a 12-week, multi-center, randomized, double-blind, placebo-controlled (with rescue medication), parallel group study. Subjects meeting all the eligibility criteria during visit 1 entered a four-week run-in period. At visit 3 (end of run-in), subjects were stratified according to their concurrent asthma medication (ICS or ICS/LABA). Once stratified, subjects were randomized to one of the following treatments via the NDPI for 12 weeks:

- FF/VI (100 mcg/25 mcg) once daily in the evening
- FF (100 mcg) once daily in the evening
- Placebo once daily in the evening

Randomized subjects attended four on-treatment visits at visits 4, 5, 6 and 7 (weeks 2, 4, 8 and 12, respectively). A follow-up clinic visit (visit 8) was performed 2 weeks after completing study medication. Subjects participated in the study for up to a maximum of 18 weeks from screening to follow-up. The schedule of assessments is shown in Table 12.

Table 12. Study Assessments: Trial HZA106827

Visit	1	2	3	4	5	6	7	EW	8
Week	-4	-2	0	2	4	8	12		
Day	-28	-14	0	14	28	56	84		14 post V7 or EW
Written Informed Consent	X								
Subject Demography	X								
Medical History	X								
Asthma History	X								
Therapy History	X								
Physical Exam	X						X	X	
Inclusion/ Exclusion Criteria	X		X						
Efficacy Assessments									
Spirometry Pulmonary Function	X		X	X	X	X	X	X	
Reversibility	X								
Serial FEV_1 (0-24h)			X[1]				X[1]		
Issue Subject Diaries	X								
Subject Diary Review & Upload		X	X	X	X	X	X	X	
Safety Assessments									
Concomitant Medication	X	X	X	X	X	X	X	X	X[2]
OP Examination	X		X	X	X	X	X	X	
12-lead ECG		X	X[3]				X[3]	X	
Vital Signs	X		X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X
Serious Adverse Events	X[5]	X[5]	X[5]	X	X	X	X	X	X
Laboratory Assessments									
Hematology	X								
Chemistry (includes liver safety testing)	X						X	X	
Glucose and Potassium in subset of subjects			X[4]				X[4]		
PGx				X[6]					

Table 12. Study Assessments: Trial HZA106827

Visit	1	2	3	4	5	6	7	EW	8
Week	-4	-2	0	2	4	8	12		
Day	-28	-14	0	14	28	56	84		14 post V7 or EW
Sampling (one visit only)									
Serum pregnancy test	X						X	X	
Urine Pregnancy test			X						X
24-hr Urine Collection Supplies dispensed		X				X			
24-hr Urine collection			X				X		
HBsAg and hepatitis C antibody screening	X								
PK sampling						X[7]	X[7]		
Questionnaires									
ACT	X		X				X	X	
AQLQ (+12)			X				X	X	
Global Change					X	X	X	X	
Inhaler use assessment			X	X	X				
Ease of use questions for inhaler					X				
Unscheduled Healthcare Contact			X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	

Source CSR 106827 Table 3

1.In addition to pre-dose assessment (within 30 minutes prior to dosing at Visit 3 and within 5 minutes prior to dosing at Visit 7), serial FEV_1 measurements were taken at 5, 15,30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours post-dose.

2.Concomitant medication details collected for adverse events only between end of treatment and Follow-up Visit.

3.ECGs: Pre-dose ECGs at Visit 2, Visit 3, Visit 7 and Early Withdrawal in all subjects. In addition post-dose (5-20minutes for VI) assessments at Visit 3 (Day 0) and Visit 7 (end of 12 weeks of treatment) in subset of subjects NOT performing Serial Lung Function measurements.

4.Potassium and Glucose: Pre-dose in all subjects at Visit 3 and Visit 7. In addition post dose (5-20 minutes) at Visit 3 (Day 0) and Visit 7 (end of 12 weeks of treatment) in subset of subjects performing Serial Lung Function measurements. Subjects were not to be fasted for ≥4hours prior to blood draw.

5.SAEs related to study participation that occurred during Run-in were recorded in the eCRF.

6.The PGx sample could be collected at any one visit after the PGx consent had been signed and the subject had been randomized.

7.Upon arrival at the clinic, a 4 mL blood sample was collected and the subjects administered their evening dose of study medication after all pre-dose assessments were completed. Prior to leaving the clinic, two more 4mL blood samples were collected from the subject between 5-15 minutes post-dose and between 1 – 1.5 hours post dose.

8.To be completed if associated with an asthma exacerbation and for any other asthma-related health care utilization.

Study Population

Inclusion Criteria

- Male or female subjects ≥ 12 years of age at visit 1
- Asthma diagnosis per NIH definition for at least 12 weeks with
    - FEV1 40-90% at visit 1 based on NHANES III
    - Post SABA ≥12% and ≥200 mL reversibility of FEV1
    - On a stable dose of ICS or ICS/LABA for at least 4 weeks prior to visit 1

Exclusion Criteria

- History of life-threatening asthma in the past 10 years
- Unresolved respiratory infection in the past 4 weeks prior to visit 1 that led to a change in asthma medication or status
- Asthma exacerbation requiring oral corticosteroids or overnight hospitalization within 3 months prior to visit 1
- Concurrent respiratory disease or any clinically significant uncontrolled condition
- No visual evidence of candidiasis at visit 1
- Could not have used any investigational drug within 30 days prior to visit 1, or within five half-lives of the prior investigational drug
- Could not have used inhaled tobacco products in the 3 months prior to screening or have historical use of ≥10-pack years
- Severe milk protein allergy or specific drug allergies, or used prohibited medications as listed below within the specified time periods
    - Within 12 weeks of visit 1 and during the study:
        - Systemic steroids
        - Xolair
    - Within 1 day of visit 1 and during the study:
        - Inhaled, oral, or transdermal long-acting beta 2-agonists
        - Theophyllines
        - Anti-leukotrienes including suppression of leukotriene production and antagonists
        - Anticholinergics
        - Ketotifen
        - Nedocromil sodium
        - Sodium cromoglycate
    - Up to and including the morning of randomization (visit 2):
        - Inhaled corticosteroids: Subjects must have been maintained on a stable dose for 4 weeks prior to visit 1 and throughout the run-in period
    - Subjects could not concurrently use any other prescription or over-the-counter medication which may affect the course of asthma, or affect ICS metabolism (visit 1 to visit 7 inclusive), such as cytochrome P450 3A4 inhibitors or β-adrenergic blocking agents
- Not have been previously treated with FF or FF/vilanterol
- No subject was permitted to perform night shift work for 1 week prior to visit 1 until completion of the study treatment period

Withdrawal Criteria

Reasons for withdrawal included:

- Subject experienced an adverse event
- Subject was lost to follow-up
- Subject experienced a protocol violation
- Subject experienced lack of efficacy
- The sponsor terminated the study
- Non-compliance
- Pregnancy
- Abnormal liver function test
- Abnormal laboratory results

A subject who met any of the following criteria was also to be withdrawn from the study:

- FEV1 below the FEV1 stability limit value (calculated as best pre-salbutamol/albuterol FEV1 at visit 2 x 80%)
- During the 7 days immediately preceding any visit, the subject experienced either at least 4 days in which the PEF fell below the PEF stability limit (calculated as the mean morning PEF from the available 7 days preceding Visit 2 x 80%) or at least 3 days in which ≥12 inhalations/day of albuterol/salbutamol were used
- Subjects who experienced a protocol-defined severe exacerbation
- Clinical asthma worsening, which in the opinion of the investigator required additional asthma treatment other than study medication or study supplied albuterol/salbutamol
- When liver chemistry threshold criteria were met
    - ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
    - ALT ≥8xULN
    - ALT ≥5xULN, but <8xULN that persists for ≥2 weeks
    - ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
    - ALT ≥5xULN, but <8xULN and cannot be monitored weekly for >2 weeks

Permitted Medications

- Stable dose, for at least 4 weeks prior to visit 1, of an ICS
- Decongestants
- Intranasal corticosteroids
- Immunotherapy was permitted provided it was initiated 4 weeks prior to visit 1 and the subject remained in the maintenance phase for the duration of the study
- Topical corticosteroids (≤1% hydrocortisone cream)
- Non-corticosteroid containing creams
- Short-acting and long-acting antihistamines

Study Treatments

Treatment groups were as follows:

- FF 100 mcg one inhalation once daily in the evening via DPI
- FF/VI 100/25 mcg one inhalation once daily in the evening via DPI

- Placebo one inhalation once daily in the evening via DPI

All treatments were double-blinded. For the placebo, the DPI contained the same foil packs with the active drug moieties removed with all other excipients remaining the same.

Compliance

Compliance was assessed by reviewing the dose counter on the NDPI at visits 4-7, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Co-primary Endpoints

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 84-week treatment period
- Weighted mean serial FEV1 over 0-24 hours post-dose calculated in a subset of subjects at the end of the 84-day double-blind treatment period. 24-hour serial FEV1 included post-dose assessments after 5, 15, 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours

Powered Secondary Endpoint

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period

Secondary Endpoints

- Change from baseline in the percentage of symptom-free 24-hour periods during the 12-week treatment period
- Change from baseline in total AQLQ (+12) score at the end of 12-week treatment period
- The number of withdrawals due to lack of efficacy during the 12-week treatment period

Other Endpoints

- Clinic visit 12-hour FEV1 at the end of the 84-day treatment period and was assessed in the subset of subjects that were performing serial FEV1 assessments
- Weighted mean serial FEV1 over 0-24 hours post-dose calculated in a subset of subjects on day 0
- Weighted mean serial FEV1 over 0-4 hours post-dose calculated in the subset of subjects that were performing serial FEV1 assessments, on day 0 and day 84
- Time to onset of bronchodilator effect taken from serial measurements at visit 3
- Mean change from baseline in daily AM PEF averaged over the 12-week treatment period
- Mean change from baseline in daily PM PEF averaged over the 12-week treatment period
- Change from baseline in Asthma Control Test (ACT) at the end of the 12-week treatment period
- Global Assessment of Change at the end of 4, 8, and 12 weeks of treatment
- Unscheduled healthcare contacts/resource utilization (for severe asthma exacerbations and other asthma-related health care)

- Inhaler-use assessment at randomization, at the end of 2 weeks and 4 weeks of treatment
- Ease of use questions on inhaler at end of 4 weeks of treatment

Safety Endpoints

- Incidence of adverse events throughout the 12-week treatment period
- Incidence of severe asthma exacerbations throughout the 12-week treatment period
- Incidence of oropharyngeal candidiasis assessed by examination of the oropharynx at all clinic visits, including early withdrawal
- Clinical chemistry before and after the 12-week treatment period
- Serum potassium and glucose pre-dose on day 0 and 5-20 minutes post dose (Tmax for VI) on the first and last day of dosing in subset of subjects performing serial FEV1 assessments. Subjects were fasted for ≥ 4 hours prior to blood draw. The following endpoints were derived:
    - change from baseline in potassium at day 0 and day 84
    - change from baseline in glucose at day 0 and day 84
- Liver function safety assessments at screening (visit 1) and week 12 (visit 7) or early withdrawal visit
- 24-hr urine cortisol excretion assessment before and at the end of the 12-week treatment period
- Vital signs (including pulse and blood pressure) were assessed at all clinic visits prior to dosing in all subjects. The following endpoints were derived:
    - change from baseline in systolic blood pressure (BP) at day 84
    - change from baseline in diastolic BP at day 84
    - change from baseline in pulse rate at day 84
- 12-lead ECG before dosing on day 0 and day 84 in all subjects
- In addition, for subjects NOT performing serial FEV1 measurements (~40%) 12-lead ECG was also performed post-dose at Tmax (5-20 minutes for VI) on the first and last day of dosing (day 0 and day 84) to derive the mean QTc and change from baseline in mean QTc

Statistical Plan

Approximately 570 subjects were randomized in a ratio of 1:1:1 to give 190 randomized subjects per arm. The sample size calculation assumed a 5% withdrawal rate in the first 2 weeks of the study and a 15% withdrawal rate over the whole treatment period of the study. This ensured 180 subjects per arm who contributed to the analysis of trough FEV1 and the analysis of % rescue-free 24-hour periods. 60% of all randomized subjects had serial FEV1 measurements at week 12 if they completed the treatment period. A 15% withdrawal rate ensured 96 subjects per arm who contributed to the analysis of weighted mean serial FEV1 over 0-24 hours at week 12.

The overall power of the study to detect treatment differences across the specified treatment comparisons for the co-primary endpoints and the nominated secondary endpoint was 83%.

The primary population for all analyses of efficacy and safety measures (excluding urinary cortisol analyses) was the ITT population which was comprised of all subjects who were randomized to treatment and who received at least one dose of study medication.

The primary analysis for both co-primary endpoints was performed using an Analysis of Covariance (ANCOVA) model allowing for the effects due to baseline (pre-dose measurement on day 0) FEV1, region, sex, age and treatment group. Estimated treatment differences for treatment comparisons were presented together with 95% Confidence Intervals (CIs) for the mean differences and p-values for comparisons, as appropriate.

For the analysis of trough FEV1, Last Observation Carried Forward (LOCF) was used to impute missing data. A supporting analysis was also performed using a Repeated Measures Mixed Model. Missing data were not implicitly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the day 84 treatment effects.

Protocol Amendment

The original protocol was amended twice:

- August 31, 2010
  - Applied to all sites
  - Added a new European Union and International Medical Monitor
  - Extended the pre-dose FEV1 and dosing timeline from 5 to 30 minutes
- April 6, 2011
  - Only applied to sites in Poland
  - Allowed adolescent subjects to be considered for study participation in order to meet the elements of the PIP agreed with by the EMA to randomize at least 68 adolescent subjects

5.3.1.2 Trial HZA116863

Administrative Information:

- Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study of Fluticasone Furoate/vilanterol 200/25 mcg Inhalation Powder, Fluticasone Furoate/vilanterol 100/25 mcg Inhalation Powder, and Fluticasone Furoate 100 mcg Inhalation Powder in the Treatment of Persistent Asthma in Adults and Adolescents
- Study Dates: 9/20/12-10/15-13
- Study Sites: US (31), Russia (20), Argentina (13), Germany (12), Romania (12), Ukraine (11), Chile (7), Netherlands (7), Poland (6), Mexico (3), Sweden (3)
- Study Report Date: February 2014

Objectives/Rationale

Primary:

- To compare the efficacy and safety of FF/VI 100/25 and FF 100, both administered once-daily in the evening in adolescent and adult subjects, 12 years of age and

older, with moderate to severe persistent bronchial asthma over a 12-week treatment period

Secondary:

- To assess the relative efficacy of FF/VI 200/25 and FF/VI 100/25, both administered once daily each evening

Study Design and Conduct

Overview:

This was a 12-week, multi-center, randomized, double-blind, parallel-group study with three active treatment arms. Subjects entered a 4-week run-in and then stratified according to their Visit 3 baseline FEV1 (greater than 65% or less than and equal to 65%) to one of the three study treatments:

- FF/VI 200/25 mcg once daily in the evening
- FF/VI 100/25 mcg once daily in the evening
- FF 100 mcg once daily in the evening

Randomized subjects attended four on-treatment visits at visits 4, 5, 6 and 7 (weeks 2, 4, 8 and 12, respectively). A follow-up clinic visit (visit 8) was performed 1 weeks after completing study medication. Subjects participated in the study for up to a maximum of 17 weeks from screening to follow-up. The schedule of assessments is shown in Table 13.

Table 13. Study Assessments: Study 116863

Visit	1	2	3	4	5	6	7	EW	8
Week	-4	-2	0	2	4	8	12		13
Day	-28	-14	0	14	28	56	84		14 post V7 or EW
Written Informed Consent	X								
Subject Demography	X								
Medical History	X								
Asthma History	X								
Asthma Med History	X								
Physical Exam	X						X	X	
Inclusion/ Exclusion Criteria	X		X						
Efficacy Assessments									
Spirometry Pulmonary Function	X		X	X	X	X		X	
Reversibility	X[1]		X						
Serial FEV_1 (0-24h)							X[2]		
Issue Subject	X								

Table 13. Study Assessments: Study 116863

Visit	1	2	3	4	5	6	7	EW	8
Week	-4	-2	0	2	4	8	12		13
Day	-28	-14	0	14	28	56	84		14 post V7 or EW
Diaries									
Subject Diary Review & Upload		X	X	X	X	X	X	X	
Safety Assessments									
Concomitant Medication	X	X	X	X	X	X	X	X	X[3]
OP Examination	X		X	X	X	X	X	X	
12-lead ECG		X							
Vital Signs	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X
Serious Adverse Events	X[4]	X[4]	X[4]	X	X	X	X	X	X
Laboratory Assessments									
Hematology	X								
Chemistry (includes liver safety testing)	X						X[5]	X[5]	
PGx Sampling (one visit only)				X					
Serum pregnancy test	X						X	X	
Urine Pregnancy test			X						X
24-hr Urine Collection Supplies dispensed		X							X
HBsAg and hepatitis C antibody screening	X								
Questionnaires									
ACT	X		X				X	X	
AQLQ (+12)			X				X	X	
Inhaler use assessment			X	X	X				
Ease of use questions for inhaler					X				

Table 13. Study Assessments: Study 116863

Visit	1	2	3	4	5	6	7	EW	8
Week	-4	-2	0	2	4	8	12		13
Day	-28	-14	0	14	28	56	84		14 post V7 or EW

Source CSR 116863, Table 39
1. Historical reversibility (within 6 months) was permitted at Visit 1 for inclusion.
2. Pre-dose assessment (within 30 minutes prior to dosing), post-dose 5, 15, 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours post dose
3. Concomitant Medications used for adverse events were only reported after treatment end (Medical Problems/Medications Diary Card).
4. During run-in, only SAEs related to study participation were recorded in the eCRF.
5. Liver studies only.

Study Population

Inclusion Criteria

The inclusion criteria were the same as in study HZA106827, with the exception of:

- Asthma diagnosis per NIH definition for at least 12 weeks with:
  - FEV1 40-80% at visit 1 based on NHANES III
  - 12 weeks prior, needed to be on an ICS, and for 4 weeks prior, need to be on a stable mid-high dose ICS or mid-dose ICS/LABA

Exclusion Criteria

Exclusion criteria were similar to study HZA106827 with these exceptions:

- History of life-threatening asthma in the past 5 years
- Asthma exacerbation requiring oral corticosteroids within 3 months prior to visit 1 or required overnight hospitalization within 6 months
- Not have been previously treated with FF or FF/vilanterol
- No night shift exclusions

Withdrawal Criteria
Withdrawal criteria were similar to Study HZA106827.

Permitted Medications
Permitted medications were the same as in Study HZA106827.

Study Treatments

Treatment groups were as follows:
- FF/VI 200/25 mcg once daily in the evening
- FF/VI 100/25 mcg once daily in the evening
- FF 100 mcg once daily in the evening

Compliance

Compliance was assessed by reviewing the eDiary and by using the dose-counter on the device.

Efficacy Endpoints

Co-primary Endpoints

- Weighted mean serial FEV1 over 0-24 hours post-dose at the end of the 12-week treatment period

Powered Secondary Endpoint

- Change from baseline in clinic visit trough FEV1 (pre-bronchodilator and pre-dose) at the end of the 12-week treatment period
- Change from baseline in the percentage of rescue-free 24-hour periods during the 12-week treatment period

Secondary Endpoints

- Change from baseline in the percentage of symptom-free 24-hour periods during the 12-week treatment period
- Change from baseline in AM PEF averaged over the 12-week treatment period
- Change from baseline in PM PEF averaged over the 12-week treatment period

Other Endpoints

- Clinic visit 12 hour FEV1 at the end of the 12 week treatment period
- Change from baseline in total Asthma Quality of Life Questionnaire (AQLQ+12) score at the end of 12 weeks of treatment
- The number of withdrawals due to lack of efficacy during the 12-week treatment period
- Change from baseline in Asthma Control Test (ACT) at the end of the 12-week treatment period
- Inhaler use assessment at randomization, the end of 2 weeks and the end of 4 weeks of treatment
- Ease of inhaler use questionnaire at the end of 4 weeks of treatment

Safety Endpoints

- Incidence of severe asthma exacerbations throughout the 12-week treatment period
- Incidence of adverse events throughout the 12-week treatment period
- Incidence of oropharyngeal candidiasis assessed by examination of the oropharynx at all clinic visits, including Early Withdrawal.

Statistical Plan

Approximately 990 subjects were to be randomized in this study in a ratio of 1:1:1 giving

330 randomized subjects per arm. With 290 subjects per arm (assuming withdrawal rate), this study had 97% power to detect a treatment difference of 135 mL in weighted mean serial FEV1 over 0-24 hours between FF/VI 100/25 and FF 100. This assumed a common standard deviation of 415 mL (based on previous studies) and significance at the two-sided 5% significance level.

The primary population for all analyses of efficacy and safety measures was the intent-to-treat (ITT) population.

The primary endpoint of weighted mean FEV1 at the end of the 12-week treatment period was analyzed using an analysis of covariance (ANCOVA) model allowing for the effects due to baseline FEV1, region, sex, age and treatment group.

Missing FEV1 data at Day 85 was imputed for the analysis relating to trough FEV1 using a Last Observation Carried Forward (LOCF) approach. Missing data were also analyzed using Repeated Measures, whereby missing data were not directly imputed but the correlation between visits for all patients was used to adjust the estimate of treatment effect.

Protocol Amendment

The original protocol was amended twice:

August 1, 2012:

- Sample size assumptions were changed to use 120 mL, instead of 150 mL, as the clinically relevant difference for trough FEV1 in this study

April 1, 2013

- Allowed US subjects to have been exposed to FF/VI or FF prior to entry

5.3.1.3 Trial HZA106829

Administrative Information:

- Study Title: A Randomized, Double-Blind, Parallel Group, Multicenter Study of fluticasone furoate/GW642444 inhalation powder, fluticasone furoate inhalation powder alone, and fluticasone propionate alone in the treatment of persistent asthma in adults and adolescents
- Study Dates: 6/10/10-10/18/11
- Study Sites: Russia (163), US (143), Romania (117), Germany (66), Poland (61), Japan (36)
- Study Report Date: April 30, 2012

Objectives/Rationale

Primary:

- To compare the efficacy and safety of FF/VI inhalation powder 200 mcg/25 mcg administered once daily each evening to FF inhalation powder 200 mcg

administered alone once daily each evening in adolescent and adult subjects 12 years of age and older with persistent bronchial asthma over a 24-week treatment period

Secondary:

- To compare the efficacy of FF 200 mcg administered once daily each evening with FP 500 mcg administered twice daily

Additional objectives

- To assess the safety of FF 200 mcg and FP 500 mcg over the 24-week treatment period

Study Design and Conduct

Overview:
This was a multicenter, stratified, randomized, double-blind, double-dummy, active control, parallel group study. After screening, subjects entered a 4-week run-in period. During this time, subjects remained on their baseline ICS medication. At visit 3, the end of the run-in period, subjects were stratified according to their medication (ICS or ICS/LABA) at screening. Once stratified, subjects were randomized in a 1:1:1 ratio to the treatment phase of the study where they received one of the following treatments:

• FF/VI 200/25 mcg inhalation powder via DPI once daily in the evening plus placebo diskus twice daily
• FF 200 mcg via DPI once daily in the evening plus placebo diskus twice daily
• FP 500 mcg via diskus twice daily plus placebo DPI once daily in the evening

Randomized subjects attended seven on-treatment clinic visits (visits 4, 5, 6, 7, 8, 9 and 10). Spirometry, dosing of study medication, PK and download of the electronic diary were to be conducted between 5:00 PM and 11:00 PM at all appropriate clinic visits except visit 2. A follow-up clinic contact was performed 1 week after completing study medication. The overall study duration for each subject was a maximum of 29 weeks.

Table 14. Schedule of Assessments: Trial HZA108629

Visit	1	2	3	4	5	6	7	8	9	10	EW	11
Week	-4	-2	0	2	4	8	12	16	20	24		25
Day	-28	-14	0	14	28	56	84	112	140	268		+7
Written Informed Consent	X											
Subject Demography	X											
Medical History	X											
Asthma History	X											
Therapy History	X											
Physical Exam	X										X	X
Inclusion/Exclusion Criteria	X		X									
Efficacy Assessments												

Table 14. Schedule of Assessments: Trial HZA108629

Visit	1	2	3	4	5	6	7	8	9	10	EW	11
Week	-4	-2	0	2	4	8	12	16	20	24		25
Day	-28	-14	0	14	28	56	84	112	140	268		+7
Spirometry Pulmonary Function	X			X	X	X	X	X	X	X	X	
Reversibility	X											
Serial FEV1 (subset of subjects)										X[a]		
PK Sampling							X[h]			X[h]		
Issue Subject Diaries	X											
Subject Diary Review & Upload		X		X	X	X	X	X	X			
Safety Assessments												
Oropharyngeal Examination	X		X	X	X	X	X	X	X	X	X	
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X[b]
Vital Signs (pre-dose)	X		X	X	X	X	X	X	X	X	X	
Adverse Events			X	X	X	X	X	X	X	X	X	X
Serious Adverse Events (SAEs)	X[d]	X[d]	X[d]	X	X	X	X	X	X	X	X	X
12-lead EKG		X	X[c]							X	X	
Laboratory Assessments												
Hematology	X											
Chemistry (includes liver safety testing)	X						X[e]			X	X	X
PGx Sampling (one visit only)[g]	X						X					
Serum pregnancy test	X									X	X	
Urine Pregnancy test			X									X
24-h Urine supplies dispensed		X							X			
24-h Urine collection			X							X		
PK Sampling							X[h]			X[h]		
HBsAg and hepatitis C antibody screening	X											

Table 14. Schedule of Assessments: Trial HZA108629

Visit	1	2	3	4	5	6	7	8	9	10	EW	11
Week	-4	-2	0	2	4	8	12	16	20	24		25
Day	-28	-14	0	14	28	56	84	112	140	268		+7
Questionnaires												
ACT	X		X				X			X	X	
AQLQ 12+			X				X			X	X	
Unscheduled Healthcare contact/Resource Utilization9			X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	
Global Assessment of Change					X		X			X	X	

Source CSR Table 56
a.In addition to pre-dose assessment (within 5 minutes prior to dosing), serial FEV1 measurements were taken at 5, 15, 30 minutes and 1, 2, 3, 4, 5, 12, 16, 20, 23 and 24 hours post-dose.
b. Concomitant medication details collected for adverse events only between end of treatment and follow-up contact.
c.ECG pre-dose and Tmax (5 to 20 minutes post-dose for VI) at Visit 3 (Day 0) for all subjects; ECG pre-dose and Tmax (5 to 20 minutes post-dose for VI) at Visit 10 (end of 24 weeks of treatment) in subjects not performing serial FEV1; ECGs at Visit 2 and Early Withdrawal were pre-dose only.
d. SAEs related to study participation that occurred during run-in were to be recorded in the eCRF.
e. For liver safety testing only.
f. If not performed at End of treatment.
g. The PGx sample could be collected at any one visit after the PGx consent had been signed and the subject had been randomized
h. Upon arrival at the clinic a 4 mL blood sample was collected and the subjects administered their evening dose of study medication after all pre-dose assessments were completed.
Prior to leaving the clinic, two more 4 mL blood samples were collected from the subject between 5 to 15 minutes post-dose and between 1 to 1.5 hours post-dose.
i. Completed when associated with a severe exacerbation and other asthma-related healthcare.

Study Population

Inclusion Criteria were similar to HZA106827 except that subjects were to be on an ICS or ICS/LABA combination product for at least 12 weeks prior to visit 1 as well as on a stable ICS dose equivalent to FP 500 mcg twice daily or a mid-dose combination product equivalent to Advair 250/50 twice daily for at least four weeks prior to visit 1. Exclusion criteria, randomization criteria, withdrawal criteria, permitted and prohibited medications were similar to Study HZA106827.

Study Treatments

Treatment groups were as follows:

- FF/VI 200/25 mcg inhalation powder via DPI once daily in the evening plus placebo diskus twice daily
- FF 200 mcg via DPI once daily in the evening plus placebo diskus twice daily
- FP 500 mcg via diskus twice daily plus placebo DPI once daily in the evening

All treatments were double-blinded. For the placebo, the DPI contained the same foil packs with the active drug moieties removed and all other excipients remaining the same. For the diskus placebo, only lactose was used.

Compliance

Compliance was assessed by reviewing the dose counter on the DPI and diskus at visits 4-10, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Co-primary Endpoints

- Mean change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 168-day (24 week) treatment period
- Weighted mean serial FEV1 over 0 to 24 hours post-dose, calculated in a subset of subjects performing serial FEV1 at the end of the double-blind treatment period

FEV1 was measured in the evening at clinic visit 1 and visits 3 to 10 between 5:00 PM and 11:00 PM electronically by spirometry. The highest of three technically acceptable measurements was recorded.

Nominated Powered Secondary Endpoint

- Mean change from baseline in the percentage of rescue-free 24-hour periods during the 24-week treatment period

Secondary Endpoints

- Change from baseline in the percentage of symptom-free 24-hour periods during the 24-week treatment period
- Change from baseline in total AQLQ (+12) score during 12 and 24 weeks of treatment

Other Endpoints

- Clinic visit 12 hour FEV1 at the end of the 168-day treatment period and was assessed in the subset of subjects that were performing serial FEV1 assessments
- Weighted mean serial FEV1 over 0 to 4 hours post-dose calculated in the subset of subjects performing serial FEV1 on Day 168
- Mean change from baseline in daily AM PEF averaged over the first 12 weeks and over the 24-week treatment period
- Mean change from baseline in daily PM PEF averaged over the first 12 weeks and over the 24-week treatment period
- The number of withdrawals due to lack of efficacy during the 24-week treatment period
- Change from baseline in the Asthma Control Test (ACT) at the end of 12 and 24 weeks of treatment
- Global assessment of change at the end of 4, 12, and 24 weeks of treatment
- Unscheduled healthcare contacts/resource utilization for severe asthma exacerbations and other asthma-related health care

Safety Endpoints

- Incidence of adverse events throughout the 24-week treatment period
- Incidence of severe asthma exacerbations throughout the 24-week treatment period
- Incidence of oropharyngeal candidiasis assessed by examination of the oropharynx at all clinic visits, including early withdrawal
- Clinical chemistry before and after the 24-week treatment period
- Liver function safety assessments at screening (visit 1), week 12 (visit 7), and week 24 (visit 10) or early withdrawal visit
- 24-hr urine cortisol excretion assessment before and at the end of the 24-week treatment period
- Vital signs were assessed at all clinic visits prior to dosing in all subjects. The following endpoints were derived:
    - change from baseline in systolic blood pressure (BP) at Day 168
    - change from baseline in diastolic BP at Day 168
    - change from baseline in pulse rate at Day 168
- 12-lead EKG before dosing on Day 0 and Day 168 in all subjects before dosing and at the time of maximum plasma concentration following drug administration to derive the QTc

Statistical Plan

It was planned to randomize a total of 588 subjects into this study in a ratio of 1:1:1 (196 subjects per arm). It was anticipated that there would be a 4% withdrawal rate for the first 2 weeks, which would still ensure 188 subjects per arm who contribute to the analysis of trough FEV1 and the analysis of % rescue-free 24-hour periods. Sixty percent of all randomized subjects would have had serial FEV1 measurements at week 24 if they completed the treatment period. It was anticipated that 15% of subjects would withdraw over the entire treatment period of the study, which would still ensure that 99 subjects per arm contributed to the analysis of weighted mean serial FEV1 over 0 to 24 hours at week 24.

The overall power of the study to detect treatment differences for both primary endpoints was 92%.

The primary population for all analyses of efficacy measures and safety measures was the ITT population which was comprised of all subjects randomized to treatment who received at least one dose of study medication.

The co-primary endpoints were derived by imputing any missing data with the last observation carried forward (LOCF). Statistical analysis was performed using an ANCOVA model.

Protocol Amendment

There were no protocol amendments to this study.

5.3.1.4 Trial HZA106837

Administrative Information:

- Study Title: A long-term, randomized, double-blind, parallel group study of fluticasone furoate/GW642444 inhalation powder once-daily and fluticasone furoate inhalation powder once-daily in subjects with asthma
- Study Dates: (2/22/10-9/15/11)
- Study Sites: US (373), Russia (300), Mexico (233), Ukraine (231), German (179), Argentina (159), Poland (156), Philippines (154), Romania (153),
- Japan (62), Australia (19)
- Study Report Date: March 12, 2012

Objectives/Rationale

Primary:

- To demonstrate that treatment with FF/VI once-daily administered in the evening significantly decreases the risk of severe asthma exacerbations as measured by time to first severe asthma exacerbation when compared with the same dose of FF alone administered once-daily in the evening in subjects 12 years of age and older with asthma

Study Design and Conduct

Overview:
HZA106837 was a multicenter, randomized, double-blind, parallel group study. Subjects entered a 2-week run-in , and during this time, subjects continued to use their current ICS therapy at a fixed dose. At randomization (visit 2), subjects who met the eligibility criteria were required to stop their ICS therapy for the duration of the treatment period and were randomly assigned to receive one of the following two double-blind treatments in a 1:1 ratio:

• FF/VI 100/25 via NDPI once-daily in the evening
• FF 100 via NDPI once-daily in the evening

The duration of the treatment period was variable and was dependent on the number of events (number of subjects with one or more severe asthma exacerbations) that occurred. The study continued until 330 events occurred. Treatment duration was at least 24 weeks and did not exceed 76 weeks for any completed subject. Subjects attended up to 11 on treatment visits (visits 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 13/End of Study). Visits 3-12 were to be as-needed, dependent on the subject's treatment length. Visits 2 through 13 were in the evening between 5 PM and 11 PM. A follow-up contact was performed 1 week after completing study medication. Total duration of study participation was up to a maximum of 79 weeks (including screening, treatment and follow-up).

Table 15. Schedule of Assessments: Trial HZA106837

Visit	1	2	3[2]	4[2]	5[2]	6[2]	7[2]	8[2]	9[2]	10[2]	11[2]	12[2]	EOS	EW	+14
Week	-2		2	6	12	20	28	36	44	52	60	68	76		
Day	-14	1	14	42	84	140	196	252	308	364	420	476	532		+7

Table 15. Schedule of Assessments: Trial HZA106837

Visit	1	2	3[2]	4[2]	5[2]	6[2]	7[2]	8[2]	9[2]	10[2]	11[2]	12[2]	EOS	EW	+14
Week	-2		2	6	12	20	28	36	44	52	60	68	76		
Day	-14	1	14	42	84	140	196	252	308	364	420	476	532		+7
Written Informed Consent	X														
Subject Demography	X														
Medical History	X														
Asthma History	X														
Therapy History	X														
Physical Examination	X							X					X	X	
Inclusion/Exclusion Criteria	X	X													
Dispense Investigational Product		X	X	X	X	X	X	X	X	X	X	X			
Collect Investigational Product			X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Rescue Medication	X	X	X	X	X	X	X	X	X	X	X	X			
Collect Rescue Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments															
FEV_1[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
FEV_1 Reversibility	X														
ACQ7		X			X			X					X	X	
Subject Diary Review/Collection		X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense Subject Diary	X	X	X	X	X	X	X	X	X	X	X	X			
Safety Assessments															
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG Assessment	X														
Vital Sign Assessment[4]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events Assessment			X	X	X	X	X	X	X	X	X	X	X	X	X
Serious Adverse Event Assessment		X[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
Severe Asthma Exacerbation		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
Clinical Laboratory Assessment[6]	X														
Liver Safety Assessment					X		X			X			X	X	

Table 15. Schedule of Assessments: Trial HZA106837

Visit	1	2	3[2]	4[2]	5[2]	6[2]	7[2]	8[2]	9[2]	10[2]	11[2]	12[2]	EOS	EW	+14
Week	-2		2	6	12	20	28	36	44	52	60	68	76		
Day	-14	1	14	42	84	140	196	252	308	364	420	476	532		+7
Serum Pregnancy Testing[7]	X				X		X			X			X	X	
Urine Pregnancy Testing[7]		X	X	X		X		X	X		X	X			X
PGx Sampling[8]							X[8]								

Source CSR 106837 Table 31
EOS=End of study
EW=Early Withdrawal
1.Visit 1 was performed at any time during the day. Visits 2 through 13 were performed in the evening between 5 PM and 11 PM.
2.Final treatment date was dependent on the number of events (number of subjects with one or more severe asthma exacerbation) that occurred. Final treatment day was to include all assessments as specified for Visit 13.
3.Assessment performed pre-dose.
4.Only SAEs related to study participation were supposed to be recorded in the eCRF.
5.Includes Liver Safety Assessment
6.Women of childbearing potential only
7.The PGx sample was collected at any one visit after the PGx consent was signed and the subject was randomized.

Study Population

Inclusion Criteria
Inclusion criteria were similar to studies depicted in Section 5 with the exception of:

- The lower limit of FEV1 was 50%, not 40%
- Subjects were to be on a dose of ICS equivalent to FP 200-1000 mcg/day or combination product equivalent to FP/salmeterol 200/100-500/100 mcg/day for at least 12 weeks prior to visit 1
- Subjects were to have a history of ≥1 asthma exacerbations that required treatment with systemic corticosteroids, emergency department visits, or in-patient hospitalization within 12 months prior

Exclusion Criteria
Exclusion criteria were similar to the studies depicted above with the exception that subjects could not have a history of life-threatening asthma in the past 5, not 10, years.

Prohibited Medications
Prohibited medications were similar to the studies depicted above.

Randomization Criteria
Randomization criteria were similar to the studies depicted above with the exception that evening, pre-dose FEV1 could not drop below 50%, not 40%.

Withdrawal Criteria
Withdrawal criteria were similar to the studies depicted above with the exception that subjects were not required to be withdrawn for asthma exacerbations until he/she experienced 3 protocol defined severe asthma exacerbations within any 6 month

treatment period or 4 severe asthma exacerbations during the double-blind treatment period.

Permitted medications
Permitted medications were similar to the studies depicted above.

Study Treatments

Treatment groups were as follows:
- FF/VI 100/25 via DPI once-daily in the evening
- FF 100 via DPI once-daily in the evening

All treatments were double-blinded.

Compliance
At visits 2-13, study drug administration was observed by site personnel. Subject compliance was assessed at visits 3-13 by reviewing the dose counter on the DPI.

Efficacy Endpoints

Primary Efficacy Endpoint
- Time to first severe asthma exacerbation

Secondary Efficacy Endpoints
- Rate of severe asthma exacerbation per subject per year
- Change from baseline at week 36 in PM pre-dose trough FEV1
    - At visit 1, pre-dose FEV1 was measured at any time of day. For all other visits, pre-dose PM trough FEV1 was measured between 5:00 PM and 11:00 PM.
    - The highest of three technically acceptable measurements was recorded

Other Efficacy Endpoints
- Characterization of severe asthma exacerbations through exploration of use of rescue medication ±14 days around the onset of a severe asthma exacerbation
- Change from baseline in PM pre-dose trough FEV1
- Proportion of subjects with an ACQ7 score of ≤0.75 at week 36
- Proportion of subjects with an ACQ7 score of ≤0.75 at week 12

Safety Endpoints

- Number of hospitalizations due to severe asthma exacerbations
- Number of emergency department/urgent care clinic visits due to severe asthma exacerbations
- Number of unscheduled health care provider visits due to severe asthma exacerbations
- Number of intubations due to severe asthma exacerbations
- Incidence of adverse events throughout the treatment period
- Pre-dose vital sign assessments at all visits

- Liver safety assessments at screening, week 12, week 28, week 52 and last on treatment visit
- Clinical chemistry and hematology laboratory evaluations for Japanese subjects

Statistical Plan

The following assumptions were made to calculate the approximate number of subjects to be randomized:10% of subjects in each treatment group lost to follow-up during one year and 20% of subjects within the FF treatment arm would have one or more severe asthma. A total sample size of 2000 (1000 per arm) would provide 90% power based on the above assumptions.

The primary population of all data displays was the Intent-to-Treat (ITT) population, comprised of all subjects randomized to treatment who received at least one dose of study medication. The Per Protocol (PP) population comprised all subjects in the ITT population not identified as protocol deviators.

The primary efficacy analysis of time to first severe asthma exacerbation was analyzed using a Cox proportional hazards regression model, including terms for baseline disease severity (FEV1 measured at randomization), sex, age, and region, for the ITT and the PP populations.

The analysis was repeated for the ITT population excluding all data from Investigator (b) (6) due to concerns regarding study procedures at this site. In addition, for the purposes of the primary efficacy analysis, a decision was made after the blind was broken to exclude a further investigator (Investigator (b) (6)), who randomized 16 subjects, due to GCP issues identified during an audit of his site. Therefore a second sensitivity analysis was run post-unblinding excluding both Investigator (b) (6) and Investigator (b) (6). A decision was made and documented prior to doing any sensitivity analyses that the ITT Population would remain the primary population for presentation of results.

Cumulative incidence curves using the Kaplan-Meier method were presented by country and by race. As a supportive analysis, the log-rank test was used to compare treatment groups with estimated hazard ratio, 95% confidence interval and p-value presented. Kaplan-Meier cumulative incidence curve showing time to withdrawal prior to the first severe asthma exacerbation was produced.

A sensitivity analysis was performed with stratification by center for events only (i.e., ignoring time to event). An exact estimate of the common odds ratio (OR), an exact 95% CI and exact p-value were calculated.

Protocol Amendment

The original protocol was amended once, specifically applicable to Japanese sites only:

- Change age of eligible subjects to 18 years of age and older
- Add open-label fluticasone propionate 250 mcg for use by appropriate subjects during the 2 week run-in period
- Add clinical laboratory testing at week 12, 28, 52, and last on-treatment visit

5.3.2 Long-Term Safety Trial

5.3.2.1 Trial HZA106839

Administration Information:

- Study Title: A Randomized, Double-Blind, Double Dummy, Active Comparator, Parallel Group, Multicenter Study to Evaluate the Safety of Once-Daily Fluticasone Furoate/GW642444 Inhalation Powder for 52 Weeks in Adolescent and Adult Subjects with Asthma
- Study Dates: 10/19/09-5/12/11
- Study Sites: US (17), Germany (14), Ukraine (10), Thailand (4)
- Study Report Date: May, 2012

Objectives/Rationale

- To assess the safety and tolerability of 12 months treatment with two strengths of inhaled FF/VI once-daily in the evening in subjects 12 years of age and older with asthma

Study Design and Conduct

Overview:
HZA106839 was a multicenter, randomized, double-blind, double-dummy, active control parallel group safety study. After screening, subjects entered a 4-week run-in period (all patients received FP 250 mcg BID) followed by visit 2 at which point subjects stopped their usual asthma treatments and were randomized in a 2:2:1 ratio to receive one of the following three treatments: FF 100/25 mcg once daily, FF/VI 200/25 mcg once daily, or FP 500 mcg twice daily. Subjects attended nine on-treatment clinic visits (Visits 3, 4, 5, 6, 7, 8, 9, 10 and 11) occurring at Weeks 2, 4, 8, 12, 20, 28, 36, 44 and 52. A follow-up contact was performed 1 week after completing study medication. Total duration of study participation was planned to be up to a maximum of 55 weeks (including screening, treatment and follow up). Study assessments were similar to trial HZA106837 with the exception that ophthalmic assessments were done at baseline, 28 weeks, and end of study.

Table 16. Schedule of Assessments: HZA106839

Visit	1	2	3	4	5	6	7	8	9	10	11			EW	12
Week	-2	0	2	4	8	12	20	28	36	44	52				
Day	-14	0	14	28	56	84	140	196	252	308	364				7
Written Informed Consent	X														
Subject Demography	X														
Medical History	X														
Asthma History	X														
Therapy History	X														

Table 16. Schedule of Assessments: HZA106839

Visit	1	2	3	4	5	6	7	8	9	10	11			EW	12
Week	-2	0	2	4	8	12	20	28	36	44	52				
Day	-14	0	14	28	56	84	140	196	252	308	364				7
Inclusion/Exclusion Criteria	X	X													
Dispense Investigational Product		X	X	X	X	X	X	X	X	X					
Collect Investigational Product			X	X	X	X	X	X	X	X	X			X	
Dispense Rescue Medication	X	X	X	X	X	X	X	X	X	X					
Collect Rescue Medication		X	X	X	X	X	X	X	X	X	X			X	
Efficacy Assessments															
FEV1	X	X													
FEV1 Reversibility	X														
Subject Diary Review/Collection		X	X	X	X	X	X	X	X	X	X			X	
Dispense Subject Diary	X	X	X	X	X	X	X	X	X	X	X				
Safety Assessments															
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X			X	X
ECG Assessment	X		X[1]			X[1]		X[1]			X[1]			X	
24-hour Holter	X	X						X			X			X	
Vital Sign Assessment[4]	X	X	X	X	X	X	X	X	X	X	X			X	
Adverse Events Assessment			X	X	X	X	X	X	X	X	X			X	X
Serious Adverse Event Assessment	X[2]	X[2]	X	X	X	X	X	X	X	X	X			X	X
Severe Asthma Exacerbation		X	X	X	X	X	X	X	X	X	X			X	X
Laboratory Assessments															
Clinical Laboratory Assessment	X					X		X			X			X	
Serum Pregnancy Testing[7]	X					X		X			X			X	
Urine Pregnancy Testing[7]		X	X	X	X		X		X	X					X
Population PK Collection			X			X					X				
PGx Sampling			X												

Table 16. Schedule of Assessments: HZA106839															
Visit	1	2	3	4	5	6	7	8	9	10	11			EW	12
Week	-2	0	2	4	8	12	20	28	36	44	52				
Day	-14	0	14	28	56	84	140	196	252	308	364				7

Source: CSR HZA106839 table 41
EW=Early Withdrawal
1. Assessment performed approximately 10 minutes post-dose
2. Only SAEs related to study participation were to be captured

Study Population

Inclusion Criteria
Inclusion criteria were similar to the studies depicted above with the exception of:

- Subjects were to be on a dose of ICS equivalent to FP 500-1000 mcg/day or combination product equivalent for at least 4 weeks prior to visit 1

Exclusion Criteria
Exclusion criteria were similar to the studies depicted above with the exception that subjects could not have a history of life-threatening asthma.

Prohibited/permitted medications, randomization criteria, and withdrawal criteria were similar to the studies depicted above.

Study Treatments

Treatment groups were as follows:

- FF/VI 100/25 mcg once daily
- FF/VI 200/25 mcg once daily
- FP 500 mcg twice daily

Safety Endpoints

- Incidence of adverse events or of severe asthma exacerbations throughout the 52-week treatment period
- Laboratory assessments
- 24-hour urinary cortisol excretion
- Oropharyngeal examinations
- Vital signs
- ECG assessments
- Ophthalmic assessments

Protocol Amendment

There were no amendments to the protocol.

5.3.3 Active Comparator Trial

5.3.3.1 Trial HZA113091

Administrative Information:

- Study Title: A Randomized, Double-Blind, Double-Dummy, Parallel-Group, Multicenter Study to assess efficacy and safety of Fluticasone Furoate (FF)/GW642444 Inhalation Powder and Fluticasone Propionate (FP)/salmeterol Inhalation Powder in the treatment of Persistent Asthma in Adults and Adolescents
- Study Dates: (6/11-4/12)
- Study Sites: US (26), Argentina (10),Chile (7), S. Korea (7), Netherlands (7), Philippines (7)
- Study Report Date: April 2012

Objectives/Rationale

Primary:

- To compare the efficacy of FF/VI 100/25 mcg, administered once daily in the evening with FP/salmeterol 250/50 mcg administered twice daily in subjects 12 years of age and older with persistent bronchial asthma over a 24-week treatment period

Study Design and Conduct

Overview:
This was a 24-week, multi-center, randomized, double-blind, double-dummy, parallel group study. Subjects meeting all the eligibility criteria during visit 1 entered a four-week run-in period. At visit 2 (end of run-in), subjects were randomized to receive one of the following treatments:

- FF/VI 100/25 mcg via DPI once daily in the evening and placebo via the diskus in the morning
- FP/salmeterol 250/50 mcg via the diskus twice daily and placebo via DPI once daily in the evening

Randomized subjects attended four on-treatment visits at visits 3, 4, 5, and 6 (weeks 4, 8, 16 and 24, respectively). A follow-up clinic visit was performed 1 week after completing study medication. Subjects participated in the study for up to a maximum of 29 weeks from screening to follow-up. The schedule of assessments is shown in Table 17.

Table 17. Schedule of Assessments: Trial HZA113091

Visit	1	2	3	4	5	6	EW	7
Week	-4	0	4	8	16	24		
Day	-28	0	28	56	112	168		7 post V7
Written	X							

Table 17. Schedule of Assessments: Trial HZA113091

Visit	1	2	3	4	5	6	EW	7
Week	-4	0	4	8	16	24		
Day	-28	0	28	56	112	168		7 post V7
Informed Consent								
Subject Demography	X							
Medical History	X							
Asthma History	X							
Therapy History	X							
Physical Exam	X							
Inclusion/ Exclusion Criteria	X	X						
Efficacy Assessments								
Spirometry Pulmonary Function	X	X	X	X	X	X	X	
Reversibility	X							
Serial FEV1 (0-4h)		X[1]						
Serial FEV1 (0-24h)						X[2]		
Safety Assessments								
Concomitant Medication	X	X	X	X	X	X	X	X[3]
OP Examination	X	X						
12-lead ECG	X							
Vital Signs	X	X	X	X	X	X	X	
Adverse Events	X[4]	X[4]	X	X	X	X	X	X
Serious Adverse Events	X[4]	X[4]	X	X	X	X	X	X
Laboratory Assessments								
Hematology	X							
Chemistry (includes liver safety testing)	X			X[5]				
PGx Sampling (one visit only)			X[6]					

Table 17. Schedule of Assessments: Trial HZA113091

Visit	1	2	3	4	5	6	EW	7
Week	-4	0	4	8	16	24		
Day	-28	0	28	56	112	168		7 post V7
Serum pregnancy test	X					X	X	
Urine Pregnancy test		X						X
24-hr Urine Collection		X[7]				X[7]		
HBsAg and hepatitis C antibody screening	X							
Questionnaires								
ACT	X	X				X	X	
AQLQ (+12)		X				X	X	
EQ-5D		X				X	X	
Unscheduled Healthcare Contact		X[8]	X[8]	X[8]	X[8]	X[8]	X[8]	

Source CSR HZA113091 protocol, table 2
1. 0 to 4-hour serial FEV1 will include pre-dose assessment (within 30 mins prior to dosing) and post-dose assessments after 5, 15 30 minutes and 1, 2, 3, and 4 hours.
2. 0 to 24-hour serial FEV1 will include pre-dose assessment (within 5 mins prior to dosing) and post-dose assessments after 5, 15, 30 minutes and 1, 2, 3, 4, 11, 12, 12.5, 13, 14,
16, 20, 23 and 24 hours.
3. Concomitant medication details collected for adverse events only between end of treatment and follow up contact;
4. AEs and SAEs related to study participation that occur during run-in should be recorded in the eCRF
5. For liver safety testing only;
6. The PGx sample can be collected at any one visit after the PGx consent has been signed and the subject has been randomized
7. In subset of subjects
8. To be completed associated with a severe asthma exacerbation and 'other' unscheduled asthma-related health care

Study Population

Inclusion Criteria
These were similar to the above studies with the exception:

- FEV1 40-85%
- On a stable dose of an ICS for 12 weeks and a medium ICS dose for 4 weeks

Exclusion Criteria
These were similar to the above studies with the exception:

- History of life-threatening asthma in the past 5 years

Withdrawal Criteria and Permitted Medications

- These were similar to the above studies.

Study Treatments

Treatment groups were as follows:

- FF/VI 100/25 mcg via DPI once daily in the evening and placebo diskus in the morning
- FP/salmeterol 250/50 mcg via diskus twice daily and placebo via DPI once daily in the evening

Compliance

Compliance was assessed by reviewing the dose counter on the DPI at visits 3-6, and subjects who were not compliant were counselled on appropriate dosing of study drug.

Efficacy Endpoints

Primary Endpoints

- Weighted mean for 24 h serial FEV1, calculated from serial spirometry over 0-24 h at the end of 168-day double-blind treatment period

Secondary Endpoints

- Individual serial FEV1 assessments at Visit 6 (the end of the 168 day treatment period) including the 12-h and 24-h post-dose trough values
- Time to onset of bronchodilator effect
- Weighted mean serial FEV1 over 0-4 h post dose at Visit 2
- Weighted mean serial FEV1 over 0-4 h post dose at Visit 6
- Percentage of subjects obtaining ≥12% and ≥200 mL increase from baseline in FEV1 at 12 h at Visit 6 (Day 168) of the double-blind treatment period
- Percentage of subjects obtaining ≥12% and ≥200 mL increase from baseline in FEV1 at 24 h at Visit 6 (Day 168) of the double-blind treatment period
- Change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at the end of the 168-day treatment period

Other Endpoints

- Asthma Quality of Life (AQLQ) +12 questionnaire
- Asthma Control Test (ACT)
- EQ-5D
- Unscheduled Healthcare Resource Utilization (for severe exacerbations and other asthma-related health care)

Safety Endpoints

- Incidence of AEs throughout the 24-week treatment period
- Incidence of severe exacerbations throughout the 24 week treatment period
- Vital signs (blood pressure and pulse), assessed at all clinic visits

- 24-h urine cortisol excretion assessment at baseline and at the end of the 24-week treatment period in subset of subjects (148 subjects randomized per group to give approximately 100 evaluable per group)

Statistical Plan

820 subjects were randomized (410 per treatment group) as it was estimated that a total of approximately 348 subjects with evaluable data per treatment group would provide 90% power to detect a difference of 80 mL between
FF/VI 100/25 mcg once-daily and FP/salmeterol 250/50 mcg twice-daily in weighted mean FEV1 over 24 h at the two-sided 5% significance level. This assumed a standard deviation of 325 mL.

The ITT population was the population of primary interest for all efficacy and safety Endpoints.

The weighted mean 0-24 h FEV1 was performed on the ITT population and was analyzed using an ANCOVA model with effects due to baseline FEV1, region, sex, age and treatment group.

Protocol Amendment

The original protocol was amended once:

- August 31, 2010
  - The pre-dose timeline for serial FEV1 (0-4 hours) was extended to within 30 minutes of dosing
  - Serum Pregnancy test were inserted to also be part of the early withdrawal visit

6 Review of Efficacy

Efficacy Summary

Fluticasone furoate has already been approved as monotherapy for the treatment of asthma at doses of 100 mcg and 200 mcg once daily (Arnuity Ellipta, NDA 205625). Therefore, the main goal of the combination ICS+LABA program is to demonstrate the added clinical benefit (efficacy) of vilanterol.

The asthma development program for Breo Ellipta® was designed to demonstrate the efficacy of FF/VI compared to placebo, the contribution of VI to the combination, and the added benefit of the higher dose (200/25) over the lower dose (100/25). The information to support the efficacy of FF/VI for the treatment of asthma is derived primarily from four trials (HZA106827, HZA116863, HZA106829, and HZA106837). In addition to these four key trials, GSK conducted one trial (HZA113091) in asthma comparing FF/VI to Advair (fluticasone propionate/salmeterol). This trial provides an additional benchmark comparison for FF/VI.

Trial HZA106827 was a 12-week, multinational, randomized, double-blind, placebo-controlled, parallel group trial in patients with persistent asthma that assessed FF/VI 100/25, FF 100, and placebo administered once-daily in the evening. Patients were 12

years of age and older, had a current history of asthma, a pre-bronchodilator percent (%) predicted FEV1 of 40-90% with a post-albuterol/salbutamol reversibility ≥ 12% and 200 mL, and were using a stable dose of ICS or ICS/LABA for at least 12 weeks prior to screening. The co-primary efficacy endpoints were mean change from baseline in trough FEV1 at 12 weeks and the weighted mean serial FEV1 over 0-24 hours post- dose in the subset of subjects performing serial FEV1 at the end of the double-blind treatment period. The primary treatment comparisons were between FF/VI 100/25 and FF 100, between FF/VI 100/25 and placebo, and between FF 100 and placebo for the co-primary endpoints. Trial HZA106827 included 609 patients in the ITT population, of which 201 patients received the proposed FF/VI 100/25 dose. Once-daily treatment with FF/VI 100/25 and FF 100 demonstrated statistically significant improvements compared with placebo with respect to trough FEV1 and weighted mean FEV1 at Week 12. Compared with placebo, mean treatment differences of 172 mL (FF/VI, $p<0.001$) and 136 mL (FF, $p=0.002$) were observed in trough FEV1. For weighted mean FEV1 (0-24h) (in a subset of subjects) a difference of 302 mL ($p<0.001$) was observed with FF/VI 100/25, and a difference of 186 mL ($p=0.003$) was observed following treatment with FF 100. No statistically significant treatment differences were observed with either endpoint between FF/VI 100/25 relative to FF 100 ($p>0.05$) and so the lung function contribution, as measured by FEV1, of VI to the FF/VI 100/25 combination was not demonstrated in trial HZA106827; however, two subsequent trials did show a contribution of the VI component (HZA116863 and HZA106829).

Trial HZA116863 was a 12-week, multinational, randomized, double-blind, parallel group trial in patients with moderate to severe asthma that assessed FF/VI 200/25, FF/VI 100/25, and FF 100 administered once daily in the evening. Patients were 12 years of age and older, had a current history of asthma, a pre-bronchodilator percent (%) predicted FEV1 of 40-80% with a post-albuterol/salbutamol reversibility ≥ 12% and 200 mL, and were using a stable dose of ICS or ICS/LABA for at least 12 weeks prior to screening. The primary efficacy endpoint was weighted mean serial FEV1 (0-24 hours post-dose). The primary treatment comparison was between FF/VI 100/25 and FF 100. Trial HZA116863 included 1,039 subjects in the ITT population, of which 346 patients received FF/VI 100/25 and 346 patients received FF/VI 200/25. Compared with FF 100 alone, FF/VI significantly improved pulmonary function as measured by weighted mean FEV1 (0-24h), with a treatment difference of 108 mL ($p<0.001$).

Trial HZA116863 also provided an opportunity to evaluate the benefit of the higher dose (FF/VI 200/25) over the lower dose (FF/VI 100/25).Comparisons of FF/VI 200/25 to FF/VI 100/25 showed small numerical improvements in lung function (24 mL improvement in weighted mean 0-24 hours FEV1 and 16 mL improvement in trough FEV1), and the change from baseline in the percentage of rescue-free 24 hour periods (0.9% difference favoring FF/VI 200/25). Small improvements also were seen in the percentage of symptom-free 24 hour periods (1.9% difference), morning PEF (3.4 L/min) and evening PEF (2.0 L/min) favoring FF/VI 200/25. Additionally, subjects receiving FF/VI 200/25 were 55% more likely to be well controlled (ACT score ≥20) than those taking FF/VI 100/25.

Trial HZA106829 was a 24-week, multinational, randomized, double-blind, double-dummy, parallel group trial in patients with asthma which assessed FF/VI 200/25, FF 200, and fluticasone propionate (FP) 500 BID. Patient selection criteria and co-primary endpoints were as described for HZA106827. The primary treatment comparison was

between FF/VI 200/25 and FF 200. At the end of 24 weeks' treatment, once daily treatment with FF/VI 200/25 demonstrated statistically significant improvements compared with FF 200 with respect to both co-primary endpoints. Compared with FF 200, treatment differences of 193 mL($p < 0.001$) and 136 mL ($p=0.048$), were observed for mean change from baseline in trough FEV1 and weighted mean FEV1 (0-24h), respectively.

Trial HZA106837 was a long-term, randomized, double-blind, parallel group, event-driven trial in patients with asthma, which was designed to demonstrate that treatment with FF/VI 100/25 once daily significantly decreased the risk of asthma exacerbations as measured by time to first asthma exacerbation when compared with FF 100. Participants were 12 years of age and older and had at least a one year history of asthma, were using FP 200 to 1000 mcg/day (or equivalent) or FP/salmeterol (100/50 BID or 250/50 BID, or equivalent) for at least 12 weeks prior to Visit 1, and had a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or inpatient hospitalization for the treatment of asthma within 12 months prior to Visit 1.

In this trial, the sponsor has defined "severe exacerbation" as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. An adjudication committee determined if serious adverse events were respiratory-related and ensured that all asthma exacerbations were captured as defined in the protocol.

Although the definition of severe exacerbation is per consensus guidelines [*Am J Respir Crit Care Med, 180: pp. 58-99, 2009*] the reader will take note that most exacerbations were defined by use of oral corticosteroids, rather than what might be considered to be the more "severe" components of the definition, specifically inpatient hospitalization or ED visit. As a result, for the purposes of this review, the results will be reported for "asthma exacerbation" when the efficacy of FF/VI is examined.

Once-daily treatment with FF/VI 100/25 demonstrated a statistically significant improvement compared with FF 100 with respect to time to first asthma exacerbation. The hazard ratio for FF/VI 100/25 versus FF 100 was 0.795 (95% CI 0.642, 0.985). This represents a 20% reduction in the risk of asthma exacerbation for subjects treated with FF/VI 100/25 compared with FF100 ($p=0.036$) in the overall study population. The secondary endpoint of rate of asthma exacerbation also demonstrated a 25% reduction for subjects treated with FF/VI 100/25 compared with FF 100 ($p=0.014$) in the overall study population.

Trial HZA113091 was a 24-week, randomized, double-blind, double-dummy, parallel group trial in patients with asthma that assessed FF/VI 100/25 versus Advair (FP/salmeterol) 250/50 BID. The primary efficacy endpoint was weighted mean serial FEV1 (0-24h) at 24 weeks. Trial HZA113091 included 806 subjects in the ITT population, of which 403 subjects received FF/VI 100/25. While there was no statistical difference between treatments, Advair numerically outperformed FF/VI at most time points. At the end of treatment, subjects in the FF/VI and Advair groups achieved mean increases from baseline in weighted mean serial FEV1 (0-24h) of 341 and 377 mL, respectively.

Given the potential for increased risk for serious asthma-related outcomes in pediatric patients based on both prior evidence as well as the findings of the Agency's meta-analysis in which there was an imbalance of hospitalizations in the FF/VI group in the 12-17 year old population (see Section 7.7.3), the Agency conducted subgroup analyses for lung function (weighted mean serial FEV1 and trough FEV1) in trials HZA106827, HZA116863, and HZA106829. For Trial HZA106837, the subgroup analysis was conducted for time to first exacerbation and rate of exacerbation. Subgroups were examined by age gender, race, and geographical region. While all subgroups were evaluated, pediatric patients were an area of focus, based on the data.

When examining lung function, the number of adolescents 12 to 17 years old in each subgroup was small, treatment effects within subgroups were not statistically significant, and tests for interaction between treatment and age were not statistically significant. However, there was a numerical trend towards a smaller observed treatment effect in the FF/VI treatment group compared to FF alone in younger patients in all three trials for weighted mean serial FEV1 and in two of the three trials for trough FEV1. When considering the typical efficacy of bronchodilators (such as vilanterol), the inability to consistently demonstrate the contribution of a LABA to the combination product in younger patients, even numerically, is of concern.

In trial HZA106837, the adolescent population comprised about 13 to 15% of the total study population. This trial had the largest adolescent subgroup for analysis. When the 12 to 17 year old subgroup is compared to the subgroup ≥ 18 years of age. It is notable that the 20% reduction in risk to time to first exacerbation in the overall population was in the reverse direction and showed a higher risk estimate of time to first exacerbation in patients 12 to 17 years old (HR 1.4 (0.61, 3.21)). This trend was further supported by the analysis of the rate of asthma exacerbations, which similarly showed that the 25% reduction in rate of exacerbations in the overall population was now in the reverse direction and showed a higher risk estimate for patients 12 to 17 years of age (Ratio 1.60; 95% CI (0.70, 3.61)). The numerical trend in the exacerbation data which is in favor of FF over FF/VI is also of concern.

6.1 Indication

The proposed indication for FF/VI 100/25 and 200/25 mcg is the once-daily treatment of asthma in patients 12 years of age and older.

6.1.1 Methods

The asthma development program was designed to demonstrate the efficacy of FF/VI compared to placebo, the contribution of VI to the combination, and the added benefit of the higher dose (200/25) over the lower dose (100/25). The information to support the efficacy of FF/VI for the treatment of asthma is derived primarily from four trials (HZA106827, HZA116863, HZA106829, and HZA106837). In addition, to these four key trials, GSK conducted one trial (HZA113091) in asthma comparing FF/VI to Advair (fluticasone propionate/salmeterol). This trial provides an additional benchmark comparison for FF/VI. These results of these five trials will be reviewed here. The long-term safety trial, HZA106839, will be reviewed in Section 7.

6.1.2 Demographics

Overall, the age, gender, race, and asthma severity were the same across treatment groups within in each confirmatory study. Subjects were more commonly female, white, had asthma for over 10 years, and were on other asthma medications.

Overall, an underrepresentation of subjects of African heritage and American Native heritage is evident; however the demographics are similar to other ICS/LABA combination development programs for approved products.

Table 18, Table 19, Table 20, Table 21, and Table 22 detail the demographic and baseline characteristics of subjects in the confirmatory and long-term safety trials.

Table 18. Demographic and Baseline Characteristics: HZA106827

	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Age				
Mean	38.1	40.4	40.7	39.7
Min	12	12	12	12
Max	72	84	82	84
Sex, n (%)				
Female	111 (55)	126(61)	116 (58)	353 (58)
Male	92 (45)	79 (39)	85 (42)	256 (42)
Race, n (%)				
African Heritage	14 (7)	16 (8)	13(6)	43 (7)
Amer. Indian or Alaska Native	0	1 (<1)	0	1 (<1)
Asian	9 (9)	16 (8)	16 (8)	51 (8)
White	169 (83)	171 (83)	172 (86)	512 (84)
Duration of Asthma, n (%)				
<6 mo	5 (2)	1 (<1)	5 (2)	11 (2)
≥6 mo to <1 year	11 (5)	9 (4)	12 (6)	32 (5)
≥1 to < 5 years	52 (26)	44 (21)	54 (27)	150 (25)
≥5 to <10 years	36 (18)	44 (21)	7 (23)	127 (21)
≥10 years	99 (49)	107 (52)	83 (41)	289 (47)
Screening Lung Function				
Mean pre-bronchodilator FEV1 (L)	2.277	2.174	2.227	2.226
Percent predicted	68.47	67.04	67.25	67.59
Reversibility				
Absolute FEV1 reversibility (mL)	597.6	641.9	603.1.	614.2
Percent reversibility FEV1 (%)	27.47	30.66	27.98	28.71
Concomitant Medications				
ICS alone	119 (59)	122 (60)	120 (60)	361 (59)
ICS/LABA	84 (42)	83 (40)	81 (41)	248 (41)

Source: CSR HZA 106827 Tables 5.15, 11, 12, 14

Table 19. Demographic and Baseline Characteristics: HZA116863

	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346	Total N=1039
Age				
Mean	44.7	45.9	46.6	45.7
Min	12	12	12	12
Max	178	82	79	82
Sex, n (%)				
Female	199 (57)	205 (59)	224 (65)	628 (60)
Male	148 (43)	141 (41)	122 (35)	411 (40)
Race, n (%)				
African Heritage	26 (7)	20 (6)	28 (8)	74 (7)
Amer. Indian or Alaska Native	11 (3)	15 (4)	12 (3)	38 (4)
Asian	4 (1)	2 (<1)	2 (<1)	8 (<1)
White	305 (88)	307 (89)	300 (87)	912 (88)
Duration of Asthma, n (%)				
<6 mo	5 (1)	4 (1)	1 (<1)	10 (<1)
≥6 mo to <1 year	5 (1)	3 (<1)	1 (<1)	9 (<1)
≥1 to < 5 years	48 (14)	45 (13)	42 (<12)	135 (13)
≥5 to <10 years	56 (16)	78 (23)	69 (20)	203 (20)
≥10 years	233 (67)	216 (62)	233 (67)	682 (66)
Screening Lung Function				
Mean pre-bronchodilator FEV1 (L)	1.990	1.997	1.970	1.986
Percent predicted	62.28	62.82	62.62	62.57
Reversibility				
Absolute FEV1 reversibility (mL)	576.8	560.5	552.7	563.4
Percent reversibility FEV1 (%)	30.79	29.10	29.33	29.74
Concomitant Medications				
ICS/LABA	232 (67)	224 (65)	213 (62)	669 (64)
Mid-dose ICA alone	91 (26)	96 (28)	104 (30)	291 (28)
High-dose ICS alone	24 (7)	26 (8)	29 (8)	79 (8)

Source: CSR HZA116863, tables 7, 8, 9,12

Table 20. Demographics and Baseline Characteristics: HZA106829

	FF 200 N=194	FF/VI 200/25 N=197	FP 500 BID N=195	Total N=586
Age				
Mean	44.6	46.6	47.3	46.2
Min	12	14	12	12
Max	74	74	76	76
Sex, n (%)				
Female	113 (58)	116 (59)	116 (59)	345 (59)
Male	1 (42)	81 (41)	79 (41)	241 (41)
Race, n (%)				
African Heritage	16 (8)	16 (8)	19 (10)	51 (9)
Amer. Indian or Alaska Native	0	0	1 (<1)	1 (<1)
Asian	12 (6)	15 (8)	13 (7)	40 (7)
White	165 (85)	165 (84)	162 (83)	492 (84)
Duration of Asthma, n (%)				
<6 mo	2 (1)	1 (<1)	1 (<1)	4 (<1)

Table 20. Demographics and Baseline Characteristics: HZA106829

	FF 200 N=194	FF/VI 200/25 N=197	FP 500 BID N=195	Total N=586
≥6 mo to <1 year	4 (2)	1 (<1)	2 (1)	7 (1)
≥1 to < 5 years	27 (14)	31 (16)	35 (18)	93 (16)
≥5 to <10 years	49 (25)	35 (18)	45 (23)	129 (22)
≥10 years	112 (58)	129 (65)	112 (57)	353 (60)
Screening Lung Function				
Mean pre-bronchodilator FEV1 (L)	2.072	2.017	2.017	2.035
Percent predicted	63.27	62.99	63.59	63.28
Reversibility				
Absolute FEV1 reversibility (mL)	583.3	561.7	568.0	570.9
Percent reversibility FEV1 (%)	29.17	29.58	29.56	29.44
Concomitant Medications				
On ICS	44 (23)	47 (24)	49 (25)	140 (24)
On ICS+LABA	150 (77)	150 (76)	146 (75)	446 (76)

Source: CSR HZA 106829 Table 5, 6, 7

Table 21. Demographic and Baseline Characteristics: HZA106837

	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Age			
Mean	42.3	41.1	41.7
Min	12	12	12
Max	79	82	82
Sex, n (%)			
Female	689 (68)	661 (66)	1350 (67)
Male	321 (32)	348 (34)	669 (33)
Race, n (%)			
African Heritage	47 (5)	40 (4)	87 (4)
Other[1]	110 (11)	117 (12)	227 (11)
Asian	110 (11)	112 (11)	222 (11)
White	743 (74)	740 (73)	1483 (73)
Duration of Asthma, n (%)			
<6 mo	0	0	0
≥6 mo to <1 year	0	0	0
≥1 to < 5 years	208 (21)	212 (21)	420 (21)
≥5 to <10 years	195 (19)	216 (21)	411 (20)
≥10 years	607 (60)	581 (58)	1188 (59)
Baseline Lung Function			
Mean pre-bronchodilator FEV1 (L)	2.101	2.144	2.108
Percent predicted	69.0	68.8	68.9
Reversibility			
Absolute FEV1 reversibility (mL)	500.0	499.1	499.6
Percent reversibility FEV1 (%)	24.3	24.4	24.4
Concomitant Medications			
On any asthma medication	1010 (100)	1009 (100)	2019 (100)

Source: CSR HZA 106837 tables 8, 9, 11, 12
1. Other= American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, African American/African Heritage and White, American Indian or Alaska Native and White and Asian and White

Table 22. Demographic and Baseline Characteristics: HZA113091

	FF/VI 100/25 N=403	FP/salmeterol N=403	Total N=806
Age			
Mean	43.8	41.9	42.8
Min	12	12	12
Max	79	80	80
Sex, n (%)			
Female	244 (61)	245 (61)	489 (61)
Male	159 (39)	158 (39)	317 (39)
Race, n (%)			
African Heritage	36(9)	43 (11)	79 (10)
Native Hawaiian or other Pacific Islander	1 (<1)	1 (<1)	2 (<1)
Asian	124 (31)	125 (31)	249 (31)
White	242 (60)	232 (58)	474 (59)
Duration of Asthma, n (%)			
<6 mo	3 (<1)	5 (<1)	8 (<1)
≥6 mo to <1 year	2 (<1)	3 (<1)	5 (<1)
≥1 to < 5 years	32 (8)	34 (8)	66 (8)
≥5 to <10 years	67 (17)	58 (14)	125 (16)
≥10 years	299 (74)	303 (75)	602 (75)
Screening Lung Function			
Mean pre-bronchodilator FEV1 (L)	1.885	1.930	1.907
Percent predicted	63.7	64.4	64.2
Reversibility			
Absolute FEV1 reversibility (mL)	487.1	536.3	511.7
Percent reversibility FEV1 (%)	26.4	29.0	27.7
Concomitant Medications			
ICS alone	125 (31)	123 (31)	248 (31)
ICS/LABA	279 (69)	279 (69)	558 (69)

Source: CSR HZA113901, tables 5, 6, 7, 8

6.1.3 Subject Disposition

A total of 5,059 subjects were randomized in trials HZA106827, HZA116863, HZA106829, HZA106837, and HZA113091. A majority of subjects (81-90%) completed the studies. Overall, the most common reasons for patient withdrawal were lack of efficacy or adverse events. In general, patients on active treatment withdrew less frequently for lack of efficacy than those in the placebo groups. Table 23, Table 24, Table 25, Table 26, and Table 27 depict subject disposition for the confirmatory and long-term safety trials.

Table 23. Patient Disposition: HZA106827

	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Completed	151 (74)	185 (90)	179 (89)	515 (85)
Withdrawn	52 (26)	20 (10)	22 (11)	94 (15)
Primary reason for withdrawal				

Table 23. Patient Disposition: HZA106827				
	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Total N=609
Adverse event	1 (<1)	0	2 (<1)	3 (<1)
Lack of Efficacy	32 (16)	6 (3)	7 (3)	45 (7)
Exacerbation*	9 (4)	2 (<1)	1 (<1)	12 (2)
Protocol Deviation	7 (3)	0	2 (<1)	9 (1)
Lost to Follow-up	0	1 (<1)	2 (<1)	3 (<1)
Source: CSR HZA106827 Table 7 *Sub-reason for withdrawal				

Treatment Compliance for Study HZA106827:

Overall treatment compliance was high (98.3%) with similar compliance across all treatments (97.5% to 98.8%). A low percentage of subjects (<1 to 2%) reported a mean compliance less than 80%.

Table 24. Patient Disposition: HZA116863				
	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346	Total N=1039
Completed	296 (85)	314 (91)	321 (93)	931 (90)
Withdrawn	51 (15)	32 (9)	25 (7)	108 (10)
Primary reason for withdrawal				
Adverse event	4 (1)	3 (<1)	3 (<1)	10 (<1)
Lack of Efficacy	33 (10)	13 (4)	11 (3)	57 (5)
Protocol Deviation	2 (<1)	3 (<1)	0	5 (<1)
Lost to Follow-up	0	1 (<1)	1 (<1)	2 (<1)
Source: CSR HZA116863 table 4				

Treatment Compliance for Study HZA116863:

Mean overall treatment compliance was high and comparable across the treatment groups (~99%). The majority of subjects in each treatment group (81% to 84%) were between 95% and 105% compliant with inhaler use. Few subjects were severely under compliant with treatment regiments (3 to 4 subjects per treatment group with <80% compliance) or severely over compliant (2 subjects per treatment group with >120% compliance.

Table 25. Patient Disposition: HZA106829				
	FF 200 N=194	FF 200/25 N=197	FP 500 BID N=195	Total N=586
Completed	146 (75)	169 (86)	161 (83)	476 (81)
Withdrawn	48 (25)	28 (14)	34 (17)	110 (19)
Primary reason for withdrawal				
Adverse event	3 (2)	7 (4)	2 (1)	12 (2)
Lack of Efficacy	21 (11)	6 (3)	18 (9)	45 (8)
Exacerbation*	5 (3)	0	1 (<1)	6 (1)
Protocol Deviation	5 (3)	3 (2)	5 (3)	13 (2)
Lost to Follow-up	2 (1)	0	0	2 (1)

Table 25. Patient Disposition: HZA106829				
	FF 200 N=194	FF 200/25 N=197	FP 500 BID N=195	Total N=586
Source: CSR HZA106829 table 3 *Sub-reason for withdrawal				

Treatment Compliance for Study HZA106829:

The majority of subjects in each treatment group were between 95% and 105% compliant with the use of the FF or FF/VI (79% to 84%) and the FP 500 BID (72% to 76%). Few patients were severely non-compliant (<80%) or over compliant (>120%).

Table 26. Patient Disposition: HZA106837			
	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Completed	863 (85)	885 (88)	1748 (87)
Withdrawn	147 (15)	124 (12)	271 (13)
Primary reason for withdrawal			
Adverse event	19 (2)	15 (1)	34 (2)
Lack of Efficacy	22 (2)	13 (1)	35 (2)
Exacerbation*	16 (2)	11 (1)	27 (1)
Protocol Deviation	26 (3)	17 (2)	43 (2)
Lost to Follow-up	11 (1)	9 (<1)	20 (<1)
Source: CSR 106837 table 5 *Sub-reason for withdrawal			

Treatment Compliance for Study HZA106837:

Mean overall compliance rate was high and comparable across the treatment groups (98.3% in the FF 100 group and 98.0% in the FF/VI 100/25 group). The majority of subjects in each treatment group were between 95% and 105% compliant (84% in the FF 100 group and 83% in the FF/VI 100/25 group). Few subjects were grossly non-compliant: 11 and 13 subjects were <80% compliant in the FF 100 and FF/VI 100/25 groups, respectively and 2 subjects each in the FF 100 and FF/VI 100/25 groups were >120% compliant.

Table 27. Patient Disposition: HZA113091			
	FF/VI 100/25 N=403	FP/salmeterol N=403	Total N=806
Completed	358 (89)	357 (89)	715 (89)
Withdrawn	45 (11)	46 (11)	91 (11)
Primary reason for withdrawal			
Adverse event	6 (1)	8 (2)	14 (2)
Lack of Efficacy	20 (5)	11 (3)	31 (4)
Exacerbation*	7 (2)	6 (1)	13 (2)
Protocol Deviation	7 (2)	10 (2)	17 (2)
Lost to Follow-up	5 (1)	7 (2)	12 (1)

Table 27. Patient Disposition: HZA113091			
	FF/VI 100/25 N=403	FP/salmeterol N=403	Total N=806
Source: CSR 113901 table 3 *Sub-reason for withdrawal			

Treatment Compliance for Study HZA113091:

Mean treatment compliance using either inhaler was high during the study (≥94.1% for each treatment). Overall, less than 80% compliance was reported for fewer (35 [4%]) subjects using FF/VI than for subjects using FP/Salmeterol (51 [6%] subjects). In total, 19 subjects were over-compliant (between 105% and 120%) using FF/VI and 8 subjects were over-compliant using FP/Salmeterol.

6.1.4 Analysis of Co-Primary Endpoint(s)

6.1.4.1 Trial HZA106827

Trial HZA106827 evaluated the co-primary efficacy endpoints of mean change from baseline in trough FEV1 at 12 weeks and the weighted mean serial FEV1 over 0-24 hours (in a subset of patients) at 12 weeks. These results are displayed in Table 28.

Table 28. Co-Primary Endpoints at Week 12: Trial HZA106827 (LOCF, ITT population)						
	Trough FEV_1 (mL)			Weighted Mean (0-24h) FEV_1 (mL)		
	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201
n	193	203	200	95	106	108
LS Mean Change from Baseline (mL)	196	332	368	212	398	513
Difference vs. Placebo (mL) (95% CI) p-value		136 (51, 222) 0.002	172 (87,258) <0.001		186 (62, 310) 0.003	302 (178, 426) <0.001
Difference vs. FF 100 (mL) (95% CI) p-value			36 (-48,120) 0.405			116 (-5, 236) 0.060

Table 28. Co-Primary Endpoints at Week 12: Trial HZA106827 (LOCF, ITT population)

Source: Module 5.3.5, HZA106827 CSR, Tables 17, 18.
Analysis performed using ANCOVA with covariates of baseline, region, sex, age, and treatment

Once-daily treatment with FF/VI 100/25 and FF 100 demonstrated statistically significant improvements compared with placebo with respect to trough FEV1 and weighted mean FEV1 at Week 12. Compared with placebo, treatment differences of 172 mL (FF/VI, p<0.001) and 136 mL (FF, p=0.002) were observed in trough FEV1. For weighted mean FEV1 (0-24h) (in a subset of subjects) a difference of 302 mL (p<0.001) was observed with FF/VI 100/25 and a difference of 186 mL (p=0.003) was observed following treatment with FF 100. No statistically significant treatment differences were observed with either endpoint between FF/VI 100/25 relative to FF 100 (p>0.05) and so the lung function contribution, as measured by FEV1, of VI to the FF/VI 100/25 combination was not demonstrated in trial HZA106827.

6.1.4.2 Trial HZA116863

The primary efficacy endpoint in trial HZA116863 was the change from baseline in weighted mean serial FEV1 (0-24 hours post-dose). The primary treatment comparison was between FF/VI 100/25 and FF 100, followed by a comparison of FF/VI 200/25 and FF/VI 100/25. The results are displayed in Table 29.

Table 29. Weighted Mean Serial FEV1 (0-24h) at Week 12: Trial HZA116863 (ITT population)

	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346
n	288	312	312
LS Mean Change from Baseline (mL)	366	474	499
Difference vs. FF100 (mL) (95% CI) p-value		108 (45,171) <0.001	
Difference vs. FF/VI 100/25 (mL) (95% CI) p-value			24 (-37, 86) 0.443

Source: Module 5.3.5, HZA116863 CSR, Table 16
Analysis performed using ANCOVA with covariates of baseline, region, sex, age, and treatment

Compared with FF 100 alone, FF/VI significantly improved pulmonary function as measured by weighted mean FEV1 (0-24h), with a treatment difference of 108 mL ($p<0.001$). Trial HZA116863 also provided opportunity to evaluate the benefit of the higher dose (FF 200/25) over the lower dose (FF 100/25) with respect to the primary efficacy endpoint of weighted mean serial FEV1. Comparisons of FF/VI 200/25 to FF/VI 100/25 showed small numerical improvements in lung function (24 mL improvement in weighted mean 0-24 hours FEV1). This was supported by a small numerical improvement in the trough FEV1 (powered secondary endpoint) discussed in more detail in Section 6.1.5.

6.1.4.3 Trial HZA106829

Trial HZA106829 evaluated the co-primary efficacy endpoints of mean change from baseline in trough FEV1 at 24 weeks and the weighted mean serial FEV1 over 0-24 hours at 24 weeks. These results are displayed in Table 30.

Table 30.Co-Primary Endpoints: Trial HZA106829 (ITT population)

	Trough FEV_1 (mL)			Weighted Mean (0-24h) FEV_1 (mL)		
	FF 200 N=194	**FF/VI 200/25 N=197**	**FP 500 BID N=195**	**FF 200 N=194**	**FF/VI 200/25 N=197**	**FP 500 BID N=195**
n	186	187	190	83	89	86
LS Mean Change from Baseline	201	394	183	328	464	258
Difference vs. FF200 (mL) (95% CI) p-value		193 (108, 277) <0.001			136 (1,270) 0.048	
Difference vs. FP500 BID (mL) (95% CI) p-value	18 (-66, 102) 0.676	210 (127, 294) <0.001		70 (-67, 208) 0.316	206 (73, 339) 0.003	

Source: Module 5.3.5, HZA106829 CSR, Tables 14, 16
Analysis performed using ANCOVA with covariates of baseline, region, sex, age, and treatment

At the end of 24 weeks' treatment, once daily treatment with FF/VI 200/25 demonstrated statistically significant improvements compared with FF 200 with respect to both co-primary endpoints. Compared with FF 200, a treatment differences of 193 mL ($p <$

0.001) and 136 mL (p=0.048), were observed for mean change from baseline in trough FEV1 and weighted mean FEV1 (0-24h), respectively.

6.1.4.4 Trial HZA106837

Trial HZA106837 was designed to evaluate the risk of asthma exacerbations with FF/VI 100/25 compared with FF100. The primary efficacy endpoint was time to first asthma exacerbation. An asthma exacerbation was defined as a deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an inpatient hospitalization or emergency department visit due to asthma that required systemic corticosteroids. Courses of corticosteroids separated by 1 week of more were treated as separate exacerbation events. Subjects were withdrawn from the study if they experienced 3 asthma exacerbations in any 6 month period or 4 asthma exacerbations during the double-blind treatment period.

An adjudication committee was utilized to determine if serious adverse events were classified as respiratory-related and to ensure that all asthma exacerbations were captured as defined in the protocol. The primary endpoint was time to first exacerbation.

Secondary endpoints included rate of exacerbation per subject year. Secondary endpoints will be discussed in Section 6.1.5. For the efficacy and safety analyses, on-treatment exacerbations were evaluated. On-treatment refers to any exacerbation that occurred on or after the first dose of study treatment and before the last dose date + 1 day.

A total of 2,668 subjects were screened for this study, 2,020 were randomized, and 2,019 received study drug (ITT population). The majority of subjects (87%) completed the study. The most common reason for study discontinuation was withdrawal of consent, which was balanced across both treatment arms. The majority of the study population was white (73%) and female (67%) with a mean age of 42 years. Mean baseline FEV1 percent predicted was 72%. Mean overall compliance rate was high and comparable across the treatment groups (98.3% in the FF 100 group and 98% in the FF/V1 100/25 group).

The time to first asthma exacerbation is presented in Table 31 and Figure 5.

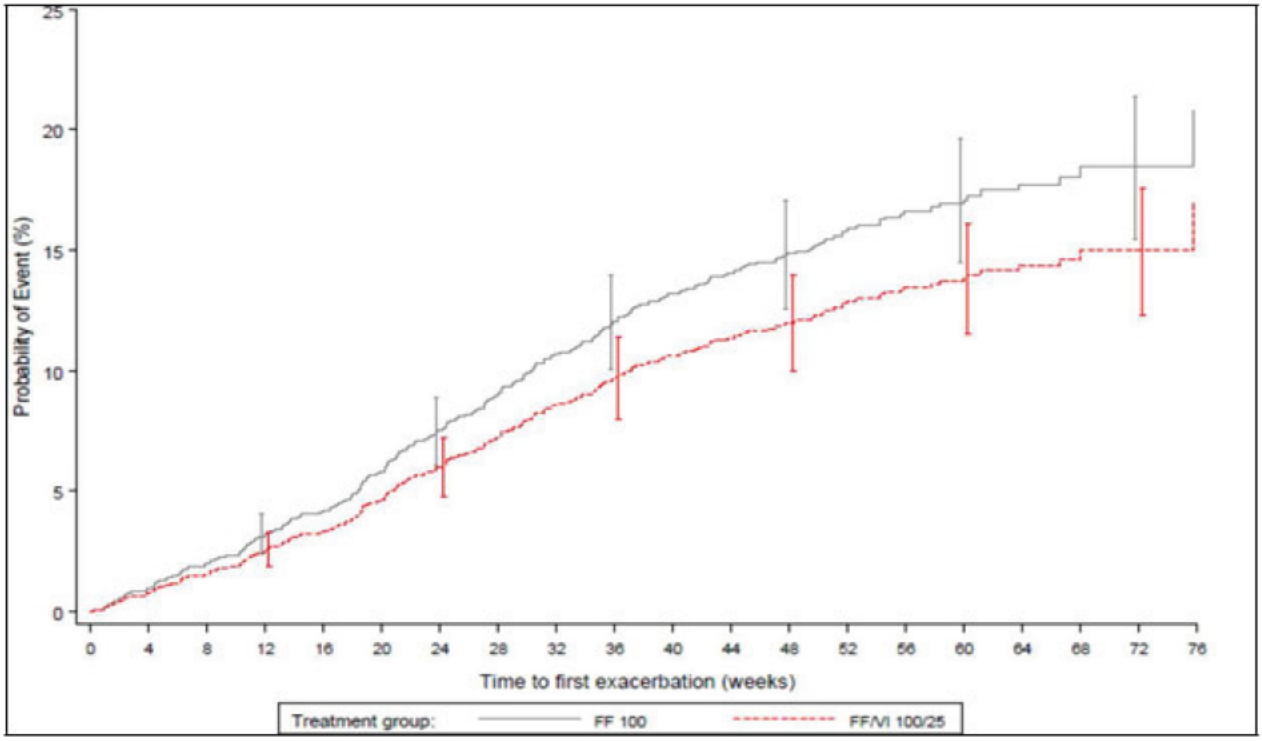
Table 31. Time to First Asthma Exacerbation: Trial HZA106837 (ITT population)

	FF 100 N=1010	FF/VI 100/25 N=1009
Number of Subjects with 1+ Asthma Exacerbation, n (%)	186 (18)	154 (15)
Adjusted probability of 1+ Asthma Exacerbation by 52 weeks, % (95% CI)	15.9 (13.5, 18.2)	12.8 (10.7, 14.9)

Table 31. Time to First Asthma Exacerbation: Trial HZA106837 (ITT population)		
	FF 100 N=1010	FF/VI 100/25 N=1009
FF/VI 100/25 vs. FF 100		
Hazard ratio*		0.795
95% CI*		(0.642, 0.985)
p-value*		0.036

Source: Module 5.3.5, HZA106837 CSR, Table 6.1, p. 388
Analysis performed using Cox proportional regression model including terms for baseline disease severity (FEV1 measured at randomization), sex, age, and region
*adjusted for interim analysis
analysis conducted of on-treatment exacerbations: which was defined as first dose date ≤ AE start date ≤ last dose date + 1

Figure 5. Time to First Asthma Exacerbation – Trial HZA106837 (ITT)



Cox Proportional Hazards Model with covariates of baseline disease severity, sex, age, region, and treatment
Vertical bars represent 95% Confidence Intervals
Source: Module 5.3.5, Clinical Study Report, HZA106837, Figure 6.1, pg. 345

Once-daily treatment with FF/VI 100/25 demonstrated a statistically significant improvement compared with FF 100 with respect to time to first asthma exacerbation. The hazard ratio for FF/VI 100/25 versus FF 100 was 0.795 (95% CI 0.642, 0.985). This represents a 20% reduction in the risk of experiencing an asthma exacerbation for subjects treated with FF/VI 100/25 compared with FF 100 (p=0.036). Results of sensitivity analyses support those shown from the Cox model.

The efficacy of the combination of FF/VI with respect to asthma exacerbations, a clinically important event and one that lies on the spectrum of the LABA asthma-related safety signal of interest (hospitalizations, intubations, and death), is an important consideration in the risk benefit evaluation. This study demonstrated benefit of the addition of a LABA to an ICS by utilizing an endpoint (time to first exacerbation) that informs both safety and efficacy in the overall study population.

Although this document focuses on the efficacy and safety unrelated to serious asthma outcomes, asthma exacerbation was an efficacy endpoint in HZA106837, so a further characterization of these events is warranted here.

As seen in Table 32, the profiles of asthma exacerbations were similar between treatment groups. Nine subjects (<1%) in the FF 100 group and 8 subjects (<1%) in the FF/VI 100/25 group experienced asthma exacerbations during the treatment period that led to hospitalization. Twenty-six (26) subjects (3%) in the FF 100 group and 22 subjects (2%) in the FF/VI 100/25 group experienced asthma exacerbations that led subjects to visit an emergency department or urgent care clinic. One hundred forty-two (142) subjects (14%) in the FF 100 group and 119 subjects (12%) in the FF/VI 100/25 group experienced asthma exacerbations that led to unscheduled healthcare provider visits.

Table 32. Hospitalizations and ED Visits due to Asthma Exacerbations: Trial HZA106837

	FF 100 N=1010	FF/VI 100/25 N=1009
Number of Subjects with 1+ Asthma Exacerbation, n(%)	186 (18)	154 (15)
Number of Subjects Hospitalized*	9 (<1%)	8 (<1%)
Number of ED/Urgent Care Clinic Visits*	26 (3%)	22 (2%)
Number of Unscheduled HCP Visits*	142 (14%)	119 (12%)

Source: Module 5.3.5, HZA106837 CSR, Tables 7.20, 7.21, 7.22, 7.23, p. 737-741
*on-treatment – first dose date ≤ AE start date ≤ last dose date + 1

When examined by the number of asthma exacerbations, the profile of asthma exacerbations between the two treatment groups also appears to be similar as seen in Table 33. All exacerbations in both groups required oral/systemic corticosteroids. Of the 271 exacerbations that occurred in the FF 100 treatment group, 7% led to withdrawal versus 6% in the FF/VI 100/25 group; 9% vs 8% led to an ER visit; 4% vs 5% led to hospitalization. There were no intubations or deaths in either treatment group. The mean duration of an asthma exacerbation was approximately 11 days in both groups. As can be seen here, most exacerbations were defined only by corticosteroid use, rather than by hospitalizations or ED visits.

Table 33. Hospitalizations and ED Visits due to Asthma Exacerbations: Trial HZA106837

	FF 100 N=1010	FF/VI 100/25 N=1009
Total Number of Asthma Exacerbations	271	200
Systemic/oral corticosteroid	271 (100%)	200 (100%)
Led to Withdrawal	19 (7%)	12 (6%)
Led to ER Visit	25 (9%)	15 (8%)
Led to Hospitalization	10 (4%)	9 (5%)
Led to Intubation	0	0
Duration of Asthma Exacerbation (days)		
Mean (SD)	11.1 (7.2)	11.3 (7.2)

Source: Module 5.3.5, HZA106837 CSR, Table 6.6, p. 393.
*on-treatment: first dose date ≤ AE start date ≤ last dose date + 1

Overall, the reasons that led to the diagnosis of asthma exacerbation in Trial HZA106837 were similar between treatment groups, as can be seen in Table 34.

Table 34. Summary of Reasons that Led to the Diagnosis of an Asthma Exacerbation

	FF 100 N=1010	FF/VI 100/25 N=1009
Number of Asthma Exacerbations	271	200
Worsening daytime symptoms	188 (69)	133 (67)
Worsening nighttime symptoms	124 (46)	79 (40)
Decreasing peak flow	17 (6)	20 (10)
Decreasing FEV1	68 (25)	42 (21)
Increasing rescue medication usage	125 (46)	80 (40)
Clinical examination	135 (50)	94 (47)
Other	17 (6)	13 (7)
No reason provided	16 (6)	17 (9)

Source: Module 5.3.5, HZA106837 CSR, Tables 6.7, p. 395
*on-treatment: first dose date ≤ AE start date ≤ last dose date + 1

6.1.4.5 Trial HZA113091

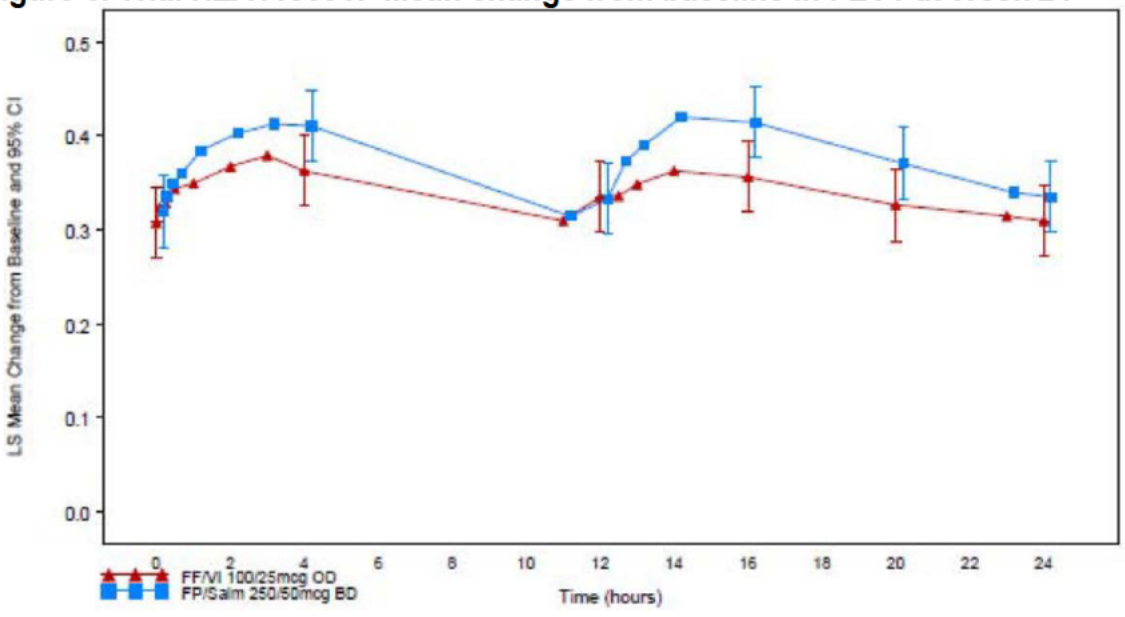
Trial HZA113091 assessed FF/VI 100/25 QD versus Advair (fluticasone propionate (FP)/salmeterol) 250/50 BID with respect to the primary endpoint of weighted mean serial FEV1 (0-24h). These results are displayed in Table 35 and Figure 6.

Table 35. Trial HZA113091: Weighted Mean Serial FEV1 (0-24h) at Week 24 (ITT population)

	FF/VI 100/25 N = 403	FP/Sal 250/50 BID N = 403
n	352	347
LS Mean Change from Baseline	341	377
Difference vs. FP/Salmeterol 250/50 BID mL (95%CI) p-value	-37 (-88,15) 0.162	

Source: CSR 113091 table 12, 15
FP=fluticasone propionate, Sal=salmeterol

Figure 6. Trial HZA113091: Mean change from baseline in FEV1 at Week 24



Source: Module 5.3.5, CSR, Figure 3.

At the end of treatment, subjects in the FF/VI and Advair groups achieved mean increases from baseline in weighted mean serial FEV1 (0-24h) of 341 and 377 mL, respectively. While Advair numerically outperformed FF/VI at most timepoints (Figure 6), there was no statistical difference between treatments (-37 mL, p=0.162).

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Trial HZA106827

In trial HZA106827, all supportive endpoints demonstrated statistically significant benefit of FF/VI 100/25 over placebo. All supportive endpoints with the exception of the ACT and AQLQ scores showed benefit of FF/VI 100/25 over FF 100.

6.1.5.2 Trial HZA116863

The change from baseline in trough FEV1 was an important secondary endpoint in trial HZA116863. The results from this analysis are presented in Table 36.

Table 36. Change from Baseline in Trough FEV1 at Week 12: Trial HZA116863

	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346
n	336	334	337
LS Mean Change from Baseline (mL)	365	441	457
Difference vs. FF100 (mL) (95% CI) p-value		77 (16,138) 0.014	
Difference vs. FF/VI 100/25 (mL) (95% CI)			16 (-46, 77)

Source: Module 5.3.5, HZA116863 CSR, Table 19
Analysis performed using ANCOVA with covariates of baseline, region, sex, age, and treatment

At Week 12, the FF/VI 100/25 group showed a LS mean change from baseline improvement in 77 mL (p=0.014) greater than the FF 100 group. The trough FEV1 assessment supports the primary endpoint of weighted mean serial FEV1 to provide evidence for the contribution of VI to the combination product. Further, there was a small numerical increase in the change from baseline in trough FEV1 for FF/VI 200/25 vs FF/VI 100/25 (16 mL, NS), similar to the numerical benefit seen in the weighted mean serial FEV1 (See Section 6.1.4.2).

In trial HZA116863, all supportive endpoints with the exception of the AQLQ score

showed benefit of FF/VI 100/25 over FF 100, and all supportive endpoints demonstrated a slight numerical benefit of FF/VI 200/25 over FF/VI 100/25.

6.1.5.3 Trial HZA106829

In trial HZA106829, all supportive endpoints with the exception of the ACT and AQLQ scores showed a benefit of FF 200/25 over FF 200.

6.1.5.4 Trial HZA106837

Over the course of the treatment period, 200 asthma exacerbations occurred in subjects treated with FF/VI 100/25 compared with 271 asthma exacerbations in subjects treated with FF 100. There were no deaths or intubations in either group.

The rate of asthma exacerbations per subject per year is displayed in Table 37. The number and rate of multiple exacerbations per subject is displayed in Table 38.

Table 37. Rate of Asthma Exacerbations: Trial HZA106837 (ITT population)

	FF 100 N=1010	FF/VI 100/25 N=1009
Mean asthma exacerbation rate per subject year	0.19	0.14
FF/VI 100/25 vs. FF 100 Ratio 95% CI p-value		 0.755 (0.603, 0.945) 0.014

Source: Module 5.3.5, HZA106837 CSR, Table 6.9, pg. 398
Analysis performed using negative binomial regression model including terms for baseline disease severity (FEV1 measured at randomization), sex, age, and region

The rate of asthma exacerbations per subject per year was 0.19 in the FF 100 group (approximately 1 in every 5 years) and 0.14 in the FF/VI 100/25 group (approximately 1 in every 7 years). The ratio of exacerbation rate from the negative binominal analysis was 0.755 (95% CI 0.603, 0.945). This represents a 25% reduction in the rate of asthma exacerbations for subjects treated with FF/VI 100/25 compared with FF 100 (p=0.014). This secondary analysis supports the primary endpoint of time to first asthma exacerbation.

Table 38. Number and Rate of Asthma Exacerbations

	FF 100 N=1010	FF/VI 100/25 N=1009
Total no. of asthma exacerbations	271	200
Number of asthma exacerbations per subject, n (%)		
0	824(82)	855(85)
1	125(12)	119(12)
2	40(4)	25(2)
3	19(2)	9 (<1)
4	1(<1)	1 (<1)
5	1(<1)	0

Source: Module 5.3.5, HZA106837 CSR, Table 6.13, pg. 402

Few subjects experienced more than one asthma exacerbation while on treatment.

6.1.5.5 Trial HZA113091

The change from baseline in trough FEV1 was an important secondary endpoint in trial HZA113091. The results from this analysis are presented in Table 39.

Table 39. Trial HZA113091: Change from Baseline in Trough FEV1 at Week 24 (ITT)

	FF/VI 100/25 N = 403	FP/Sal 250/50 BID N = 403
n	397	389
LS Mean Change from Baseline (mL)	281	300
Difference vs. FP/Salmeterol 250/50 BID (mL)	-19	
(95% CI)	(-73,34)	
p-value	0.485	

Source: CSR 113091 table 6.18, pg. 282
ANCOVA with covariates of baseline FEV1, region, sex, age, and treatment
FP=fluticasone propionate, Sal=salmeterol

Subjects in the FP/Salmeterol group achieved a greater LS mean change from baseline in trough FEV1 than subjects in the FF/VI group (300 mL and 281 mL, respectively),

however the difference was not statistically different (-19 mL, p=0.485).

Supportive endpoints are shown in Table 40.

Table 40. Secondary Endpoints

	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	FP/S 250/50 BID
HZA106827					
N	201		205		
Rescue-free 24-hour periods, %					
Difference vs. placebo	19.3 p<0.001		8.7 p=0.007		
Difference vs. FF 100	10.6 p<0.001				
Symptom-free 24-hour periods, %					
Difference vs. placebo	18.0 p<0.001		5.8 p=0.055		
Difference vs. FF 100	12.1 p<0.001				
AQLQ, units					
Difference vs. placebo	0.30 p<0.001		0.15 p=0.073		
Difference vs. FF 100	0.15 p=0.059				
AM PEF, L/min[1]					
Difference vs. placebo	33.3 p<0.001		18.7 p<0.001		
Difference vs. FF 100	14.6 p<0.001				
PM PEF, L/min[1]					
Difference vs. placebo	28.2 p<0.001		15.9 p<0.001		
Difference vs. FF 100	12.3 p<0.001				
ACT, units[1]					
Difference vs. placebo	1.9 p<0.001		1.3 p<0.001		
Difference vs. FF 100	0.6 p=0.058				
HZA116863					
N	346	346			
Rescue-free 24-hour periods, %					
Difference vs FF 100	12.2 p<0.001				
Difference vs FF/VI 100/25 (95% CI)		0.9 (-4.2,6.1)			

Table 40. Secondary Endpoints					
	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	FP/S 250/50 BID
Symptom-free 24-hour periods, %					
Difference vs FF 100	7.8 p=0.002				
Difference vs FF/VI 100/25 (95% CI)		1.9 (-3.0, 6.7)			
AM PEF, (L/min)					
Difference vs FF 100 (L/min)	25.2 p<0.001				
Difference vs FF/VI 100/25 (95% CI)		3.4 (-2.8, 9.7)			
PM PEF, (L/min)					
Difference vs FF 100 (L/min)	24.2 p<0.001				
Difference vs FF/VI 100/25 (95% CI)		2.0 (-4.2, 8.2)			
AQLQ, units					
Difference vs FF 100	0.08 p=0.303				
Difference vs FF/VI 100/25 (95% CI)		0.14 (-0.01, 0.28)			
ACT, units					
Difference vs FF 100	0.9 p=0.002				
Difference vs FF/VI 100/25 (95% CI)		0.7 (0.1, 1.2)			
HZA106829					
N		197		194	
Rescue-free 24-hour periods, %					
Difference versus FF 200		11.7 p<0.001			
Symptom-free 24-hour periods, %					
Difference versus FF 200		8.4 p=0.010			
AQLQ, units					
Difference versus FF 200		0.05 p=0.587			
ACT, units					
Difference versus FF 200		0.3 p=0.484			

Table 40. Secondary Endpoints					
	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	FP/S 250/50 BID
AM PEF, (L/min)					
Difference versus FF 200 (L/min)		33.5 p<0.001			
PM PEF, (L/min)					
Difference versus FF 200 (L/min)		30.7 p<0.001			
HZA113091					
N	403				403
AQLQ, units					
Difference FF/VI 100/25 vs FP/S 250/50	0.09 p=0.130				
ACT, units					
Difference FF/VI 100/25 vs FP/S 250/50	0.2 p=0.310				
Source: ISE tables 10, 13, 15; CSR113091 tables 16, 17 1.These were considered "other" endpoints; however, as they were secondary endpoints in the other studies, they are included here to allow for comparison.					

6.1.6 Other Endpoints

Other endpoints examined by the sponsor are shown in the table below. The results trended with the primary and secondary endpoints. In trial HZA106827, there was a statistically significant benefit of FF/VI 100/25 over placebo, without substantial evidence of benefit of FF/VI 100/25 over FF 100, in regards to withdrawals due to lack of efficacy. There was also no statistically significant difference in global assessment of change between FF/VI 100/25 over FF 100. However, in trials 116863 and 106829 there was evidence of benefit of FF/VI over FF with respect to withdrawals due to lack of efficacy and global assessment of change. In trial HZA106837, 36% of subjects in the FF group versus 44% of subjects in the FF/VI group had an ACQ7 score of >0.75 indicating asthma control (OR: 1.5; CI 1.23, 1.82). In trial HZA113091, there once again was no significant difference between FF/VI 100/25 and FP/salmeterol 250/50.

Other endpoints are shown in Table 41.

Table 41. Other Endpoints					
	FF/VI 100/25	**FF/VI 200/25**	**FF 100**	**FF 200**	**FP/S 250/50 BID**
HZA106827[1, 2]					
N	201		205		

Table 41. Other Endpoints					
	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	FP/S 250/50 BID
Withdrawals due to lack of efficacy, n (%)					
Difference vs. placebo	7 (3) <0.001		6 (3) <0.001		
Difference vs. FF 100	7 (3) 0.785				
Global Assessment of Change, OR					
Difference vs. placebo	2.57 <0.001		2.13 0.005		
Difference vs. FF 100	1.21 0.498				
HZA116863[2]					
N	346	346			
Withdrawals Due to Lack of Efficacy, n (%)					
Difference vs FF 100	13 (4) 0.003				
HZA106829					
N		197		194	
Withdrawals Due to Lack of Efficacy, n (%)					
Difference versus FF 200		29.1 <0.001			
Unscheduled Healthcare Contacts, n (%)					
		0 (0)		5 (<1)	
Global Assessment of Change, OR					
Difference versus FF 200		1.91 0.015			
HZA106837					
N	978		970		
ACQ7, OR					
Difference versus FF 100	1.50 <0.001				
HZA113091					
N	403				403
EQ-SD					
Difference FF/VI 100/25 vs FP/S 250/50	1.4 0.110				

Source: ISE Table 33, CSR HZA106827 table 6.40, CSR HZA106829 table 28, section 6.11, table 34; CSR HZA113091 table 19
1. HZA106827 also examined unscheduled healthcare contacts, but there were none reported for any treatment arm so Is not included here.
2. Trials HZA106827 and 116863 also examined inhaler use, but all treatment groups were able to utilize the inhaler correctly (95 and 97%, respectively) so Is not included here.

6.1.7 Subpopulations

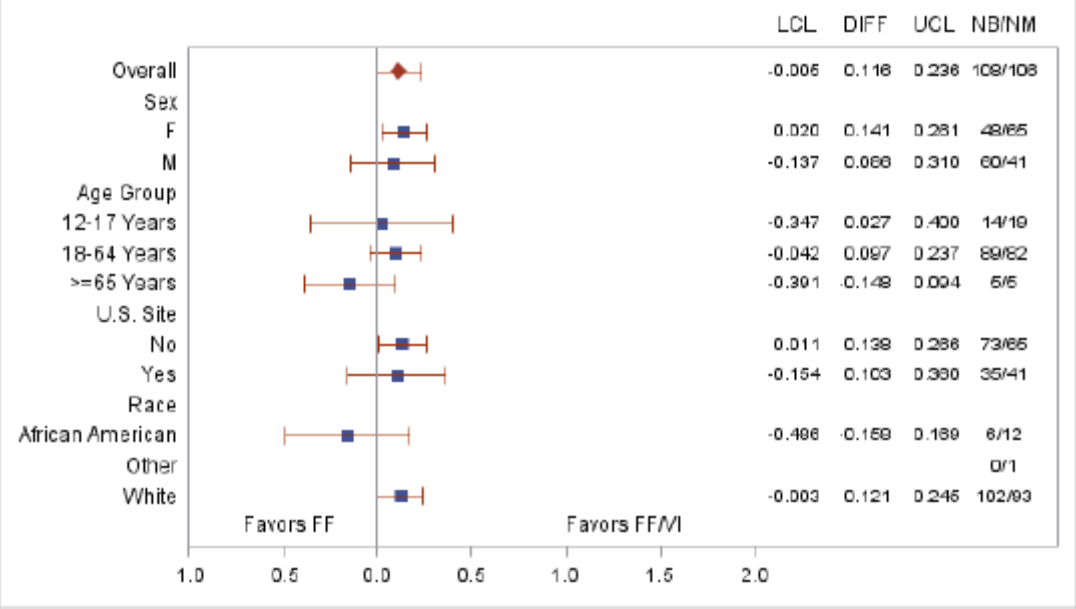
The Agency conducted subgroup analyses for weighted mean serial FEV1 and trough FEV1 for trials HZA106827, HZA116863, and HZA106829. In addition, subgroup analyses were conducted for HZA106837, for the time to first exacerbation.
As FF monotherapy (Arnuity Ellipta, NDA 205625) is already approved for the treatment of asthma, the most important comparison is of FF/VI to FF, in order to demonstrate the contribution of VI to the combination. For Trial HZA113091, FF/VI100/25 was compared with Advair.

Each of the following subgroups were examined:

- Age
- Gender
- Race
- Geographical region

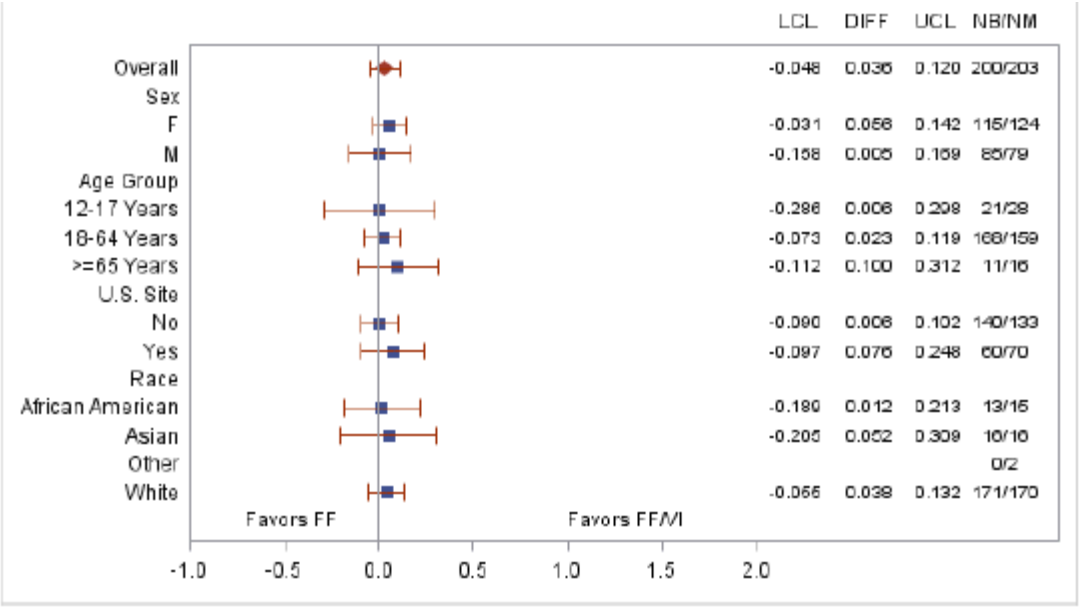
The forest plots for the overall subgroup analyses for each of the studies are presented in this section in the following order: HZA106827, HZA116863, HZA106829, HZA113091, and HZA106837. It is important to note that the trials were not powered to detect differences based on subgroup analysis.

Figure 7. Subgroup Analysis of Trial HZA106827 for Weighted Mean FEV1: Estimated Difference of FF/VI 100/25 vs. FF100 with 95% CI



Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NB/NM: Number of patients under the FF/VI (Breo) arm versus number of patients under the FF (Mono Therapy) arm.

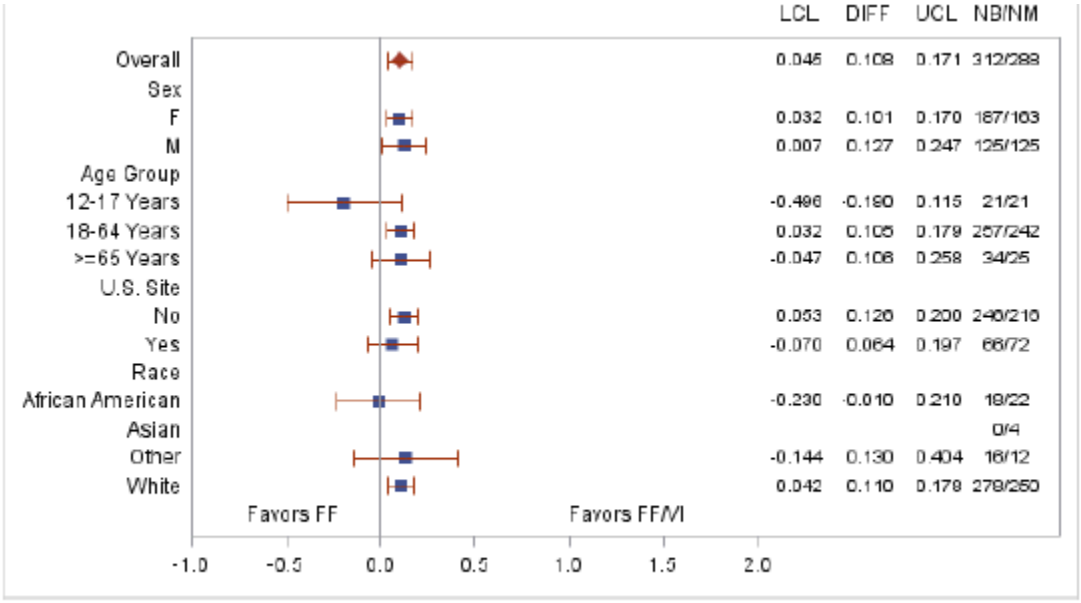
Figure 8. Subgroup Analysis of Trial HZA106827 for Trough FEV1: Estimated Difference of FF/VI 100/25 vs. FF100 with 95% CI



Source:

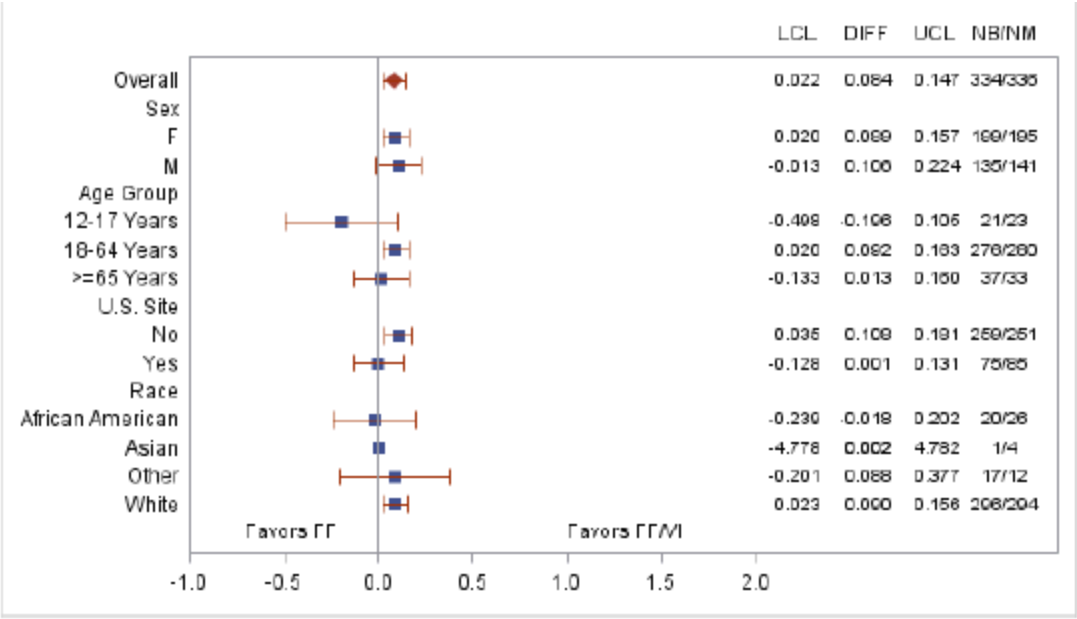
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NB/NM: Number of patients under the FF/VI (Breo) arm versus number of patients under the FF (Mono Therapy) arm.

Figure 9. Subgroup Analysis of Trial HZA116863 for Weighted Mean FEV1: Estimated Difference of FF/VI 100/25 vs. FF100 with 95% CI



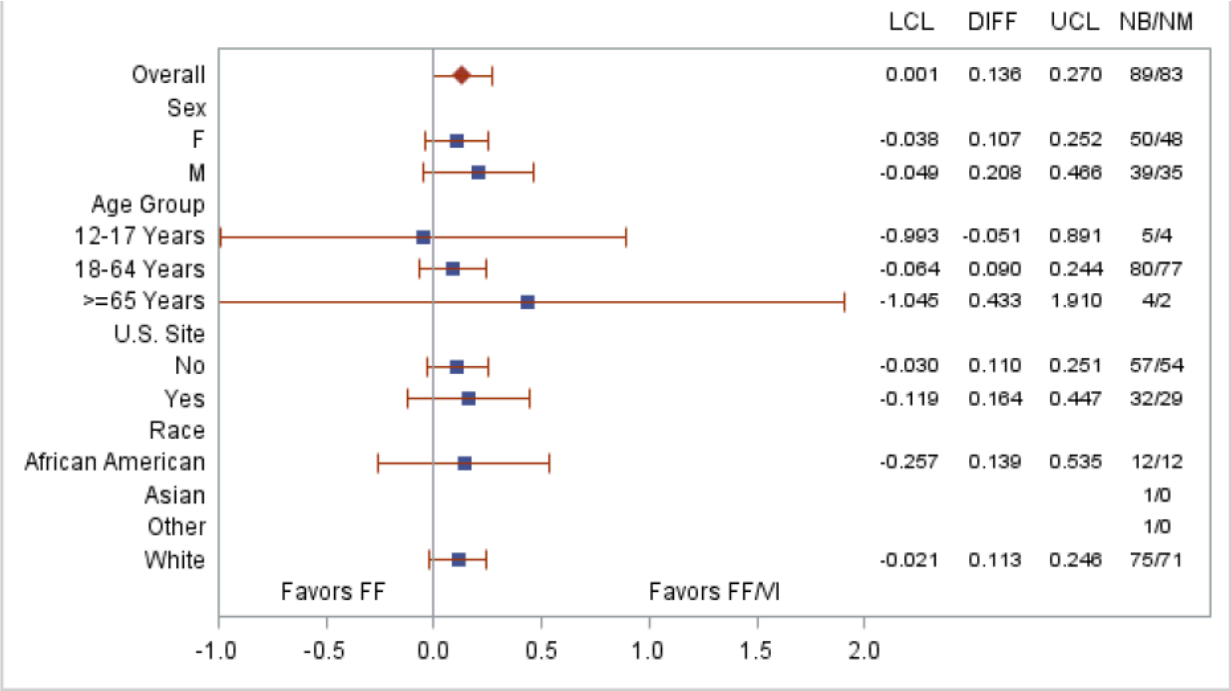
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NB/NM: Number of patients under the FF/VI (Breo) arm versus number of patients under the FF (Mono Therapy) arm.

Figure 10. Subgroup Analyses of Trial HZA116863 for Trough FEV1: Estimated Difference of FF/VI 100/25 vs. FF100 with 95% CI



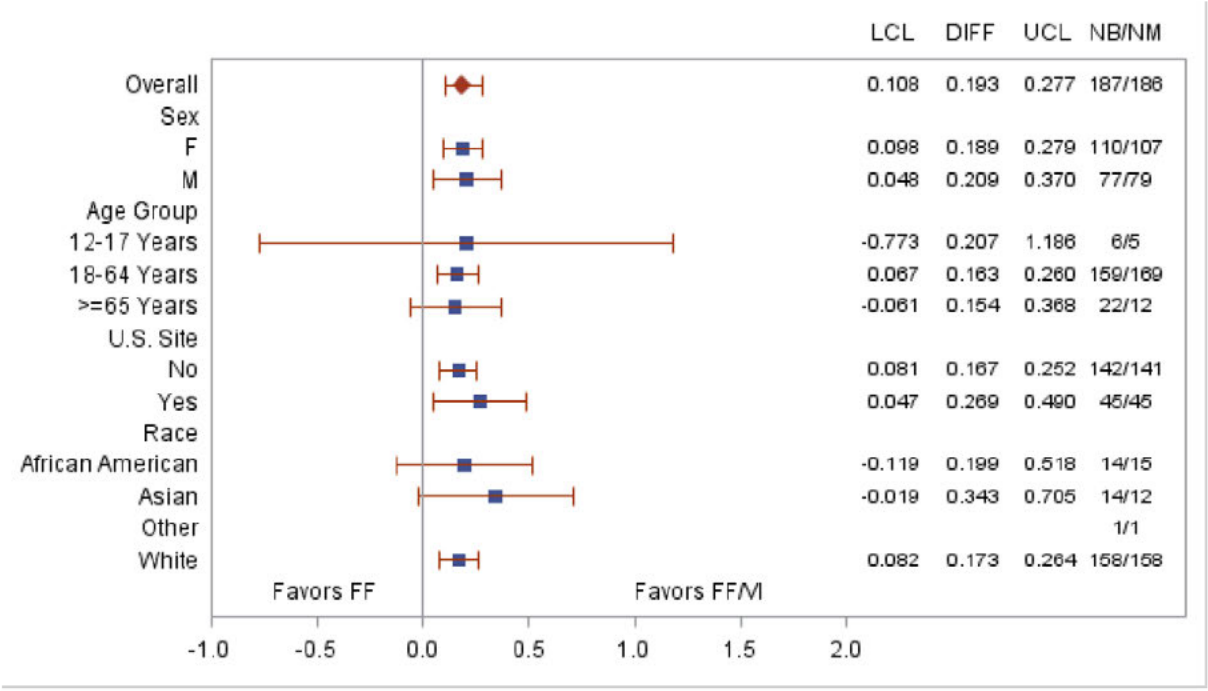
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NB/NM: Number of patients under the FF/VI (Breo) arm versus number of patients under the FF (Mono Therapy) arm.

Figure 11. Subgroup Analysis HZA106829 for Weighted Mean FEV1: Estimated Difference of FF/VI 200/25 vs. FF200 with 95% CI



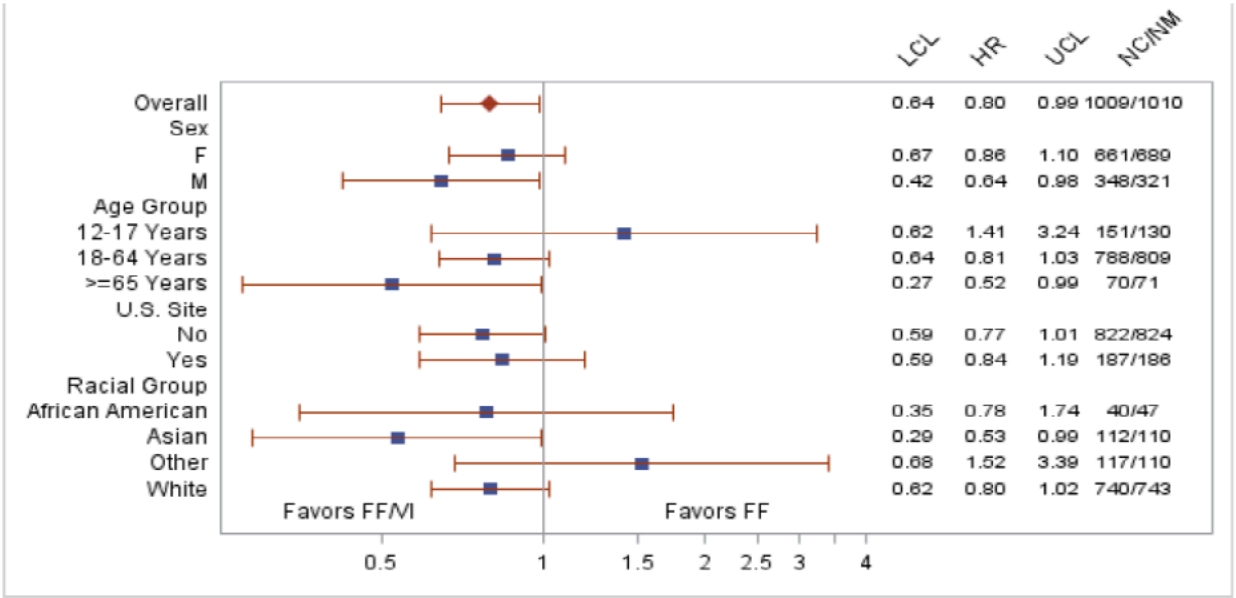
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NB/NM: Number of patients under the FF/VI (Breo) arm versus number of patients under the FF (Mono Therapy) arm.

Figure 12. Subgroup Analysis HZA106829 for Trough FEV1: Estimated Difference of FF/VI 200/25 vs. FF200 with 95% CI

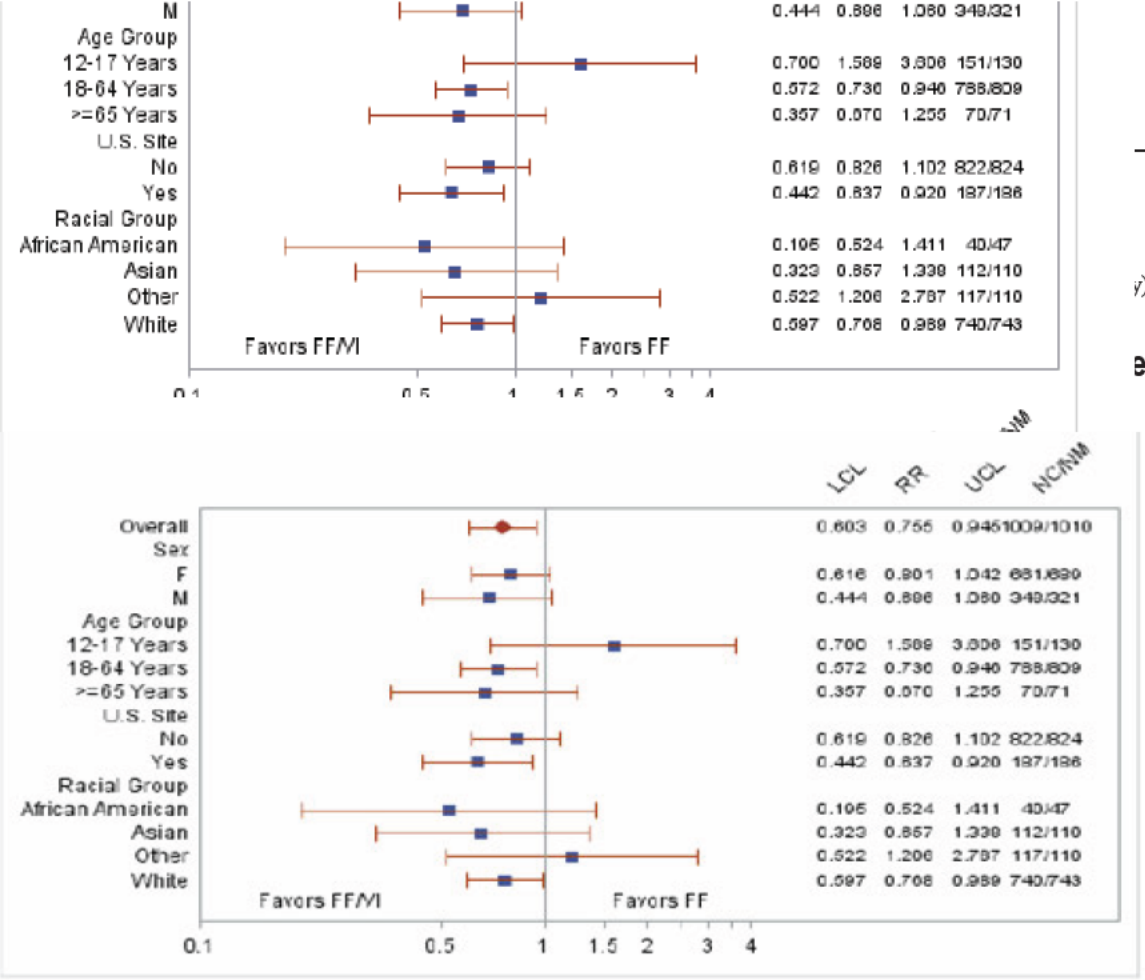


Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Breo) arm versus number of patients under the FF (Mono Therapy) arm.

Figure 13. Subgroup Analysis of Trial HZA106837 for Time to First Asthma Exacerbation



Source: Agency's Statistical Reviewer
HR: Estimated hazard ratio from analysis with a Cox Proportion hazard model of time to first asthma exacerbation between the



Source: Agency's Statistical Reviewer
HR: Estimated hazard ratio from analysis with a Cox Proportion hazard model of time to first asthma exacerbation between the FF/VI and FF.
LCL: Lower limit of the confidence interval of the hazard ratio;
UCL: Upper limit of the confidence interval of the hazard ratio
NC/NM: Number of patients under the FF/VI (Combination) arm versus number of patients under the FF (Mono Therapy) arm.

6.1.7.1 Pediatric patients – 12 to 17 years old

Based on examination of the subgroups in each of the trials, along with the existing concern that there is a greater risk of LABA-related serious asthma outcomes in pediatric patients, the efficacy of FF/VI in the pediatric subgroup of 12 to 17 year olds was analyzed further with respect to FEV1 response and time to first exacerbation.

Section 6.1.7.1.1 describes the weighted mean serial FEV1 response in trials HZA106827, HZA116863, and HZA106829. Section 6.1.7.1.2 describes the trough FEV1 response for these same three trials, including some data from the pediatric subgroup analysis of FF alone from the Arnuity Ellipta (NDA 205625) development program. Section 6.1.7.1.3 includes a more focused analysis of adolescents 12 to 17 years of age in Trial HZA113091, in which Breo Ellipta was compared with Advair. To conclude this section, Section 6.1.7.1.4 includes a subgroup analysis in the same age group in Trial HZA106837, examining time to first asthma exacerbation.

6.1.7.1.1 Weighted Mean Serial FEV1 – 12 to 17 year olds

The following section shows the subgroup analyses for weighted mean serial FEV1 (0-

24 hours) for the subgroup of patients included in studies HZA106827, HZA116863, and HZA106829. The forest plots show three age groups (12 to 17, 18 to 64, and ≥ 65 years and older. For the purposes of the tables, the adult populations were grouped together. Weighted mean serial FEV1 is intended to show the contribution of vilanterol to the combination of FF/VI. Therefore, the comparison of interest is of FF/VI to FF.

Table 42. Trial HZA106827: Change from Baseline in Weighted Mean Serial FEV1 at Week 12

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	Placebo N=24	**FF100 N=19**	**FF/VI 100/25 N=14**	**Placebo N=71**	**FF100 N=87**	**FF/VI 100/25 N=94**
LS Mean Change from Baseline (mL)	442	648	675	184	343	452
Difference vs. Placebo (mL) 95% CI p-value		207 (-116, 530) 0.21			159 (15, 303) 0.03	
Difference vs. FF100 (mL) 95%CI p-value			27 (-347,400) 0.89			109 (-27, 244) 0.12

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.80

Table 43. Trial HZA116863: Change from Baseline in Weighted Mean Serial FEV1 at Week 12

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	FF 100 N=21	FF/VI 100/25 N=21	FF/VI 200/25 N=13	FF 100 N=267	FF/VI 100/25 N=291	FF/VI 200/25 N=299
LS Mean Change from Baseline (mL)	967	770	985	343	447	463
Difference vs. FF100 (mL) 95% CI p-value		-190 (-496, 115) 0.22			104 (36, 171) <0.01	
Difference vs. FF/VI 100/25 (mL) 95%CI p-value			215 (-155, 584) 0.25			17 (-49, 82) 0.62

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.12

Table 44. Trial HZA106829: Change from Baseline in Weighted Mean Serial FEV1 at Week 24

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	FP 500 N=5	FF 200 N=4	FF/VI 200/25 N=5	FP 500 N=81	FF 200 N=79	FF/VI 200/25 N=84
LS Mean Change from Baseline (mL)	1084	695	644	197	345	428
Difference vs. FP 500 (mL) 95% CI p-value		-390 (-1212, 433) 0.31	-441 (-1382, 500) 0.31		148 (-5, 302) 0.06	231 (82, 380) <0.01

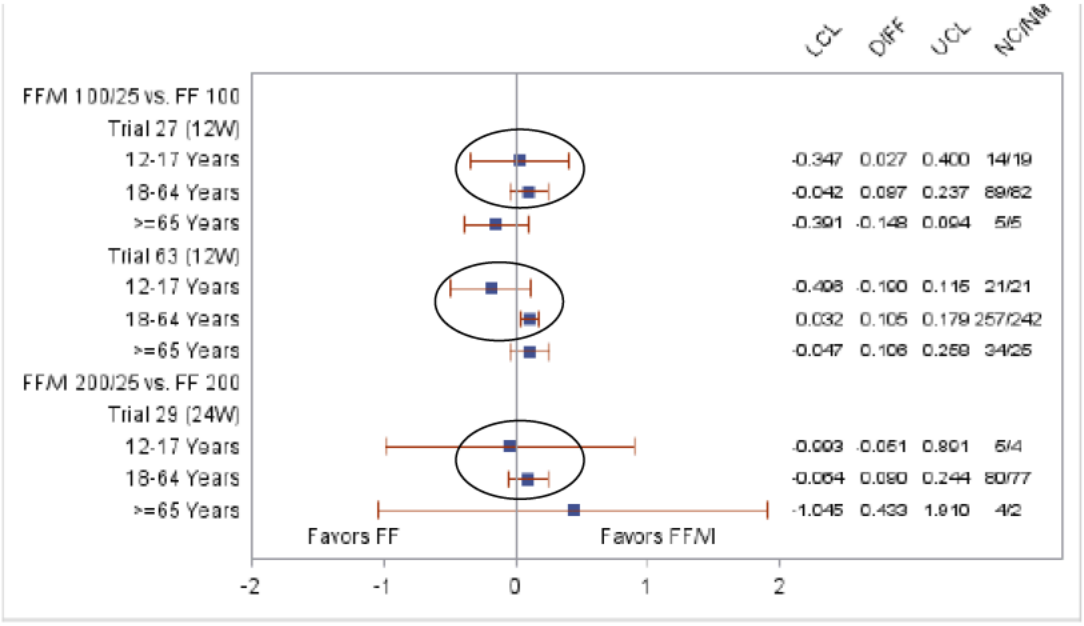
Table 44. Trial HZA106829: Change from Baseline in Weighted Mean Serial FEV1 at Week 24

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	FP 500 N=5	FF 200 N=4	FF/VI 200/25 N=5	FP 500 N=81	FF 200 N=79	FF/VI 200/25 N=84
Difference vs. FF200						
(mL)			-51			83
95%CI			(-993, 891)			(-68, 234)
p-value			0.90			0.28

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.27

A summary of the data is provided in the figure below.

Figure 15. Estimated Treatment Difference of FF/VI vs. FF for Weighted Mean Serial FEV1 (0-24 hours in Trials HZA106827, 116863, and 106829 for Subgroups of Patients by Age



Source: Agency's Statistical Reviewer
LCL: Lower limit of the confidence interval of the hazard ratio;
UCL: Upper limit of the confidence interval of the hazard ratio
NC/NM: Number of patients under the FF/VI (Combination) arm versus number of patients under the FF (Mono Therapy) arm.

The number of patients in each subgroup is small. With the exception of the subgroup ≥ 18 years old in Trial HZA116863, none of the differences within subgroups is statistically significant. The treatment difference between subgroups is also not statistically significant. With this limitation in mind, when the 12 to 17 year old subgroup is compared to the subgroup 18-64 years of age, there is a numerical trend towards a smaller observed treatment effect in younger patients in the FF/VI treatment arm compared to the FF alone treatment arm in all three studies for weighted mean serial FEV1 (0-24 hours).

6.1.7.1.2 Trough FEV1 – 12 to 17 year olds

The following section shows the subgroup analyses for change from baseline in trough FEV1 for the subgroup of patients included in studies HZA106827, HZA116863, and HZA106829. The forest plots show three age groups (12 to 17, 18 to 64, and ≥ 65 years and older). For the purposes of the tables, the adult populations were grouped together. Some results of the pediatric subgroup analysis in the FF program are shown in this section as a means of reference.

Table 45. Trial HZA106827 Change from Baseline in Trough FEV1 at Week 12

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	Placebo N=33	FF100 N=28	FF/VI 100/25 N=21	Placebo N=160	FF100 N=175	FF/VI 100/25 N=179
LS Mean Change from Baseline (mL)	365	520	526	197	292	327
Difference vs. Placebo (mL) 95% CI p-value		155 (-105,415) 0.24			95 (1,189) 0.05	
Difference vs. FF100 (mL) 95%CI p-value			6 (-286,300) 0.97			36 (-555,127) 0.44

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.63

Table 46. Trial HZA116863: Change from Baseline in Trough FEV1 at Week 12

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	FF 100 N=23	FF/VI 100/25 N=21	FF/VI 200/25 N=14	FF 100 N=313	FF/VI 100/25 N=313	FF/VI 200/25 N=323
LS Mean Change from Baseline (mL)	954	758	854	341	425	414
Difference vs. FF100 (mL) 95% CI p-value		-196 (-498, 105) 0.20			84 (18,150) 0.01	
Difference vs. FF/VI 100/25 (mL) 95%CI p-value			96 (-262,455) 0.59			-11 (-76, 55) 0.75

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.17

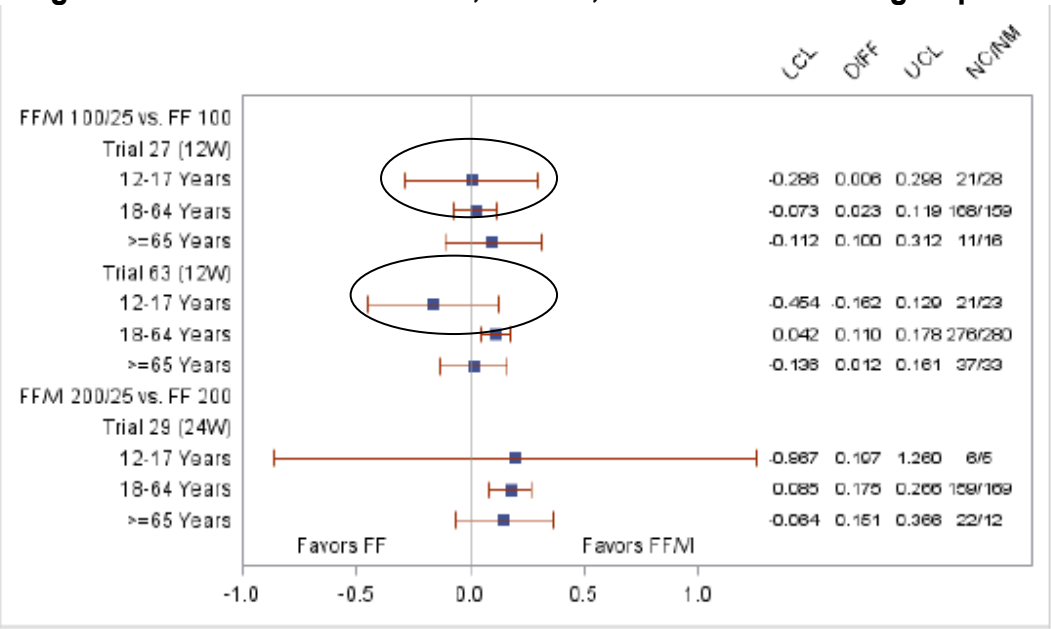
Table 47. Trial HZA106829: Change from Baseline in Trough FEV1 at Week 24

	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	FP 500 N=8	FF 200 N=5	FF/VI 200/25 N=6	FP 500 N=182	FF 200 N=181	FF/VI 200/25 N=181
LS Mean Change from Baseline (mL)	648	836	1043	151	205	364
Difference vs. FP 500 (mL) 95% CI p-value		198 (-693, 1090) 0.64	405 (-452, 1262) 0.33		54 (-35,144) 0.24	214 (125, 303) <0.0001
Difference vs. FF200 (mL) 95%CI p-value			207 (-773, 1186) 0.66			160 (70, 249) 0.0005

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.71

A summary of the data are provided in the figure below:

Figure 16.Estimated Treatment Difference of FF/VI vs. FF, Change from Baseline in Trough FEV1 in Trials HZA106827, 116863, and 106829 for Subgroups of Patients

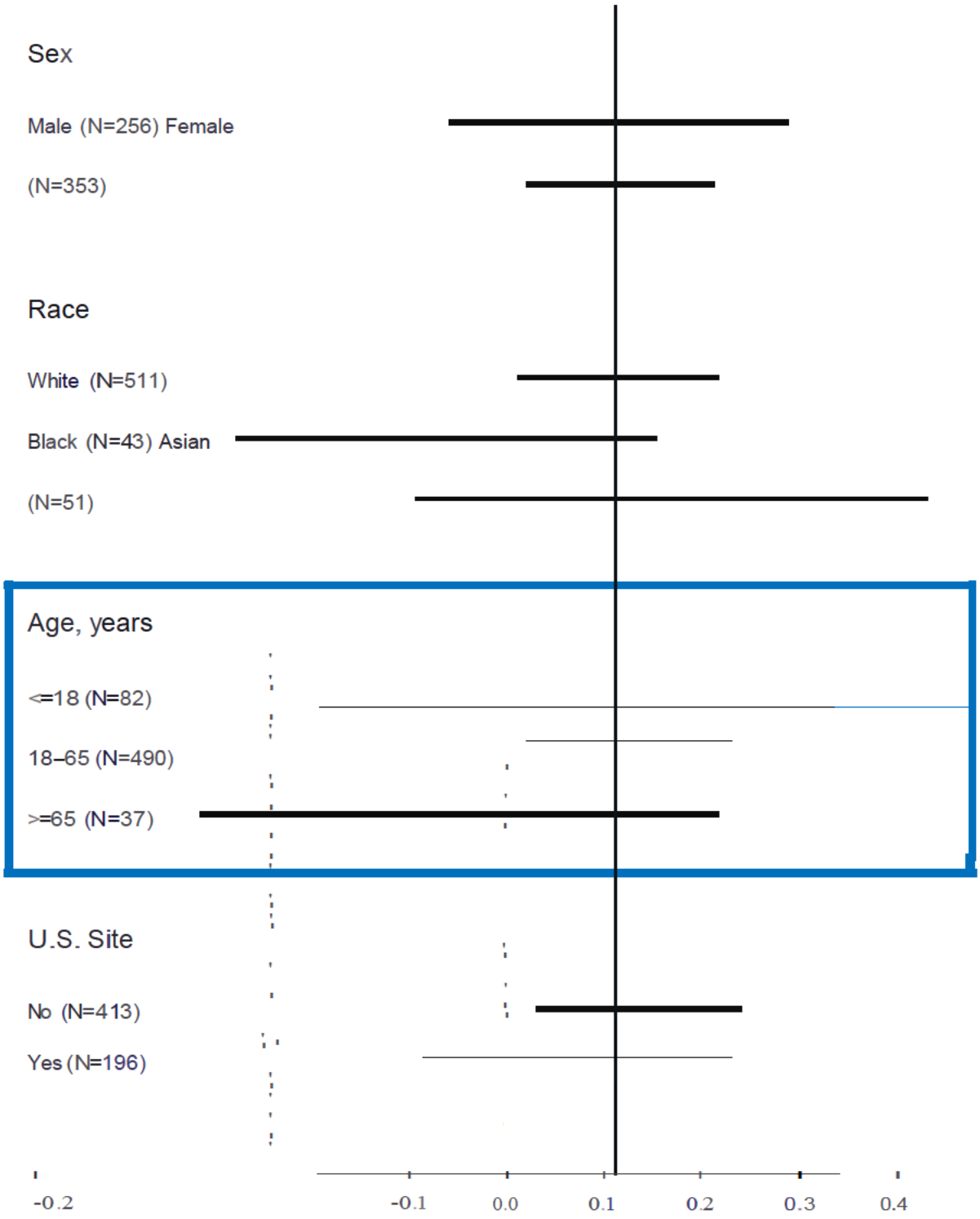


Source: Agency's Statistical Reviewer
LCL: Lower limit of the confidence interval of the hazard ratio;
UCL: Upper limit of the confidence interval of the hazard ratio
NC/NM: Number of patients under the FF/VI (Combination) arm versus number of patients under the FF (Mono Therapy) arm.

The number of patients in each subgroup is small. The treatment effect within subgroups and the difference between the two subgroups are not statistically significant. With this limitation in mind, when the 12 to 17 year old subgroup is compared to the subgroup ≥ 18 years of age, the treatment effect is more variable across trials, with two trials showing a numerical trend towards a smaller observed treatment effect in younger patients (HZA106827 and HZA116863) and one trial showing a slightly larger numerical effect, albeit with wide confidence intervals (Trial HZA106829).

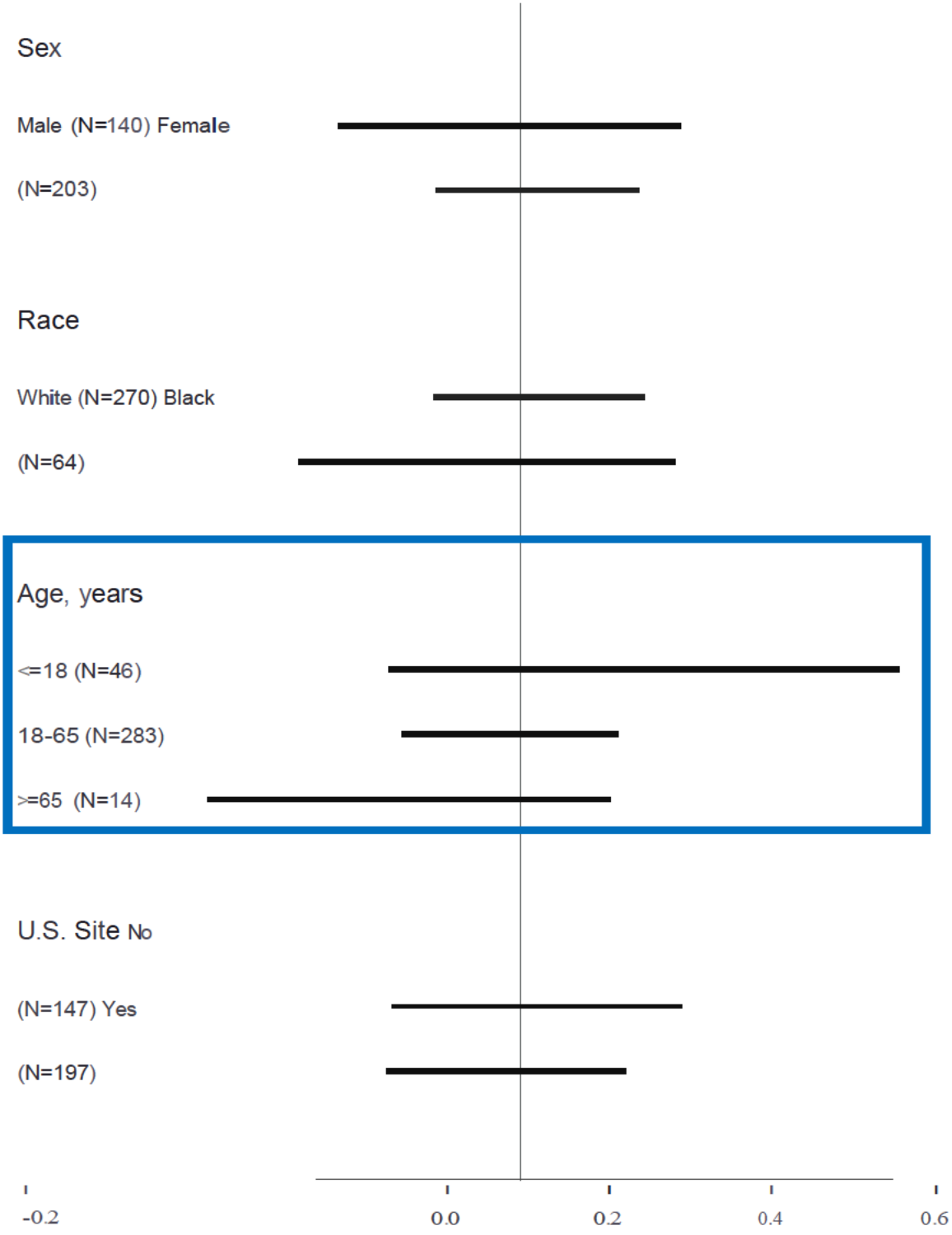
As discussed, FF monotherapy has already been shown to have efficacy in asthma. The subgroup analysis with an emphasis on the analysis by age are included below in Figure 17 and Figure 18 for reference. As can been seen from the Forest plots below, FF alone has a numerically comparable treatment effect when the 12 to 17 year old subgroup (<18 years) is compared with the subgroup ≥18 years old, and to the overall population.

Figure 17. Estimated Treatment Effect of FF, Stratified by Selected Subgroups in HZA106827. (Solid vertical line represents estimated treatment effect in overall population, and dashed vertical line represents no difference)



Source: Agency's Statistical Review, Arnuity Ellipta NDA 205625

Figure 18. Estimated Treatment Effect of FF, Stratified by Selected Subgroups in FFA112059. (Solid vertical line represents estimated treatment effect in overall population, and dashed vertical line represents no difference)



Source: Agency's Statistical Review, Arnuity Ellipta NDA 205625

6.1.7.1.3 Comparison to Advair – Trial HZA113091 – 12 to 17 year olds

Analysis of the lung function endpoints revealed a consistent, numerically lower treatment response in pediatric patients. Given that data, and that the serial FEV1 data in pediatrics for trial HZA113091 were also available, and this is most reflective of the LABA effect, a more focused analysis of pediatrics vs. the overall population was evaluated.

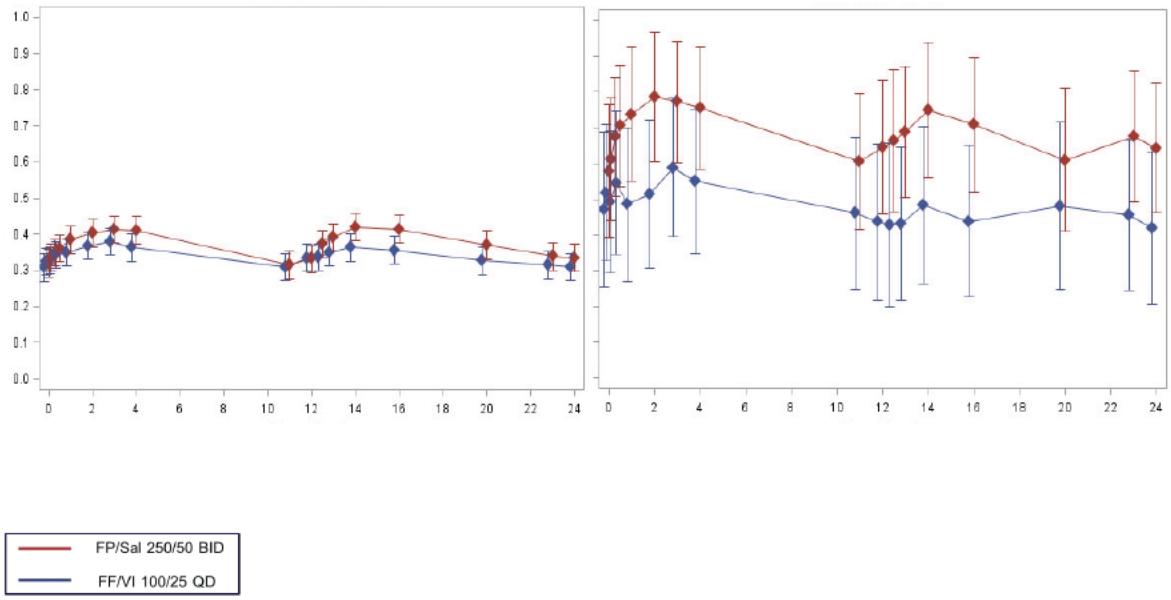
Table 48. Mean Change from Baseline in Weighted Mean Serial FEV1 at Week 24: Trial HZA113091

	All Patients		Patients 12-17 years of Age	
	FP/Sal N=347	FF/VI N=352	FP/Sal N=38	FF/VI N=29
LS Mean Change from Baseline (mL)	377	341	691	488
Difference vs. Fp/Salm 250/50 (mL) 95% CI		-37 (-88, 15)		-203 (-478, 71)

Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.18

As is displayed in Table 48, FF/VI 100/25 tended to show a numerically smaller response compared to Advair 250/50 BID in subjects 12 to 17 years of age. Although Breo performed numerically worse in the overall population as well (-37mL; 95% CI -88, 15, see Table 35), the effect was more pronounced when examining the younger subgroup, again suggesting a differential response to vilanterol in this age group. The treatment effect within subgroups and the difference between the two subgroups are not statistically significant. While the numbers of patients in the pediatric subgroup are small, the numbers appear adequate to assess a bronchodilator effect.

Figure 19: LS Mean Change from Baseline in FEV1 at Week 24 (Left panel, all patients; right panel, 12 to 17 year olds)



Source: Agency's Statistical Reviewer

6.1.7.1.4 Asthma Exacerbations – Trial HZA106837 – 12 to 17 year olds

In Trial HZA106837, the primary endpoint was time to first asthma exacerbation, and a secondary endpoint was rate of asthma exacerbations. The data was once again examined by the subgroups of gender, age, geographical region, and race. Because of the known safety concerns with respect to serious asthma related events in particular subpopulations as well as the increased number of asthma hospitalizations in 12-17 year olds seen in the Agency's meta-analysis, the review was then focused on the pediatric and African American subgroups in the exacerbation trial as well. Table 49, Table 50, Figure 13, and Figure 14 illustrate these sub-group analyses. Unlike in the Forest plots above, please note that in the following tables, > 18 year olds encompass those > 65 years of age as well.

Table 49. Time to First Asthma Exacerbation: Trial HZA106837 (Subgroup Analysis by Age 12 to 17 Years Old)

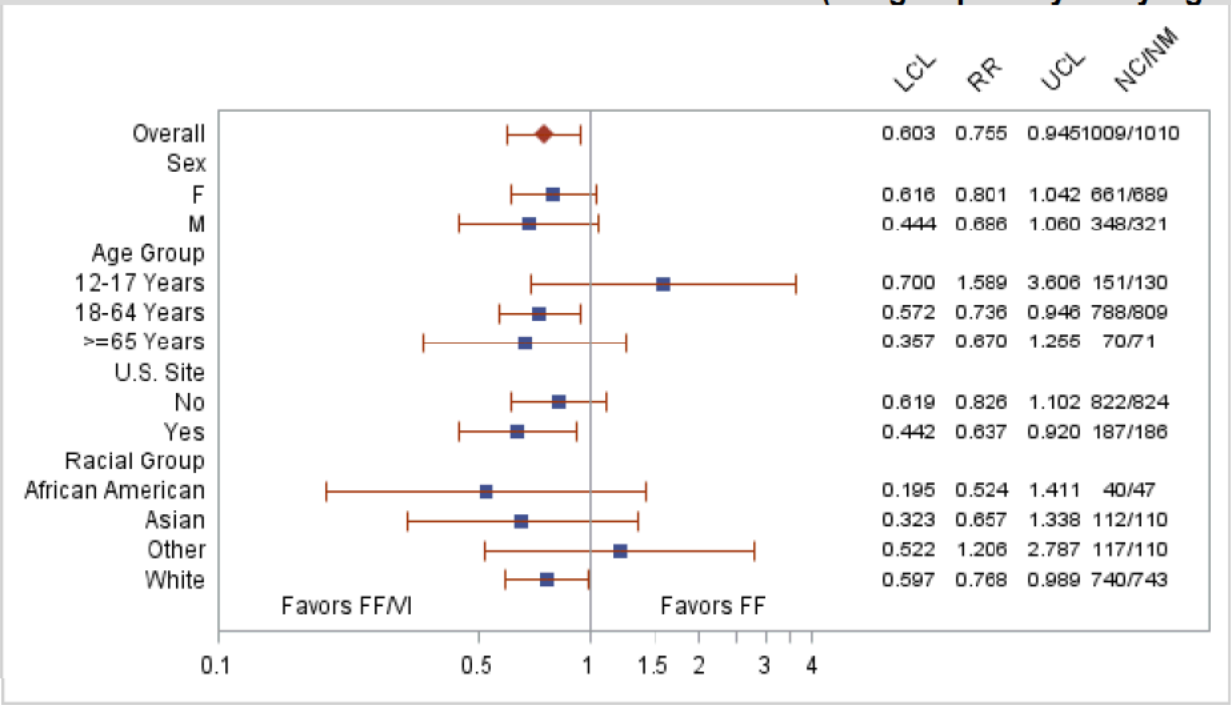
	ITT Population		12 to 17 years		≥ 18 years	
	FF 100 N=1010	FF/VI 100/25 N=1009	FF 100 N=130	FF/VI 100/25 N=151	FF 100 N=880	FF/VI 100/25 N=858
Number of Subjects with 1+ Asthma Exacerbation, n	186	154	9	15	177	139

Table 49. Time to First Asthma Exacerbation: Trial HZA106837 (Subgroup Analysis by Age 12 to 17 Years Old)

	ITT Population		12 to 17 years		≥ 18 years	
	FF 100 N=1010	FF/VI 100/25 N=1009	FF 100 N=130	FF/VI 100/25 N=151	FF 100 N=880	FF/VI 100/25 N=858
Adjusted probability of 1+ Asthma Exacerbation by 52 weeks, % (95% CI)	15.9 (13.5, 18.2)	12.8 (10.7, 14.9)	8.7 (3.0, 14.0)	12.0 (6.0, 17.6)	16.8 (14.2, 19.4)	13.1 (10.8, 15.4)
FF/VI 100/25 vs. FF 100 Hazard ratio 95% CI p-value		0.795 (0.642, 0.985) 0.04		1.405 (0.614, 3.213) 0.42		0.764 (0.612, 0.955) 0.02

Source: Agency's Statistical Reviewer
Interaction analysis performed with a cox proportional hazard model by including treatment, baseline FEV1, region, sex, age group and age group * treatment interaction as covariates, Interaction test p=0.16
analysis conducted of on-treatment exacerbations: which was defined as first dose date ≤ AE start date ≤ last dose date + 1

Table 50. Rate of Asthma Exacerbation: Trial HZA106837 (Subgroup Analysis by Age



In trial HZA106837, the adolescent population comprised about 13 to 15% of the total study population. This trial had the largest adolescent subgroup for analysis. When the

12 to 17 year old subgroup is compared to the subgroup ≥ 18 years of age, it is notable that the 20% reduction in risk to time to first exacerbation in the overall population was in the reverse direction and showed a higher risk estimate of time to first exacerbation in patients 12 to 17 years old (HR 1.4 (0.61, 3.21)). This trend was further supported by the analysis of the rate of asthma exacerbations, which similarly showed that the 25% reduction in rate of exacerbations in the overall population was now in the reverse direction and showed a higher risk estimate for patients 12 to 17 years of age (Ratio 1.60; 95% CI (0.70, 3.61)). The numerical trend in the exacerbation data which is in favor of FF over FF/VI is also of concern.

As shown in Table 51, of these subjects 12 to 17 years of age, 2% of subjects were hospitalized or visited the ED/urgent care, as compared to none in the FF 100 arm. Similar to the adults, most exacerbations were defined by corticosteroid use rather than hospitalizations or ED visits.

Table 51. Hospitalizations and ED Visits due to Asthma Exacerbations: Trial HZA106837 (Subgroup Analysis by Age 12 to 17 Years Old)

	FF 100 N=1010	FF/VI 100/25 N=1009
Number of subjects 12 to 17 years old	**n = 130**	**n = 151**
Number of Subjects with 1+ Asthma Exacerbation, n(%)	9 (7)	15 (10)
Number of Subjects Hospitalized*	0	3 (2)
Number of ED/Urgent Care Clinic Visits*	0	3 (2)
Intubations/Deaths	0	0

Source: Information Request Response to Information Request Dates 11/12/14
exacerbations were counted if on-treatment: first dose date ≤ AE start date ≤ last dose date + 1

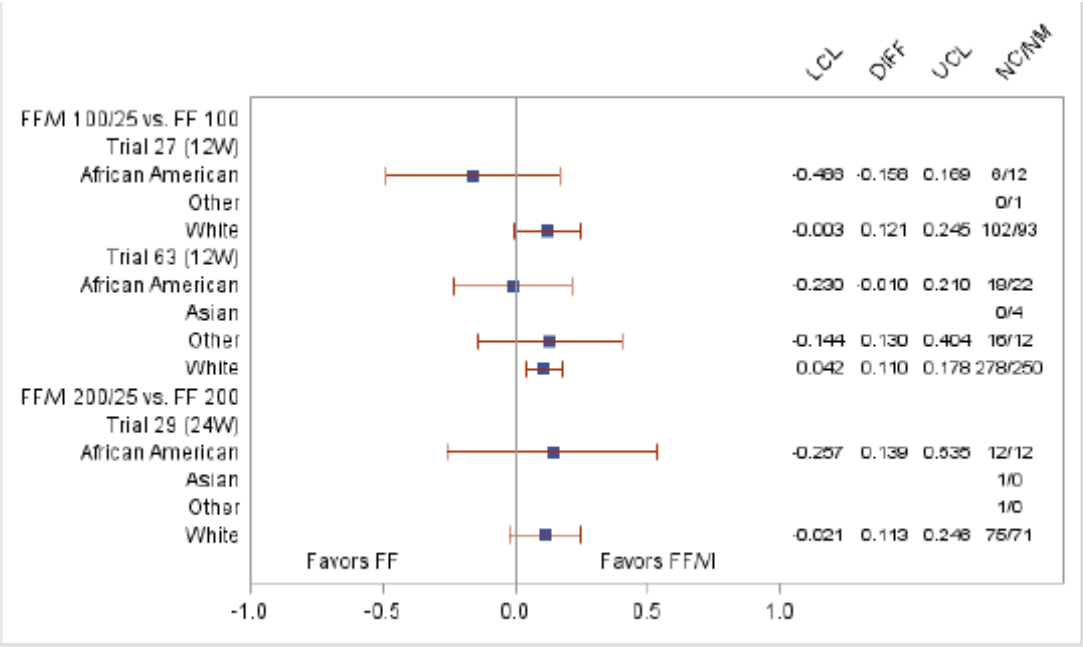
Similar to lack of consistent FEV_1 response in patients 12 to 17 years, the exacerbation response was also not consistent with response in the total study population. The numerical trend was against FF/VI compared to FF.

6.1.7.2 Race

Based on the concern for greater risk with LABA use for African American patients, the efficacy of FF/VI was further examined in regards to lung function for racial subgroups. Groups analyzed include African Americans (or those of African Ancestry), Asian, Other and White. The other group is a category that consists of a Native Hawaiian, Pacific Islander, American Indian or Alaskan Native, and Mixed Race. The majority of the "other" category is "mixed race" which includes Asian/White, African/White, American Indian/White, Alaskan/White. While the confidence intervals are overlapping and the numerical differences are small, the point estimate for the treatment difference between FF/VI and FF is numerically smaller for African American patients for weighted mean

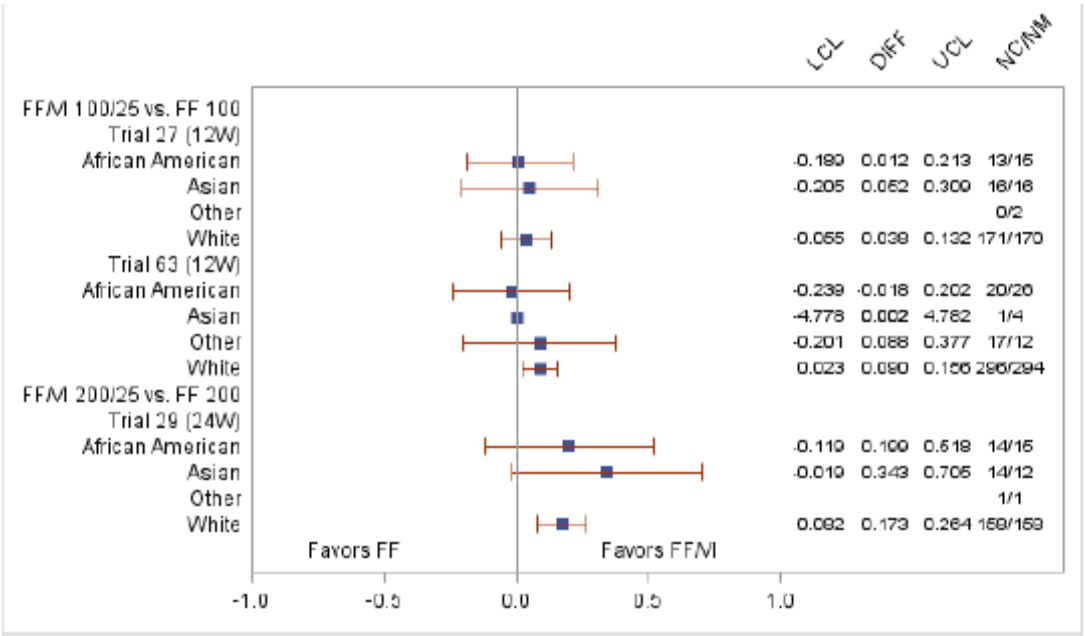
FEV1 in two of the three trials when compared to white patients (Figure 20) and for trough FEV1 in one trial (Figure 21).

Figure 20. Weighted Mean FEV1 – Race Groups in Trials 27, 63, and 29



Source: Agency's Statistical Reviewer
LCL: Lower limit of the confidence interval of the hazard ratio;
UCL: Upper limit of the confidence interval of the hazard ratio
NC/NM: Number of patients under the FF/VI (Combination) arm versus number of patients under the FF (Mono Therapy) arm.

Figure 21. Trough FEV1 – Race Groups in Trials 27, 63, and 29



Source: Agency's Statistical Reviewer
LCL: Lower limit of the confidence interval of the hazard ratio;

UCL: Upper limit of the confidence interval of the hazard ratio
NC/NM: Number of patients under the FF/VI (Combination) arm versus number of patients under the FF (Mono Therapy) arm.

In trial HZA106837, when examined for the time to first exacerbation, the point estimate for the African American subgroup falls to the left of the line, favoring FF/VI with a treatment effect that is generally consistent with the effect in the overall population (Figure 13). This is also seen in rate of exacerbation (Figure 14).

Reviewer's Comment: There does not appear to be a consistent difference between race and the overall treatment population in regards to efficacy of FF/VI.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See information regarding dose-ranging studies in Section 4.4.2.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Efficacy persisted over the treatment period based on the data provided.

6.1.10 Additional Efficacy Issues/Analyses

Additional analyses were conducted in the adolescent population and by race as described in Section 6.1.7.

7 Review of Safety

Safety Summary

Given the risk of serious asthma outcomes (hospitalizations, intubations, and death) with the use of LABA for asthma, the Agency conducted a meta-analysis of the submitted data to examine the risk of serious asthma outcomes with FF/VI (see Section 7.7.3, and a detailed discussion of the meta-analysis can be found in the statistical review by Dr. Janelle Charles). In this meta-analysis, there were no asthma-related intubations or deaths. There were a total of 18 asthma-related hospitalizations observed in the 4 trials included in the meta-analysis. There were 10 hospitalizations in the FF/VI group, and 8 in the FF group, which translated to a crude incidence rates of 0.7 per 100 person-years and 0.6 per 100 person-years for FF/VI and FF, respectively. The incidence rate difference was 0.1 per 100 person-years (95% CI -0.5, 0.8). Seventeen of the 18 hospitalization events were noted in Trial 37. As a result, subgroup analysis was conducted for this trial. A numerical imbalance was observed in the < 18 years age group with 4 hospitalizations observed in the FF/VI arm and no hospitalizations observed in the FF arm.

The safety data in this review will focus on safety findings unrelated to serious asthma-related outcomes.

In general, the safety profile unrelated to serious asthma outcomes of FF/VI is similar to that for other ICS/LABA products in asthma, and current product labeling contains warning language regarding these risks (i.e. class labeling for ICS effects, LABA effects).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The sponsor submitted a pooled safety analysis of eighteen parallel group Phase 2 and Phase 3 trials with FF/VI and/or an individual component (FF or VI). An additional 5 trials were not included into the pooled safety analysis by the sponsor because they had a different design (e.g. crossover or open label) or did not use the Ellipta inhaler.

The studies in the pooled safety database analyzed by the sponsor are listed below:

Table 52. Sponsor's Pooled Safety Database

Study	Phase	Study Design	Run-in (weeks)	Treatment (weeks)	Follow-up (weeks)	Treatment details (mcg; OD unless otherwise noted)	Total # of Subjects Randomized[1]
FFA109684	IIb	R, DB, DD, PC, AC, PG	4	8	1	FF 200 ELLIPTA FF 400 ELLIPTA FF 600 ELLIPTA FF 800 ELLIPTA FP 500 BD DISKUS Placebo	99 101 107 102 110 103
FFA109685	IIb	R, DB, DD, PC, AC, PG	4	8	1	FF 100 ELLIPTA FF 200 ELLIPTA FF 300 ELLIPTA FF 400 ELLIPTA FP 250 BD DISKUS Placebo	105 101 103 99 100 107
FFA109687	IIb	R, DB, DD, PC, AC, PG	4	8	1	FF 25 ELLIPTA FF 50 ELLIPTA FF 100 ELLIPTA FF 200 ELLIPTA FP 100 BD DISKUS Placebo	97 100 110 95 102 94
B2C109575	IIb	R, DB, PC, PG	2	4	1	VI 3 ELLIPTA (ICS) VI 6.25 ELLIPTA (ICS) VI12.5 ELLIPTA (ICS) VI 25 ELLIPTA (ICS) VI 50 ELLIPTA (ICS) Placebo (ICS)	101 101 100 101 102 102
HZA106827	III	R, DB, PC, PG	4	12	2	FF/VI 100/25 ELLIPTA FF 100 ELLIPTA Placebo	201 205 203

Study	Phase	Study Design	Run-in (weeks)	Treatment (weeks)	Follow-up (weeks)	Treatment details (mcg; OD unless otherwise noted)	Total # of Subjects Randomized[1]
HZA106829	III	R, DB, DD, AC, PG	4	24	1	FF/VI 200/25 ELLIPTA FF 200 ELLIPTA FP 500 BD DISKUS	197 194 195
HZA113091	III	R, DB, DD, AC, PG	4	24	1	FF/VI 100/25 ELLIPTA FP/SALM 250/50 BD DISKUS[2]	403 403
HZA113714	III	R, DB, DD, AC, PG	2	12	1	FF/VI 200/25 ELLIPTA FP 500 BD DISKUS	155 154
HZA113719	III	R, DB, PC, PG	2	12	1	FF/VI 100/25 ELLIPTA Placebo	153 154
HZA116863	III	R, DB, PG	4	12	1	FF/VI 100/25 ELLIPTA FF/VI 200/25 ELLIPTA FF 100 ELLIPTA	346 346 347
HZA106837	III	R, DB, PG	2	24 to 76	1	FF/VI 100/25 ELLIPTA FF 100 ELLIPTA	1009 1010
HZA106839	III	R, DB, DD, AC, PG	2	52	1	FF/VI 100/25 ELLIPTA FF/VI 200/25 ELLIPTA FP 500 BD DISKUS	201 202 100
HZA106851	III	R, DP, PC, AC, PG	1 to 2	6	1	FF/VI 100/25 ELLIPTA FF/VI 200/25 ELLIPTA Placebo + Prednisolone Placebo	56 56 15 58
FFA112059	III	R, DB, DD, PC, AC, PG	4	24	1	FF 100 ELLIPTA FP 250 BD DISKUS Placebo	114 114 115
FFA114496	III	R, DB, PG	4	24	1	FF 100 ELLIPTA FF 200 ELLIPTA	119 119
FFA115283	III	R, DB, PC, PG	2	12	1	FF 50 ELLIPTA Placebo	121 121
FFA115285	III	R, DB, DD, PC, AC, PG	2	24	1	FP 50 ELLIPTA FP 100 BD DISKUS Placebo	117 115 115
B2C112060	III	R, DB, DD, PC, AC, PG	4	12	2	VI 25 ELLIPTA (ICS) SALM 50 BD DISKUS (ICS) Placebo (ICS)	115 116 116

R=randomized, DB=double-blind, DD=double-dummy, PC=placebo-controlled, AC=active-controlled, PG=parallel group, (ICS) = on a consistent background of ICS, FF=fluticasone furoate, FP=fluticasone propionate, VI=vilanterol, BD=twice daily, SALM=salmeterol

1. Number of randomized subjects who received at least one dose of study medication
2. FP/SALM data from Study HZA113091 is only included in the integrated data sets for the summary of pneumonias; see Section 1.1.8 for additional details

The clinical development program for Breo Ellipta includes individual development programs for FF and VI. As a result, while the pooled safety database consisted of a large number of trials and patients, some of the pooled trials did not contain an FF/VI treatment arm, and therefore, were of limited utility in evaluating the safety of FF/VI in asthma. Trials that did include an FF/VI treatment arm were: HZA106827, HZA106829, HZA113091, HZA113714, HZA113719, HZA116863, HZA106837, HZA106839, and HZA106851. Trials HZA113714 and HZA113719 were small trials conducted in patients with Asian ancestry only; trial HZA106851 was an HPA axis study that was reviewed as part of the Arnuity Ellipta NDA (NDA205625). As a result, this clinical review focuses on the safety information for FF/VI in trials HZA106827, HZA116863, HZA106829, HZA106837, and HZA106839, for the review of safety information unrelated to serious asthma-related outcomes. Because each of these trials was either of a different duration or included different treatment arms, the review examines the safety of FF/VI in asthma by study. Summary data of the sponsor's pooled analysis will be provided throughout this review where relevant.

7.1.2 Categorization of Adverse Events

Adverse events (AEs) were defined as any untoward medical occurrence in a patient or clinical investigational subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE was therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. A Serious Adverse Event (SAE) is defined according to the regulatory definition[1].

All adverse events in the ISS were coded or re-coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.1. For specific safety concerns associated with use of ICS and LABA, GSK identified a list of specific Adverse Events of Special Interest and defined these using a comprehensive list of MedDRA Preferred Terms. The events, categorized into Groups and Subgroups, are as follows in Table 53.

Table 53. Adverse Events of Special Interest

Special Interest AE Group	Special Interest AE Subgroup
Bone Disorders	Bone Disorders
Cardiovascular Effects	Acquired Long QT
	Cardiac Arrhythmia
	Cardiac Failure
	Cardiac Ischemia
	Hypertension
	Sudden Death
Effects on Glucose	Effects on Glucose
Effects on Potassium	Effects on Potassium
Hypersensitivity	Hypersensitivity
Local Steroid Effects - e.g.- Oropharyngeal candidiasis, hoarseness	Local Steroid Effects
Ocular Effects	Ocular Effects
Pneumonia and Lower Respiratory Tract Infection (LRTI)	Pneumonia
	LRTI (Excluding Pneumonia)
Systemic Corticosteroid Effects – Effect on HPA-Axis	Systemic Corticosteroid Effects – Effect on HPA Axis
Tremor	Tremor

1 Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience(defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The pooling of the data included 18 phase 2 and 3 studies using the Ellipta device, some of which did not include an FF/VI arm. Therefore, this is not a clinically relevant pooling strategy so will not be utilized for this majority of this review. Instead, the pertinent studies with FF/VI arms are being reviewed separately as discussed in Section 7.1.1.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

7.2.1.1 Extent of Exposure

From the pooled safety database provided by the sponsor, a total of 13,379 subjects received at least one dose of any study medication in the FF/VI asthma clinical development program (including n=403 receiving FP/Salmeterol). Of this total (which includes the monotherapies of FF and VI), 3,325 subjects received at least one dose of FF/VI (See Table 54).

Table 54. Total Subjects Treated in the FF/VI Asthma Clinical Program (ITT)

	Total Subjects Treated[1]			
Study Grouping	ITT[2]	FF/VI[3]	FF[3]	VI[3]
Integrated Studies[4]	10,322[5]	3325	3565	620
Non-integrated Studies[4, 6]	1729	153	1162	61
Clinical Pharmacology	1328	397	747	395
Adult (18-75 years)	1247	372	696	368[7]
Pediatric (5-11 years)	81	25	51	27
Program Total	13,379	3875	5474	1076

Source: Table 1.02, Table 11.3, Table 11.22, Table 12.3

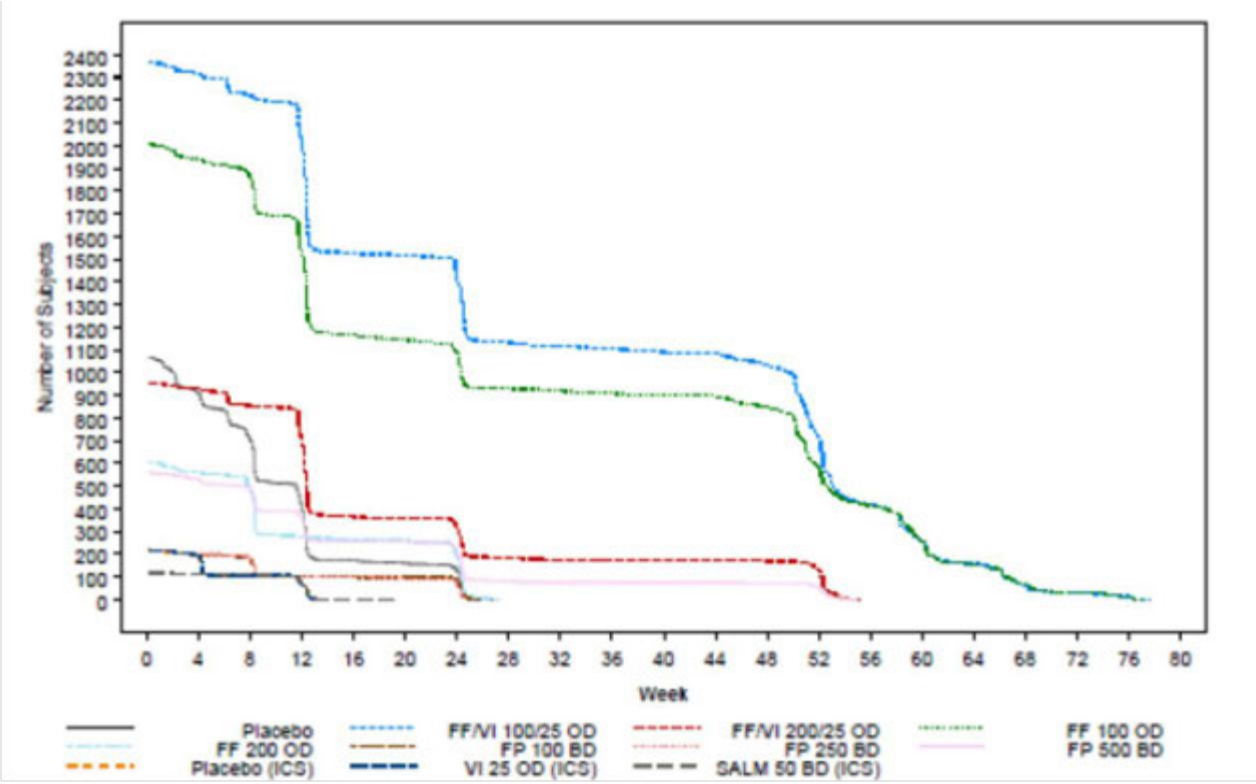
1. Numbers provided are not unique subjects (i.e., subjects who participated in more than one study or subjects in the Clinical Pharmacology Program who participated in multiple periods in crossover design studies are counted more than once).
2. Includes subjects treated with at least one dose of any study medication (placebo, active, or comparator) given by any route of administration.
3. All orally inhaled doses studied (regardless of inhaler used).
4. Integrated and Non-integrated Studies included adolescent and adult subjects (≥12 years of age).
5. Includes 403 subjects who were randomized to FP/SALM 250/50 BD.
6. For the two crossover studies (FFA112202 and HZA113310), only the first treatment period was used for counting subjects.
7. 135 of these subjects received the (b) (4) of VI

Source: Module 5.3.5.3, ISS, Table 7, pg. 50

Of the 9,969 subjects randomized into the pooled safety database, 9919 (>99%) received at least one dose of study medication. Not each subject is unique in this total, since 437 subjects participated in more than one clinical study and are counted two times (415 subjects), three times (20 subjects) or four times (2 subjects). The majority of these subjects participated in one Phase II study (B2C109575, FFA109684, FFA109685, or FFA109687) and subsequently participated in a Phase III study (HZA106827, HZA106829, HZA106837, HZA106839, HZA116863, HZA113091, FFA112059, FFA115283, FFA115285, FFA114496 or B2C112060).

In the Sponsor's pooled safety database, the treatment groups to which the largest number of subjects were exposed were FF 100 or FF/VI 100/25, primarily because this treatment was administered in the large, long-term exacerbation study, HZA106837, for up to 76 weeks (See **Error! Reference source not found.**).

Figure 22. Treatment Exposure – Pooled Safety Database (ITT Population)



Source: Module 5.3.5.3, ISS, Figure 2, Page 52

A total of 7447 subjects were included in what the sponsor identified as seven key treatment groups of interest. This is shown in Table 55.

Table 55. Sponsor's Pooled Safety Database (ITT)

	Number of Subjects						
	Placebo	FF/VI 100/25	FF/VI 200/25	FF 100	FF 200	Placebo (ICS)	VI 25 (ICS)
All Studies	1070	2369	956	2010	608	218	216
B2C109575	0	0	0	0	0	102	101
B2C112060	0	0	0	0	0	116	115
FFA109684	103	0	0	0	99	0	0
FFA109685	107	0	0	105	101	0	0
FFA109687	94	0	0	110	95	0	0
FFA112059	115	0	0	114	0	0	0
FFA114496	0	0	0	119	119	0	0
FFA115283	121	0	0	0	0	0	0
FFA115285	115	0	0	0	0	0	0
HZA106827	203	201	0	205	0	0	0
HZA106829	0	0	197	0	194	0	0
HZA106837	0	1009	0	1010	0	0	0
HZA106839	0	201	202	0	0	0	0
HZA106851	58	56	56	0	0	0	0
HZA113091	0	403	0	0	0	0	0
HZA113714	0	0	155	0	0	0	0
HZA113719	154	153	0	0	0	0	0
HZA116863	0	346	346	347	0	0	0

Source: Module 5.3.5.3, ISS, Table 9, pg. 53

Of those trials shown in the table above, only a subset included an FF/VI treatment group. Table 56 displays the total number of subjects exposed in the clinical trials that contained a FF/VI treatment arm.

Table 56. Number of Subjects Exposed in Trials Including an FF/VI Treatment Arm

		FF (mc) QD		FP 500 mcg	FP/Salm	FF/VI (mcg) once a day	
	Placebo	100	200	BID	250/50 BID	100/25	200/25
Total	430	1562	194	449	403	2369	956
6 week							
HZA106851 (PK study)	73*					56	56
12 week							
HZA106827	203	205				201	
HZA113719	154					153	
HZA116863		347				346	346
HZA113714				154			155
HZA113091					403	403	
24 week							
HZA106829			194	195			197
52 weeks							
HZA106839				100		201	202
Up to 76 weeks							
HZA106837		1010				1009	

Table 56: Number of Subjects Exposed in Trials Including an FF/VI Treatment Arm
Source: Module 5.3.5.3, ISS, Table 2, p.30 *Includes placebo and placebo+prednisolone groups talicized/boldstudiesare reviewed individually in Section 7

A total of 2,369 subjects were exposed to FF/VI 100/25 mcg, and 956 subjects to FF/VI 200/25 mcg. A total of 1371 subjects were exposed to FF/VI 100/25 for over six months, and 283 subjects to FF/VI 200/25 for over six months. A total of 645 subjects were exposed to FF/ VI 100/25 for over one year, and a total of 100 subjects were exposed to FF/VI 200/25 for over one year. Trial HZA106837 was an event driven trial that targeted a total of 330 asthma exacerbations, and therefore exposure was variable between 24 to 76 weeks.

Table 57 depicts the extent of exposure to both doses of FF/VI. The mean exposure for FF/VI 100/25 was 237 days and for FF/VI 200/25 was 146.3 days.

Table 57. Extent of Exposure to FF/VI 100/25 and FF/VI 200/25		
Study drug	FF/VI 100/25 N=2369	FF/VI 200/25 N=956
Exposure (Days)		
Mean (SD)	237.0 (148.2)	146.3 (110.1)
Total Subject Years*		
	1537.33	382.16
Range of Exposure, n (%)		
1 day – 4 weeks	60 (3)	32 (3)
>4 – 8 weeks	94 (4)	71 (7)
>8 – 12 weeks	358 (15)	285 (30)
>12 – 16 weeks	331 (14)	205 (21)
>16 – 20 weeks	11 (<1)	4 (<1)
>20 – 24 weeks	144 (6)	74 (8)
>24 – 28 weeks	240 (10)	100 (10)
>28 – 32 weeks	16 (<1)	8 (<1)
>32 – 36 weeks	10 (<1)	1 (<1)
>36 – 40 weeks	16 (<1)	2 (<1)

Table 57. Extent of Exposure to FF/VI 100/25 and FF/VI 200/25

Study drug	FF/VI 100/25 N=2369	FF/VI 200/25 N=956
>40 – 44 weeks	7 (<1)	1 (<1)
>44 – 48 weeks	55 (2)	3 (<1)
>48 – 52 weeks	381 (16)	68 (7)
>52 weeks	646 (27)	100 (10)

Source: ISS Table 10
* Sum across subjects of (treatment stop date – treatment start date +1) divided by 365.25

Exposure examined by age is shown in Table 58.

Table 58. Treatment Exposure by Age in the Pooled Safety Database (ITT)

Age	Placebo N=1070	FF/VI 100/25 N=2369	FF/VI 200/25 N=956	FF 100 N=2010	FF 200 N=608	Placebo (ICS) N=218	VI 25 (ICS) N=216
Adolescent 12-17, n	115	261	66	236	41	21	25
Subject Years	27.48	194.53	39.38	152.55	9.88	3.52	4.83
Mean (Days)	88.0	272.2	217.9	236.1	88.0	61.3	70.6
Median (Days)	83.0	350.0	170.0	257.5	58.0	82.0	83.0
>52 weeks, n (%)	0	84 (32)	19 (29)	56 (24)	0	0	0
Adult 18-64, n	890	1930	816	1630	525	184	177
Subject Years	175.76	1239.76	317.02	1013.25	149.31	26.61	25.17
Mean (Days)	72.5	234.6	142.2	227.3	104.70	52.8	51.9
Median (Days)	58.0	171.0	85.0	169.0	59.0	29	29
>52 weeks, n (%)	0	519 (27)	76 (9)	445 (27)	0	0	0
Elderly >=65, n	65	178	74	144	42	13	14
Subject Years	11.70	103.04	25.77	87.34	9.97	2.03	2.42
Mean (Days)	65.7	211.4	127.2	221.5	86.7	57.1	63.1
Median (Days)	57.0	166.5	86.0	168.0	57.0	71.0	82.5
>52 weeks, n (%)	0	43 (24)	5 (7)	36 (25)	0	0	0

Source: Module 5.3.5.3, ISS, Table 12, p. 56

The ITT Population in the sponsor's pooled safety database included 855 adolescent subjects (12 to 17 years) (10%), 7099 adult subjects (18 to 64 years) (83%), and 599 elderly subjects (≥65 years) (7%). Similar to the overall population, duration of exposure was greatest for subjects treated with FF/VI 100/25, FF 100, and FF/VI 200/25 in each age category. Sixty-six adolescent subjects were exposed to FF/VI 200/25; however, a greater proportion of adolescent subjects were treated with FF/VI 200/25 for more than

52 weeks (29%) compared with the other age groups (9% adults, 7% elderly) and the overall population (10%) (See Table 58).

7.2.1.2 Disposition

The disposition of subjects is displayed for the studies HZA106827, HZA116863, HZA106829, and HZA106837 in Section 6. It is displayed for study HZA106839 in Section 7.7.2.1. Subject disposition by treatment group in the sponsor's pooled database is shown below in Table 59.

Table 59. Subject Disposition (Sponsor's Pooled Safety Database, ITT)

	Placebo N=1070	FF/VI 100/25 N=2369	FF/VI 200/25 N=956	FF 100 N=2010	FF 200 N=608	Placebo (ICS) N=218	VI 25 (ICS) N=216
Total Completed	728 (68)	2082 (88)	842 (88)	1722 (86)	504 (83)	185 (85)	194 (90)
Total Withdrawn	342 (32)	287 (12)	114 (12)	288 (14)	104 (17)	33 (15)	22 (10)
Primary reason for withdrawal							
Lack of Efficacy	250 (23)	67 (3)	33 (3)	94 (5)	50 (8)	17 (8)	13 (6)
Withdrew Consent	42 (4)	87 (4)	18 (2)	78 (4)	17 (3)	6 (3)	1 (<1)
Protocol Deviation	20 (2)	38 (2)	11 (1)	34 (2)	13 (2)	3 (1)	1 (<1)
Adverse Event	10 (<1)	35 (1)	15 (2)	32 (2)	10 (2)	3 (1)	2 (<1)
Investigator discretion	11 (1)	19 (<1)	14 (1)	22 (1)	6 (<1)	1 (<1)	2 (<1)
Lost to Follow-up	9 (<1)	18 (<1)	6 (<1)	13 (<1)	4 (<1)	0	1 (<1)
Met stopping criteria*	0	15 (<1)	17 (2)	1 (<1)	1 (<1)	3 (1)	2 (<1)
Study Terminated	0	8 (<1)	0	14 (<1)	3 (<1)	0	0

Source: Module 5.3.5.3, ISS, Table 15, p. 61
*Includes pre-defined stopping criteria for abnormal EKG, Holter monitor, liver function tests, pregnancy, or ophthalmic exam

In the pooled safety database, lack of efficacy was the most common reason for withdrawal, with the highest proportion of patients withdrawing in the placebo group (23%). Consent withdrawn and protocol deviations were the next most frequent reasons for withdrawal. Subject withdrawal secondary to adverse events was low across all treatment groups.

7.2.1.3 Demographics

The demographic information of subjects is displayed in Section 6 for the individual relevant studies HZA106827, HZA116863, HZA106829, and HZA106837. Study HZA106839 is displayed in Section 7.7.1. The demographic information for the pooled safety database is displayed in Table 60.

Table 60. Demographics (Sponsor's Pooled Safety Database, ITT)

	Placebo N=1070	FF/VI 100/25 N=2369	FF/VI 200/25 N=956	FF 100 N=2010	FF 200 N=608	Placebo (ICS) N=218	VI 25 (ICS) N=216
Age (years)							
Mean	40.1	42.3	44.2	42.1	43.3	40.9	41.5
Min	12	12	12	12	12	12	12
Max	84	82	79	84	77	75	79
Sex, n (%)							
Female	635 (59)	1470 (62)	583 (61)	1290 (64)	378 (62)	120 (55)	129 (60)
Male	435 (41)	899 (38)	373 (39)	720 (36)	230 (38)	98 (45)	87 (40)
Race, n (%)							
African Heritage	67 (6)	124 (5)	62 (6)	126 (6)	29 (5)	15 (7)	19 (9)
Asian	216 (20)	457 (19)	224 (23)	167 (8)	57 (9)	11 (5)	9 (4)
White	610 (57)	1652 (70)	652 (68)	1550 (77)	468 (77)	149 (68)	141 (65)
Mixed	75 (7)	125 (5)	14 (1)	151 (8)	41 (7)	3 (1)	1 (<1)
Ethnicity, n (%)							
Not Hispanic/Latino	857 (80)	2052 (87)	871 (91)	1669 (83)	479 (79)	171 (78)	159 (74)
Hispanic/Latino	213 (20)	317 (13)	85 (9)	341 (17)	129 (21)	47 (22)	57 (26)

Source: Module 5.3.5.3, ISS, Table 17, p. 65

The majority of subjects in the ITT population were White (69%) and female (62%) and had a mean age of 42.3 years. Subjects of Hispanic/Latino ethnicity comprised 16% of the ITT Population. The mean age of subjects in the key treatment groups ranged from 40 to 44. Seven percent (7%) to 12% of subjects in the key treatment groups were 12 to 17 years of age and 6% to 8% of subjects in the key treatment groups were 65 to 84 years of age.

7.2.2 Explorations for Dose Response

The inclusion of two doses of FF (100 mcg, 200 mcg) combined with a single dose of VI (25 mcg) into the phase 3 trials allows for an exploration of dose dependency for ICS safety as well as short term LABA safety and is discussed throughout this review.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or in-vitro testing was performed for this application.

7.2.4 Routine Clinical Testing

Routine testing in this development program included serum chemistry, hematology, pregnancy testing, hepatitis B testing, and hepatitis C testing. Other testing, depending on the study, included pharmacogenetics, urinary cortisol, and 12-lead ECGs. 24-hour Holter monitoring and ophthalmic examinations were conducted in trial HZA106839.

Serum chemistry evaluation generally included measurements of albumin, alkaline phosphatase, alanine amino-transferase, aspartate amino-transferase, direct/indirect/total bilirubin, calcium, chloride, bicarbonate, creatinine, creatinine phosphokinase, gamma glutamyl transferase, glucose, phosphorus, potassium, total protein, sodium, urea nitrogen and uric acid. The hematology evaluation included hemoglobin, hematocrit, platelet count, white blood cell count, neutrophil, segmented neutrophils, basophils, eosinophils, lymphocytes and monocytes.

7.2.5 Metabolic, Clearance, and Interaction Workup

Two drug interaction studies were conducted to investigate the pharamacokinetic and pharmacodynamic effects of co-administration of FF/VI (trial HZA105548) and VI (trial BC112205) with ketoconazole. The clinical impact of these studies is summarized in Section 7.5.5; the results are discussed in further detail in the Clinical Pharmacology Summary Document.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

ICS
The pivotal trials incorporated monitoring for toxicities associated with ICS use by evaluating AEs for episodes of pneumonia, bone disorders, local and systemic corticosteroid effects, and ocular disorders. Details of the AE analyses are found in Section 7.1.2 and the results in Section 7.3.4.

LABA
The pivotal trials incorporated monitoring for toxicities associated with LABA use by evaluating for specific cardiac AEs and monitoring the laboratory, vital sign, and ECG parameters for adrenergic and metabolic effects. Details of the adverse event analyses are found in Section 7.1.2. Analysis of serious asthma related-outcomes are summarized in the statistical review by Dr. Janelle Charles.

7.3 Major Safety Results

For review of major safety results, this review will focus on those studies as outlined in Section 7.1.1; the review examines the safety of FF/VI in asthma of each study individually as the pooled safety database contained studies that did not include FF/VI.

7.3.1 Deaths

In the four efficacy/safety trials that are the focus of this clinical review, there were three deaths, one in an FF/VI 100/25 treatment group and two in the FF 100 treatment group. These deaths all occurred in Study HZA106837.

Three deaths occurred in the pertinent clinical studies. A 68-year-old subject receiving FF/VI 100/25 (HZA106837) died in a car accident. A 65-year-old subject receiving FF 100 (HZA106837) was diagnosed with stage IV lung cancer 172 days after starting treatment with FF 100. A 62-year-old subject developed pneumonia and sepsis 114 days after starting FF 100 (HZA106837). There were four deaths in total; one 21-year-old subject in trial B2C112060 in the placebo group (not discussed as part of this review) died in his sleep, with no cause found. There were no asthma-related deaths.

7.3.2 Nonfatal Serious Adverse Events

SAEs for each of the individual studies of interest are summarized below. In general, the occurrence of SAEs was low, and balanced across treatment groups. Individual SAEs occurred in < 3 patients across these trials with the exception of asthma and pneumonia in Trial HZA106837. Overall, no new safety signal was identified based on evaluation of these SAEs.

Trial HZA106827

Four SAEs were reported throughout the study; none of these SAEs led to withdrawal. These are summarized below in Table 61.

Table 61. Trial HZA106827: Serious Adverse Events

Treatment	Age/gender	SAE (preferred term)
FF 100	34/F	Pancreatitis
	18/M	Appendicitis
FF/VI 100/25 (13 days post dose)	62/M	Prostate cancer
Pre-treatment	21/F	Cystitis

Source: CSR HZA106827, case narratives

Trial HZA116863

Eight SAEs were reported as shown in the table below.

Table 62. Trial HZA116863: Serious Adverse Events

Treatment	Age/gender	SAE (preferred term)
FF 100	60/F	Borderline mucinous tumor of ovary
	58/F	Pneumonia
	44/F	Pneumonia
FF/VI 100/25	71/F	Biliary colic
	47/F	Pancreatitis acute
	46/F	Thermal burn
	53/F	Occipital neuralgia
FF/VI 200/25	23/F	Abortion threatened

Source: CSR HZA116863, table 34

Trial HZA106829

Nine on-treatment SAEs occurred, and one SAE occurred during the run-in period as shown in the table below; a higher number of SAEs occurred in the FF/VI 200/25 group than the FF 200 or FP 500 groups; however, each SAE was an individual occurrence, so no clear pattern was observed.

Table 63. Trial HZA106829: Serious Adverse Events

Treatment	Age/gender	SAE (preferred term)
FF 200	14/F	Asthma
FF/VI 200/25	56/F	Thyroid cancer
	47/M	Hematuria
	46/M	Traumatic amputation
	53/F	Atrial fibrillation
	50/M	Inguinal hernia
	67/M	Pneumonia
FP 500 BID	56/F (during run-in)	Pancreatitis
	32/M	Hemoptysis
	43/M	Lower limb fracture

Source: CSR HZA106829, case narratives

Trial HZA106837

A total of 86 non-fatal SAEs were reported in 68 subjects during the treatment period (38 SAEs (3%) in 28 subjects in the FF100 group and 48 SAEs (4%) in 40

subjects in the FF/VI 100/25 group). Twelve (12) SAEs were reported for eight (8) subjects during the post-treatment period (4 SAEs (<1%) in 8 subjects in the FF 100 group and 4 SAEs (<1%) in 4 subjects in the FF/VI 100/25 group).

Of the 86 non-fatal SAEs reported for 68 subjects during the treatment period, 17 subjects had SAEs that were considered asthma-related by the Adjudication Committee (7 (<1%) in the FF 100 group and 10 (<1%) in the FF/VI 100/25 group). One subject treated with FF 100 had two SAEs of asthma: one considered asthma-related and one considered not asthma-related, as it occurred in conjunction with an SAE of pneumonia (Subject (b) (6)). Two subjects treated with FF 100 had SAEs of asthma considered not asthma-related, as they occurred in conjunction with SAEs of pneumonia (Subject (b) (6) and Subject (b) (6)). One subject treated with FF/VI 100/25 had an SAE of asthma considered not asthma-related as it occurred in conjunction with an SAE of acute trachea-bronchitis (Subject (b) (6)).

Eight subjects had SAEs that resolved with sequelae: 3 subjects in the FF 100 group (Subject (b) (6) upper limb fracture; Subject (b) (6), diabetic foot) and 5 subjects in the FF/VI 100/25 group (Subject (b) (6) asthma; Subject (b) (6) labyrinthitis; Subject (b) (6), bronchial hyper-reactivity, sepsis and anemia; Subject (b) (6) pneumonia; Subject (b) (6), nasal polyps) and 2 subjects had SAEs that were unresolved at study end: 1 subject in the FF 100 group (Subject (b) (6) subarachnoid hemorrhage) and 1 subject in the FF/VI 100/25 group (Subject (b) (6) metastases to lung). Ten subjects were withdrawn from the study due to their SAEs (6 subjects in the FF 100 group and 4 subjects in the FF/VI 100/25 group). Of the 12 non-fatal SAEs reported during the post-treatment period, only 1 (<1%) in the FF/VI 100/25 group was considered asthma-related by the Adjudication Committee. The following table is provided by the Sponsor.

Table 58. Serious Adverse Events Occurring On-Treatment and Post-Treatment (Study HZA106837, ITT)

Subject	Age/Sex	SAE (Preferred term)	Onset (study day)[1]	Maximum Intensity	Duration (days)	Outcome	Led to Withdrawal
FF 100							
(b) (6)	29/M	Pleurisy[3]	213	Severe	3	Resolved	No
		Pneumonia	213	Severe	3	Resolved	No
		Meningitis aseptic[2]	216	Severe	4	Resolved	No
	72/M	Anaphylactic reaction	250	Severe	3	Resolved	No
	55/F	Breast cancer	257	Moderate	57	Resolved	No
	43/F	Asthma[3]	99	Severe	3	Resolved	No
	47/F	Anxiety	233	Mild	2	Resolved	No
		Intervertebral disc degeneration	233	Moderate	2	Resolved	No
		Radiculopathy	233	Moderate	2	Resolved	No
	61/F	Non-cardiac chest pain[3]	11	Severe	2	Resolved	No
	21/F	Asthma	221	Moderate	5	Resolved	No
		Lobar pneumonia	222	Moderate	6	Resolved	No
		Asthma	289	Severe	2	Resolved	Yes
	48/F	Asthma	226	Severe	32	Resolved	Yes
		Pneumonia	226	Severe	32	Resolved	No
	19/F	Abortion spontaneous[2]	277	Severe	1	Resolved	No
	40/F	Abortion spontaneous[2]	264	Moderate	2	Resolved	No
	52/F	Upper limb fracture	202	Moderate	52	Resolved with sequelae	No
	36/F	Asthma	372	Moderate	6	Resolved	Yes
		Pneumonia	372	Moderate	6	Resolved	Yes
	26/F	Limb traumatic amputation	115	Severe	2	Resolved	No
	42/F	Diabetic foot	91	Severe	49	Resolved with sequelae	No
	59/F	Renal cell carcinoma	224	Severe	32	Resolved	Yes
	51/F	Cholelithiasis	182	Mild	120	Resolved	No
	60/F	Intervertebral disc protrusion	72	Moderate	2	Resolved	No
	47/M	Pulmonary embolism	224	Severe	12	Resolved	Yes
	52/F	Ovarian cyst	126	Mild	192	Resolved	No
	20/F	Intra-uterine death[2]	50	Moderate	1	Resolved	No
	45/F	Osteochondroma	286	Mild	93	Resolved	No
	37/M	Deafness unilateral	89	Moderate	17	Resolved	No
		Otitis media	89	Moderate	17	Resolved	No
		Vertigo	89	Mild	17	Resolved	No
	48/F	Asthma	118	Moderate	17	Resolved	No
	70/F	Asthma	101	Moderate	23	Resolved	No
		Bronchitis	101	Moderate	23	Resolved	No
	52/M	Asthma	273	Moderate	16	Resolved	No
	69/F	Angioedema	206	Moderate	9	Resolved	No
	51/F	Hypertension	41	Moderate	11	Resolved	No
	73/F	Cerebrovascular accident	84	Moderate	107	Resolved	No
	51/F	Asthma	171	Severe	15	Resolved	No
	49/F	Asthma	72	Moderate	20	Resolved	No
	55/F	Subarachnoid haemorrhage	27	Severe	N/A	Not resolved	Yes

Subject	Age/Sex	SAE (Preferred term)	Onset (study day)[1]	Maximum Intensity	Duration (days)	Outcome	Led to Withdrawal
FF/VI 100/25							
(b) (6)	47/F	Asthma	44	Moderate	2	Resolved	No
	24/F	Abortion spontaneous[2]	479	Moderate	9	Resolved	No
	54/F	Asthma	320	Severe	19	Resolved with sequelae	No
	34/F	Asthma	75	Moderate	7	Resolved	Yes
	29/M	Meningitis viral	73	Severe	9	Resolved	No
	76/F	Breast cancer	205	N/A	100	Resolved	No
	50/M	Asthma	323	Moderate	3	Resolved	Yes
	61/F	Labyrinthitis	51	Severe	3	Resolved	No
	41/F	Nausea	93	Severe	2	Resolved with sequelae	No
	14/M	Hand fracture	29	Moderate	28	Resolved	No
	12/M	Pneumonia	88	Severe	25	Resolved	No
		Bronchial hyperreactivity[2]	96	N/A	16	Resolved with sequelae	No
		Pleural effusion[2]	96	Severe	17	Resolved	No
		Sepsis[2]	96	Severe	17	Resolved with sequelae	No
		Urinary tract infection[2]	97	Moderate	16	Resolved	No
		Anemia[2]	99	Severe	9	Resolved with sequelae	No
	30/F	Premature labour[2]	348	Moderate	3	Resolved	No
	19/F	Pharyngitis	371	Moderate	14	Resolved	No
		Viral infection	371	Moderate	14	Resolved	No
	30/M	Fear	250	Moderate	2	Resolved	No
		Tachycardia	250	Moderate	2	Resolved	No
	54/F	Chronic sinusitis	283	Mild	6	Resolved	No
	52/M	Tachyarrhythmia[3]	105	Severe	2	Resolved	No
	66/F	Hypertension	276	Severe	2	Resolved	No
	62/F	Metastases to lung	237	Severe	N/A	Not resolved	No
	34/F	Subcutaneous abscess	58	Moderate	2	Resolved	No
	43/F	Abdominal pain	66	Mild	5	Resolved	No
		Anal abscess	169	Moderate	3	Resolved	No
		Anal fistula	234	Moderate	8	Resolved	No
	46/F	Osteoarthritis	183	Severe	10	Resolved	No
	44/F	Skin infection	22	Mild	12	Resolved	No
	30/M	Dermatitis allergic	134	Moderate	6	Resolved	No
	69/F	Acute coronary syndrome	101	Moderate	7	Resolved	No
	41/F	Dysfunctional uterine bleeding	422	Mild	4	Resolved	No
	38/F	Hydrocholecystis	27	Moderate	12	Resolved	No
	52/F	Coronary artery disease	266	Moderate	10	Resolved	No
	52/F	Pneumonia	170	Moderate	9	Resolved	No
	72/F	Diabetic microangiopathy	83	Mild	6	Resolved	No
	61/F	Tracheobronchitis	163	Moderate	15	Resolved	No
		Asthma	166	Moderate	12	Resolved	No
	45/F	Asthma[2]	241	Severe	17	Resolved	No

Subject	Age/Sex	SAE (Preferred term)	Onset (study day)[1]	Maximum Intensity	Duration (days)	Outcome	Led to Withdrawal
FF/VI 100/25 (continued)							
(b) (6)	32/F	Appendicitis	189	Severe	10	Resolved	No
	63/F	Renal cancer stage I	171	Moderate	36	Resolved	Yes
	56/F	Asthma	177	Severe	11	Resolved	No
	56/F	Asthma	126	Moderate	22	Resolved	No
	22/M	Pneumonia	413	Moderate	14	Resolved	No
	16/M	Asthma	64	Moderate	18	Resolved	No
	16/F	Asthma	189	Moderate	12	Resolved	No
		Asthma	205	Severe	17	Resolved	No
		Syncope	349	Severe	5	Resolved	No
	16/F	Asthma	110	Moderate	29	Resolved	No
	56/M	Pneumonia	209	Moderate	15	Resolved with sequelae	No
	13/F	Asthma	201	Severe	26	Resolved	No
		Asthma	212	Severe	15	Resolved	No
	55/F	Nasal polyps	76	Moderate	26	Resolved with sequelae	No
	45/F	Subarachnoid haemorrhage	343	Severe	36	Resolved	Yes

Source: Listing 7.6
1. Time since 1st dose
2. Occurred post-treatment
3. Considered drug-related by the investigator

Source: Module 5.3.5.3, HZA106837 CSR, Table 32, p.74

7.3.3 Dropouts and/or Discontinuations

This section discusses rates of adverse events leading to study drug discontinuation or withdrawal; rates of overall study dropout are discussed in Section 6.1.3. Review of the adverse events leading to dropout/discontinuation does not reveal any new safety signals. In general, the adverse events leading to dropouts/discontinuations are those adverse events that are known to occur in asthma clinical development programs of ICS/LABA products.

Trial HZA106827

The incidence of events leading to withdrawal ranged from 0-<1% across treatment groups; a total of three subjects were withdrawn secondary to AEs (placebo: dizziness/dyspnea/headache/non-cardiac chest pain; FF/VI 100/25: skin rash, nasopharyngitis).

Trial HZA116863

The incidence of events leading to withdrawal occurred <1% across treatment groups; a total of ten subjects were withdrawn secondary to AEs (FF 100: nasopharyngitis, ovarian tumor, pneumonia, intervertebral disc protrusion; FF/VI 100/25: pancreatitis, headache, vertigo, dermatitis; FF/VI 200/25: headache, tachycardia, abortion threatened, nasopharyngitis, pyrexia).

Trial HZA106829

The incidence of events leading to withdrawal ranged from 1-4% across treatment groups; a total of twelve subjects were withdrawn secondary to AEs (FF 200 (2%): asthma exacerbation, respiratory infection-viral, ventricular extrasystoles; FF/VI 200/25 (4%): thyroid cancer, atrial fibrillation, urticaria, lymphadenopathy, rheumatoid arthritis, menorrhagia/oral candidiasis, headache/chest pains/palpitations; FP 500 (1%): hemoptysis, myalgia/pruritic facial rash).

Trial HZA106837

Thirty-five subjects were withdrawn from the study drug/study due to AEs: 19 subjects (2%) in the FF 100 group and 16 subjects (2%) in the FF/VI 100/25 group. Thirteen of the 35 subjects were withdrawn due to SAEs. Those AEs that led to discontinuation that occurred in more than one subject (by treatment group) were: 1) FF100 – asthma (n=3), pneumonia (n=2), oral candidiasis (n=3); 2) FF/VI 100/25 – asthma (n=2), muscle spasms (n=2, dysphonia (n=2)). The asthma events leading to discontinuation were all serious adverse events (SAEs).

7.3.4 Significant Adverse Events

Adverse events of special interest for ICS and LABA are discussed in Section 7.3.5. Serious adverse events are discussed in 7.3.2. Rates of study drug discontinuation and withdrawals due to Adverse Events are discussed in Section 7.3.3.

7.3.5 Submission Specific Primary Safety Concerns

Trial HZA106827

Adverse events of special interest ranged from 5-10% across treatment groups. The most common adverse event of special interest was oropharyngeal pain; the adverse events of special interest occurring in ≥ 2 subjects across treatment groups are summarized below in Table 64.

Table 64. Trial HZA106827: Adverse Events of Special Interest

AE of Special Interest	Placebo N=203	FF 100 N=205	FF/VI 100/25 N=201
Any AE of special interest	11 (5)	13 (6)	20 (10)
Any local steroid effect	3 (1)	10 (5)	13 (6)
Oropharyngeal pain	0	2	1
Dysphonia	0	3 (1)	5 (2)
Oral candidiasis	0	2 (<1)	4 (2)
Cardiovascular effects	2 (<1)	2 (<1)	4 (2)
LRTI excluding pna	4 (2)	0	1 (<1)
Any hypersensitivity	3 (1)	1 (<1)	1 (<1)
Rash	1 (<1)	0	1 (<1)
Bronchitis	4 (2)	0	1 (<1)
Effects on Glucose	0	1 (<1)	0
Tremor	0	0	1 (<1)

Source: CSR HZA106827 Table 7.9

Trial HZA116863

Adverse events of special interest ranged from 7-8% across treatment groups. The most common adverse event of special interest was oropharyngeal pain. The adverse events of special interest occurring in ≥ 2 subjects across treatment groups are summarized below in the table below.

Table 65. Trial HZA116863: Adverse Events of Special Interest

AE of Special Interest (Preferred Term), n (%)	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346
Any AE of special interest	27 (8)	27 (8)	25 (7)
Any local steroid effect	10 (3)	14 (4)	15 (4)
Oropharyngeal pain	5 (1)	7 (2)	7 (2)
Dysphonia	3 (<1)	5 (1)	3 (<1)
Oral candidiasis	1 (<1)	2 (<1)	4 (1)
Cardiovascular effects	3 (<1)	6 (2)	1 (<1)
LRTI excluding pna	9 (3)	3 (<1)	7 (2)
Hypertension	2 (<1)	2 (<1)	0

Table 65. Trial HZA116863: Adverse Events of Special Interest

AE of Special Interest (Preferred Term), n (%)	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346
Pneumonia	2 (<1)	1 (<1)	0
Any hypersensitivity	2 (<1)	4 (1)	3 (<1)
Bone disorders	1 (<1)	1 (<1)	1 (<1)
Bronchitis	6 (2)	3 (<1)	7 (2)
Effects on Glucose	1 (<1)	1 (<1)	0

Source: CSR HZA116863, Table 36

Trial HZA106829

Adverse events of special interest ranged from 6-10% across treatment groups. The most common adverse event of special interest was oropharyngeal pain. The adverse events of special interest occurring in ≥ 2 subjects across treatment groups are summarized below in the table below.

Table 66. Trial HZA106829: Adverse Events of Special Interest

AE of Special Interest (Preferred Term), n	FF 200 QD N=194	FF/VI 200/25 QD N=197	FP 500 BD N=195
Any AE of special interest	24 (12)	34 (17)	32 (16)
Any local steroid effect	12 (6)	19 (10)	16 (8)
Oropharyngeal pain	8 (4)	4 (2)	7 (4)
Dysphonia	2 (1)	6 (3)	4 (2)
Oral candidiasis	2 (1)	4 (2)	4 (2)
Oropharyngeal	1 (<1)	5 (3)	2 (1)
Any cardiovascular	5 (3)	4 (2)	5 (3)
Palpitations	1 (<1)	1 (<1)	0 (0)
Hypertension	2 (1)	1 (<1)	4 (2)
Syncope	1 (<1)	0 (0)	1 (<1)
LRTI excluding pna	6 (3)	7 (4)	7 (4)
Pneumonia	1 (<1)	1 (<1)	0 (0)
Any hypersensitivity	2 (1)	5 (3)	3 (2)
Bone disorders	1 (<1)	2 (1)	4 (2)
Effects on Glucose	0 (0)	1 (<1)	1 (<1)

Source: CSR HZA106829, Table 42

Trial HZA106837

Of the AESI, local corticosteroid effects and lower respiratory tract infections excluding pneumonia were the most common as seen in the table below. The only AEs of special interest that occurred in ≥1% of subjects in either treatment group were oropharyngeal pain (5% of subjects in the FF 100 group and 4% of subjects in the FF/VI 100/25 group), dysphonia (2% of subjects in the FF 100 and FF/VI 100/25 groups), bronchitis (7% of subjects in the FF 100 group and 6% of subjects in the FF/VI 100/25 group) and hypertension (2% of subjects in the FF 100 and FF/VI 100/25 groups). These specific AESI were included under the umbrellas of local steroid effects (oropharyngeal pain, dysphonia), LRTI excluding pneumonia (bronchitis), cardiovascular effects (hypertension, blood pressure), respectively. In addition, 14 subjects (1.4%) in the FF group and 12 subjects (1.2%) in the FF/VI group had AE terms related to oropharyngeal candidiasis.

Table 67. Trial HZA106837: Adverse Events of Special Interest

AE of Special Interest (Preferred Term), n (%)	FF 100 N=1010	FF/VI 100/25 N=1009
Any AE of special interest	248 (25)	216 (21)
Any local steroid effect	83 (8)	78 (8)
LRTI excluding pneumonia	90 (9)	68 (7)
Cardiovascular effects	55 (5)	55 (5)
Any hypersensitivity	32 (3)	29 (3)
Bone Disorders	19 (2)	12 (1)
Pneumonia	9 (<1)	11 (1)
Effects on Glucose	7 (<1)	4 (<1)
Ocular effects	4 (<1)	1 (<1)
Effects on Potassium	1 (<1)	0
Tremor	1 (<1)	0

Source: CSR HZA106837 Table 7.12, p.572.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The common adverse events seen in the FF/VI development program are typical of orally-inhaled ICS and LABA products. In the tables below, common adverse events are defined as preferred terms occurring in > 3% patients in the FF/VI treatment group.

Trial HZA106827

The most common adverse events were nasopharyngitis and headache; no other event occurred in ≥3% incidence as seen in the table below.

Table 68. Trial HZA106827: Most Frequent Adverse Events Occurring in >3% in Any Treatment Group

	Placebo N=203	FF 100 N=205	FF 100/25 N=201
Preferred Term, n (%)			
Any AE	43 (21)	52 (25)	59 (29)
Headache	8 (4)	9 (4)	10 (5)
Nasopharyngitis	15 (7)	14 (7)	20 (10)

Source: CSR HZA106827, table 7.4

Trial HZA116863

The most common AEs were headache, nasopharyngitis, upper respiratory infection, and influenza. No other AEs occurred ≥ 3% in any treatment group as seen in the table below.

Table 69. Trial HZA116863: Most Frequent Adverse Events Occurring in > 3% in Any Treatment Group

	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346
Preferred Term, n (%)			
Any AE	127 (37)	127 (37)	123 (36)
Headache	32 (9)	29 (8)	29 (8)
Nasopharyngitis	26 (7)	22 (6)	25 (7)
Upper respiratory infection	12 (3)	8 (2)	7 (2)
Influenza	4 (1)	10 (3)	9 (3)

Source: CSR HZA116863, table 7.2

Trial HZA106829

The most frequently reported AEs were nasopharyngitis, headache, and cough as seen in the table below. Nasopharyngitis and cough occurred more in the FP treatment group. No other AEs occurred in ≥ 3% of subjects in any treatment group.

Table 70. Trial HZA106829: Most Frequent Adverse Events Occurring in > 3% in Any Treatment Group

	FF 200 N=194	F/VI 200/25 N=197	FP 500 BID N=195
Preferred Term, n (%)			
Any AE	90 (46)	92 (47)	97 (50)
Nasopharyngitis	27 (14)	25 (13)	39 (20)
Headache	13 (7)	11 (6)	15 (8)
Cough	6 (3)	3 (2)	13 (7)
Respiratory Tract infection - viral	7 (4)	7 (4)	7 (4)
Influenza	8 (4)	5 (3)	7 (4)
Bronchitis	6 (3)	7 (4)	6 (3)
Oropharyngeal pain	8 (4)	4 (2)	7 (4)
Sinusitis	7 (4)	3 (2)	4 (2)
Dysphonia	2 (1)	6 (3)	4 (2)
Pharyngitis	2 (1)	4 (2)	6 (3)
Rhinitis	2 (1)	1 (<1)	7 (4)
Oropharyngeal candidiasis	1 (<1)	5 (3)	2 (1)

Source: CSRHZA106829, table 7.4

Trial HZA106837

The most frequently reported AEs during the treatment period in either treatment group were headache, nasopharyngitis, and upper respiratory tract infection as in the table below.

Table 71. Trial HZA106837: Most Frequent Adverse Events Occurring in > 3% in Any Treatment Group

	FF 100 N=1010	FF/VI 100/25 N=1009
Preferred term, n (%)		
Any AE	652 (65)	636 (63)
Headache	179 (18)	188 (19)
Nasopharyngitis	131 (13)	155 (15)
Upper respiratory tract infection	93 (9)	73 (7)
Bronchitis	74 (7)	59 (6)
Cough	64 (6)	55 (5)
Oropharyngeal pain	55 (5)	41 (4)

Table 71. Trial HZA106837: Most Frequent Adverse Events Occurring in >3% in Any Treatment Group

	FF 100	FF/VI 100/25
Preferred term, n (%)		
Influenza	38 (4)	50 (5)
Back Pain	40 (4)	41 (4)
Sinusitis	38 (4)	42 (4)
Pharyngitis	41 (4)	30 (3)
Rhinitis allergic	26 (3)	39 (4)
Abdominal Pain Upper	23 (2)	36 (4)
Nasal Congestion	26 (3)	33 (3)
Rhinitis	25 (2)	29 (3)
Arthralgia	29 (3)	24 (2)
Respiratory tract infection	21 (2)	26 (3)

Source: CSR,HZA106837, Table 22, p. 57

7.4.2 Laboratory Findings

No clinically meaningful effects on hematologic or chemistry parameters were noted from the confirmatory trials.

7.4.3 Vital Signs

No clinically meaningful effects on vital signs were noted from the confirmatory trials.

7.4.4 Electrocardiograms (ECGs)

No clinically meaningful effects on EKG parameters are noted from the confirmatory trials.

7.4.5 Special Safety Studies/Clinical Trials

Trial HZA106851

This trial was a 6-week, double-blind, placebo-and active-controlled study in asthmatic subjects to evaluate HPA axis suppression at the therapeutic doses. Fifty-six subjects each were given multiple, once daily inhalations of either FF/VI 100/25 or 200/25, 58 subjects received placebo, and 15 subjects received placebo plus prednisolone 10 mg daily on the last 7 days of treatment. 0-24 hour weighted mean serum cortisol was assessed at baseline and at the end of a 6-week treatment period. The derived serum cortisol weighted means (0-24 h) were similar at baseline and 6 weeks for placebo and the FF/VI groups (<3% change from baseline).

Additional Safety Trials

Long term safety results from trial HZA106839 is reviewed under Section 7.7.2.

7.4.6 Immunogenicity

Immunogenicity is not applicable to this product.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted in Section 7.2.2, the dose dependency for adverse events is discussed throughout this review.

7.5.2 Time Dependency for Adverse Events

GSK provided summary tables for adverse events with an onset during the first 6 months of studies and with onset greater than 6 months after randomization for trials HZA106839 and HZA106837. An analysis of both reveals no difference in the most common adverse events, and overall, the occurrence of AEs decreases slightly after 6 months.

7.5.3 Drug-Demographic Interactions

The application includes an analysis of adverse events by gender, age, and race. Overall, the same adverse events are reported by male and female patients as well as those 18- 64 and > 65 years of age. Examination of the safety for the subgroup of 12-17 year old subjects is discussed further in the Agency's meta-analysis (see review by Dr. Janelle Charles) as well as in Section 7.7.3. A review of the data by race is limited by the low number of patients in non-white race groups; however no consistent pattern is evident in the pooled safety database. A review of AEs by geographic region (USA vs. EU vs. the rest of the country study sites) showed no differences.

7.5.4 Drug-Disease Interactions

The application includes an analysis of adverse events based on renal and hepatic impairment. The effect of renal impairment was assessed in trial HZA113970, an open-label, non-randomized, PK and safety study which examined the use of FF/VI 100/25 in 9 subjects with severe renal impairment. Systemic FF exposure was lower in severe renal impairment patients; at day 7, FF median $AUC_{(0-24)}$ and C_{max} were 21% and 27%,

respectively, lower in subjects with severe renal impairment compared to subjects with normal renal function. No AEs were reported.

The effect of hepatic impairment was assessed in trial HZA111789 in 18 subjects with mild-to-moderate hepatic impairment given FF/VI 200/25 and in 8 subjects with severe hepatic impairment given FF/VI 100/12.5, and the results indicate that FF exposure increases in patients with all severities of hepatic impairment. Mean percentage change in FF AUC for subjects with mild, moderate and severe hepatic impairment versus normal hepatic function were 34%, 83%, and 75%, respectively. The biggest observed PD change was a 34% decrease in serum cortisol with the 200 mcg dose in moderate hepatic impairment patients. This change in serum cortisol is similar to the level when 200 mcg FF is co-administered with ketoconazole (27%). There was only one AE in the FF/VI 200/35 group of mild nasopharyngitis.

These results were reviewed by the Clinical Pharmacology team (see review by Dr. Jianmeng Chen for details). The Clinical Pharmacology team recommends no dosage adjustments for use in renal or hepatic impairment.

7.5.5 Drug-Drug Interactions

Two drug interaction studies were conducted to investigate the PK and PD effects of co-administration of FF/VI (trial HZA105548) or VI (Trial B2C112205) with ketoconazole.

Trial HZA105548 demonstrated that co-administration with ketoconazole resulted in modest increases in mean FF $AUC_{(0-24)}$ and C_{max} (by 36% and 33%, respectively). Steroid-mediated systemic effects were observed with a 27% reduction in weighted mean serum cortisol (0-24 h). The Clinical Pharmacology team has reviewed this data (see review by Dr. Jianmeng Chen for further details); no dose adjustment with concomitant use of ketoconazole is recommended.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans.

7.6.2 Human Reproduction and Pregnancy Data

Trial HZA106827
One subject reported a pregnancy following completion of placebo.

Trial HZA116863
Three pregnancies were reported; one in each treatment group. The pregnancy in the FF/VI 100/25 group was ongoing at the time of reporting. The pregnancy in the FF/VI 200/25 group led to fetal loss, and the pregnancy in the FF 100 group was ongoing at the time of reporting.

Trial HZA106829
Per the case narratives, three pregnancies were reported: 1 subject in the FF/VI 200/25 group and 2 subjects in the FP 500 group. The outcome of the birth for the subject in the FF/VI 200/25 group was unknown at the time of reporting; of the two cases in the FP 500 group, one subject delivered a live, female infant, and the other subject, two months after discontinuation of study drug, experienced fetal demise.

Trial HZA106837
There were 5 pregnancies in the FF group and 6 in the FF/VI group. Nine outcomes were known at the time of reporting. In the FF group, there were 2 normal births, 2 spontaneous abortions, and 1 intra-uterine death, and in the FF/VI group, there were 2 normal births, 1 normal birth with congenital heart abnormalities, and 1 premature delivery leading to the death of a neonate due to respiratory distress.

Pooled Safety Database
As of January 31, 2014, 43 pregnancies have been reported from the completed FF/VI clinical studies. At that time, the outcomes of 9 pregnancies were unknown or ongoing at the time of reporting. Of the 34 known outcomes, 19 pregnancies resulted in live births, 11 were spontaneous abortions, 3 were electively terminated, and 1 was a stillbirth. Of the 19 live births, one neonate had a congenital anomaly (patent ductus arteriosus, ventricular septal defect) and one was premature (29 weeks gestation). For the neonate with the congenital anomaly (FF/VI 100/25 group), there was a family history of ductus, as it was also present in the neonate's sister. The premature baby (FF/VI 100/25 group) had acute respiratory distress syndrome and died 5 days after birth.

7.6.3 Pediatrics and Assessment of Effects on Growth

Efficacy and safety information for the adolescent population 12-17 years of age is presented throughout this review. (b) (4)

[redacted]

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Given the nature of the drug components, drug abuse, withdrawal, and rebound are not

anticipated. Additionally, the mode of administration and low systemic bioavailability make abuse less likely. However, theoretically, abrupt stoppage of excessive dosages may result in an adrenal crisis. The product labels for other ICS-containing products contain warning language regarding this risk.

7.7 Additional Submissions / Safety Issues

7.7.1 Evaluation of Long-Term Safety

7.7.1.1 Trial HZA106839

Trial HZA106839 was a multicenter, randomized, double-blind, double-dummy, active control parallel group safety study to assess the safety and tolerability of 12 months treatment with two strengths of inhaled FF/VI, and FP 500 mcg twice daily was utilized as an active comparator.

Table 72. Demographic and Baseline Characteristics: HZA106839

	FF/VI 100/25 N=201	FF/VI 200/25 N=202	FP 500 BID N=100	Total N=503
Age				
Mean	39.7	38.5	38.6	39.0
Min	12	12	12	12
Max	73	72	69	73
Sex, n (%)				
Female	130 (65)	124 (61)	62 (62)	316 (63)
Male	71 (35)	78 (39)	38 (38)	187 (37)
Race, n (%)				
African Heritage	15 (7)	17 (8)	6 (6)	38 (8)
Other[1]	1 (<1)	0	0	1 (<1)
Asian	50 (25)	51 (25)	26 (26)	127 (25)
White	135 (67)	134 (66)	68 (68)	337 (67)
Duration of Asthma, n (%)				
<6 mo	2 (<1)	1 (<1)	3 (3)	6 (1)
≥6 mo to <1 year	2 (<1)	2 (<1)	1 (1)	5 (<1)
≥1 to < 5 years	28 (14)	22 (11)	25 (25)	75 (15)
≥5 to <10 years	51 (24)	48 (24)	18 (18)	117 (23)
≥10 years	118 (59)	129 (64)	53 (53)	300 (60)

Table 72. Demographic and Baseline Characteristics: HZA106839				
	FF/VI 100/25 N=201	**FF/VI 200/25 N=202**	**FP 500 BID N=100**	**Total N=503**
Baseline Lung Function				
Mean pre-bronchodilator FEV1 (L) Percent predicted	2.305 74.2	2.290 74.1	2.353 75.2	2.308 74.4
Reversibility				
Absolute FEV1 reversibility (mL) Percent reversibility FEV1 (%)	542.4 23.6	500.9 24.0	522.9 23.8	522.1 23.8
Concomitant Medications				
On any asthma medication	7 (3)	11 (5)	5 (5)	23 (5)
Source: CSR HZA106839 tables 5, 6, 8 1. Other = African American/African Heritage and White				

Table 73. Patient Disposition: Trial HZA106839				
	FF/VI 100/25 N=201	FF/VI 200/25 N=202	FP 500 BID N=100	Total N=503
Completed	161 (80)	161 (80)	71 (71)	393 (78)
Withdrawn	40 (20)	41 (20)	29 (29)	110 (22)
Primary reason for withdrawal				
Adverse event	5 (2)	3 (1)	6 (6)	14 (3)
Lack of Efficacy	1 (<1)	4 (<2)	1 (1)	6 (1)
Exacerbation*	1 (<1)	4 (2)	2 (<1)	6 (1)
Protocol Deviation	8 (4)	8 (4)	2 (2)	18 (4)
Lost to Follow-up	1 (<1)	3 (1)	4 (4)	8 (2)
Source: CSR HZA106839 table 2 *Sub-reason for withdrawal				

Deaths
No deaths occurred during the study.

Non-fatal SAEs
In the FF/VI 100/25 group, 3 SAEs occurred. In the FF/VI 200/25 group, 1 SAE occurred, and in the FP group, 7 SAEs occurred. No safety signals surfaced, and these SAEs were consistent with those found in the short-term studies.

Dropouts and/or Discontinuations
In the FF/VI 100/25 group, 5 subjects were withdrawn secondary to AEs. In the FF/VI 200/25 group, 3 subjects were withdrawn secondary to AEs, and in the FP group, 6 subjects were withdrawn secondary to AEs. No new safety signals were noted.

Adverse Events of Special Interest
Cardiovascular events were the most frequent AESI, and occurred in the FF/VI groups with a higher incidence (FF/VI 100/25: 12%, FF/VI 200/25: 18%, FP: 5%); extrasystoles in the FF/VI 200/25 group was the most common cardiovascular event (8%). Local steroid effects occurred next most frequently at similar rates amongst treatment groups (FF/VI 100/25: 12%, FF/VI 200/25: 15%, and FP: 15%). Other AESI that occurred in ≥ 3% of the subjects were lower respiratory tract infections excluding pneumonia (FF/VI 100/25: 3%, FF/VI 200/25: 5%, and FP: 3%) and hypersensitivity (FF/VI 100/25: 3%, FF/VI 200/25: 5%, and FP: 0%). As described above, the sponsor has submitted a labeling supplement to include hypersensitivity reactions into the product label.

Common Adverse Events
The most frequent AEs were headache (17-23%), upper respiratory tract infection (15-18%), and nasopharyngitis (9-12%), all occurring at approximately the same frequency in each treatment group. Other AEs occurring in ≥ 3% in either FF/VI group included cough, dysphonia, oropharyngeal pain, pyrexia, oral candidiasis, back pain, extrasystoles, bronchitis, upper abdominal pain, respiratory tract infection, sinusitis, diarrhea, rhinitis allergic, toothache, and rhinitis.

Laboratory Findings, Vital Signs, and ECGs
Five subjects had increased glucose levels; two of the subjects had a concomitant diagnosis of diabetes mellitus. Three subjects had an increase in liver enzymes; one subject had underlying hepatitis B, and one subject ad underlying hepatitis C. There were no other clinically meaningful changes in chemistry or hematology parameters.

There were no clinically meaningful changes in vital signs.

One subject had a change from baseline QTc(F) of > 60 msec; no AEs occurred. In the FF/VI 100/25 and 200/25 groups, 7 and 8%, respectively, had ECG findings of potential clinical significance as opposed to 5% of the FP group. Three subjects in the FF/VI 200/25 group had a new finding of sinus tachycardia. Otherwise, there were no noticeable differences in EKG parameters.

Seven subjects in the FF/VI groups (6% each group) had Holter monitor findings of potential clinical importance compared with one subject in the FP group (2%), with the most common finding being arrhythmias. More subjects in the FF/VI as opposed to the FP groups had ventricular ectopies. Otherwise, there were no clinically meaningful differences in Holter monitor findings between the groups.

Ophthalmic Examinations
There were no clinically meaningful differences in ophthalmic examinations between treatment groups; 3 subjects in the FF/VI 100/25 group, 2 subjects in the FF/VI 200/25 group, and 1 subject in the FP group met the protocol-defined stopping criteria: five had reduced visual acuity, and one 40-year old in the FF/VI 200/25 group developed a cortical cataract.

Pregnancies
Five subjects reported pregnancy during the study. One subject was later found to be a false-positive. At the time of reporting, pregnancy outcomes were known for three subjects: in the FF/VI 200/25 group, one subject gave birth to healthy twins and one subject gave birth to a healthy infant. In the FF/VI 100/25 group, one subject had a spontaneous abortion.

This data is consistent with the safety data obtained in the shorter term clinical trials and does not indicate any new safety issues with longer-term use.

Reviewer's Comment: This data is consistent with the safety data obtained in the shorter term clinical trials and does not indicate any new safety issues with longer-term use.

7.7.2 Evaluation of Serious Asthma Outcomes

7.7.2.1 Meta-analysis

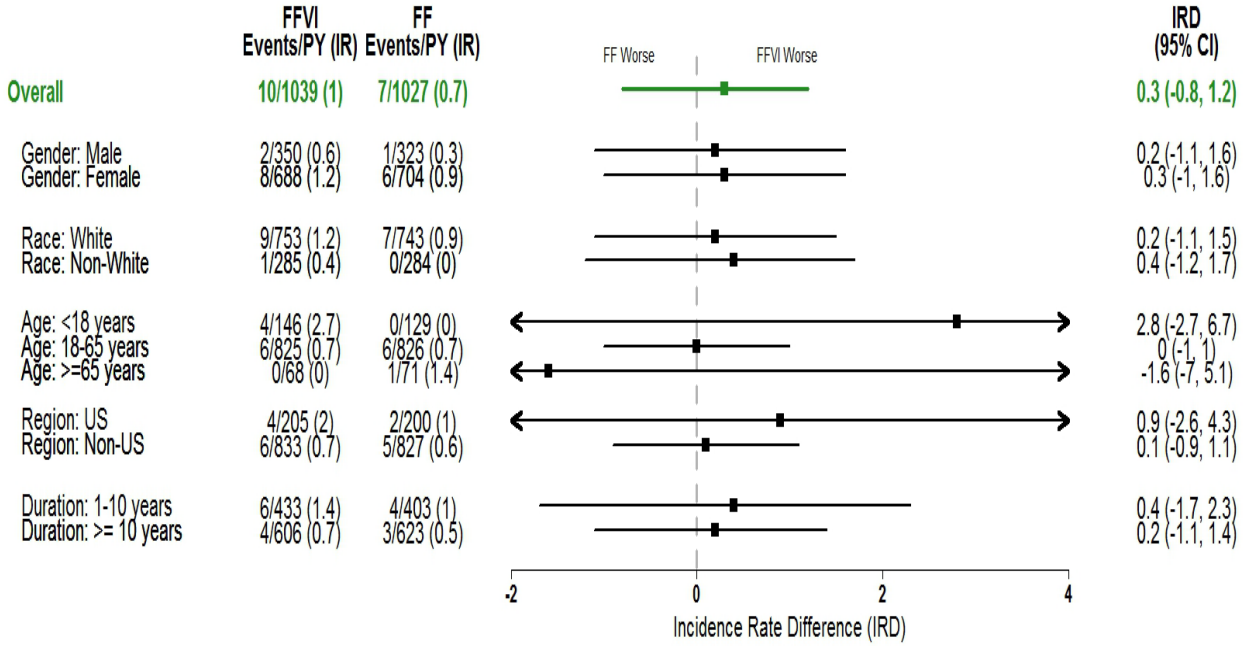
The known safety concerns, including asthma-related death, with the use of LABA for asthma, prompted the Agency to conduct a meta-analysis of the submitted data (Trials 37, 29, 63, and 27) to examine the risk of asthma-related outcomes with FF/VI. The details of the meta-analysis can be found in the Agency's statistical briefing document by Dr. Janelle Charles and are summarized here.

As there were no asthma-related deaths or intubations, the focus of the analysis was on hospitalizations, which were defined by GSK as a hospital admission or emergency room visit for more than one day with or without use of systemic corticosteroid treatment.

There were a total of 18 asthma-related hospitalizations observed in the 4 trials included in the meta-analysis. The crude incidence rate was estimated to be 0.7 per 100 person-years for FF/VI and 0.6 per 100 person-years for FF. The incidence rate difference was 0.1 per 100 person-years (95% CI -0.5, 0.8). Seventeen of the 18 hospitalizations were in Trial 37, so further subgroup analysis was conducted for this trial. Only one event was in a non-white subject. An imbalance was noted in the 12-17 year old age group as

seen in Figure 23; 4 hospitalizations occurred in the FF/VI arm and no hospitalizations occurred in the FF arm. This imbalance is concerning as is discussed under the risk benefit analysis above.

Figure 23. Subgroup Results in Trial HZA106837



PY=person-years, IR=incidence rate per 100 patient-years, IRD=incidence rate difference per 100 patient-years, AR=asthma-related.
Source: Agency's Statistical Reviewer

7.7.4 120-Day Safety Update

The sponsor submitted its 120-day safety update on October 23, 2014, which includes all new clinical safety data from the clinical program from February 1 to September 5, 2014. In general, the data from this safety update are similar to those seen within the sNDA application. There were no additional deaths in any of the trials. The adverse event profile reported in the safety update was similar to that which has been described in this review. Post-marketing data was also included; five deaths occurred in those receiving FF/VI. One death was of unknown cause who was receiving FF/VI for an unknown indication, one death occurred from infectious colitis, myocardial ischemia, and volvulus (66-receiving FF/VI for COPD), one death occurred from sepsis (66-year-old male receiving FF/VI for COPD), one death occurred from pneumonia and respiratory failure (58-year-old female receiving FF/VI for COPD), and one death occurred from pneumonia and septic shock (77 year-old male receiving FF/VI for

COPD). A total of 122 SAEs occurred, with pneumonia being the most frequent. Thus, no new safety signals were noted in the 120-day safety update.

8 Postmarket Experience

8.1 Hypersensitivity

In a review of the global post-marketing experience since product launch on May 10, 2013, there have been a total of 91 spontaneous reports. A new safety signal of hypersensitivity was identified. There were two deaths, one of which was a patient of unspecified age who experienced angioedema and swelling of the tongue. There were a total of 13 serious cases. Of these, there were three cases of hypersensitivity: one female subject of unknown age experienced swelling of face and hypersensitivity, one 49-year-old female experienced anaphylactic reaction and pharyngeal edema, and one 62-year-old female experienced facial and laryngeal edema.

The sponsor then conducted an internal post-marketing safety monitoring for hypersensitivity searching the worldwide safety database as well as the medical literature. Seventeen post-marketing spontaneous reports were considered consistent with hypersensitivity, and seven cases were identified as possible hypersensitivity reactions. Four cases were serious, and two were considered life-threatening.

Given this new safety signal, the event of hypersensitivity has been added to the USPI. No other new safety signals were identified since product launch.

8.2 Palpitations and tachycardia

A safety signal of palpitations/tachycardia arose from spontaneous postmarketing reports. Therefore, the sponsor performed a review of all cardiac arrhythmia SMQ cases for FF/VI and VI monotherapy with a database lock of June 30, 2014. Sixty spontaneous cases and 89 unblinded clinical trial cases were identified within the cardiac arrhythmia SMQ. Most of these cases reported palpitations and tachycardia. Given this, as well as the known class effect of LABA medications, a labeling supplement was submitted to the Agency on January 23, 2015 requesting that palpitations and tachycardia be added to the USPI. This labeling supplement will be addressed during labeling revisions as part of this sNDA.

8.3 Dysphonia

The Office of Surveillance and Epidemiology within the Agency detected postmarketing reports of dysphonia and recommends addition of this to the post-marketing section of the label (the sponsor had already added dysphonia to Adverse Reactions for this version of the USPI). This recommendation will be addressed during labeling revisions as part of this sNDA.

9 Appendices

9.1 Literature Review/References

Literature Review

The application included a listing of references but no systemic literature review.

A PubMed search performed by this Reviewer [search term: fluticasone furoate AND vilanterol; no limits] was conducted on March 21, 2015, and yielded 53 references. A brief review of these reports was performed. No new safety signals were identified from these reports.

References

Reddel et al. An Official American Thoracic Society/European Respiratory Society Statement: Asthma Control and Exacerbations: Standardizing Endpoints for Clinical Asthma Trials and Clinical Practice. *Am J Respir Crit Care Med.,* 180: pp. 58-99, 2009.

9.2 Labeling Recommendations

While the label has not been finalized at the time of this review, the following major revisions are proposed:

Section 1: Indications and Usage

- Treatment of Asthma
  - The indication should be revised to include only patients 18 years and older.
- As asthma is being added to the label, the COPD information should remain in Section 1.1. The asthma information should be added to 1.2. This order of indication should be applied to Sections 6 and 14 as well (see below).

Section 6: Adverse Reactions

- LABA warning paragraph should be concordant with class labeling.

6.1 Clinical Trials Experience in COPD:

- Sections should be re-ordered as for Section 1.

6.2 Clinical Trials Experience in Asthma

- This section should include information from Trials 27, 63, 29, 39, and 37.
- First paragraph of this section should describe the trials and the demographic information.
- Following the first paragraph, organize the safety sections based on trial duration with underlined subsections as outlined below.

➢ Subsection*:* 12 Week-Trials

Similar to the Arnuity label, (b) (4) , as trial durations and treatment arms varied. Therefore, we request that you organize your adverse event tables in the following way:

- Table 1: Adverse Reactions ≥ 2% from Trial 27 – 12 Week Trial
  - Treatment Arms in Table: FF/VI 100/25, FF 100, Placebo
- Table 2: Adverse Reactions ≥ 2% from Trial 63- 12 Week Trial
  - Treatment Arms: FF/VI 200/25, FF/VI 100/25, FF 100

➢ Subsection*:* 24-Week Trial

- In this section, describe similarities or differences in common adverse events that occurred when comparing to the 12 week trials. Another table is not necessary.

➢ Subsection*:* 12 month Trial

- No changes proposed to language at this time.

➢ Subsection*:* Exacerbation Trial

- First paragraph: Include demographics of Trial 37 and highlight that although 12 -17 year olds were included in this population, FF/VI is not approved in this age group with a reference to Section 8.4 Pediatric Use.
- Second paragraph: Include information regarding serious asthma related outcomes in this study.

Section 8.4 Pediatric Use

- Revise the first sentence to indicate that the safety and efficacy in pediatric patients have not been established.
- Include a description of Trial 37 results to explain why it is not approved in this age group. Discuss exposure, efficacy, and safety findings in this section.

Section 14. Clinical Studies

14.1 Chronic Obstructive Pulmonary Disease

- Sections should be re-ordered to leave the COPD indication first, as for Sections 1 and 6.
- Re-organize the information for the COPD indication into the following underlined subsections:
  - Subsection: Dose Selection for Vilanterol
  - Subsection: Dose Selection for FF (refer to asthma FF dose selection section)
  - Subsection: Lung Function
  - Subsection: Exacerbations

14.2 Asthma

- Re-organize the information for the Asthma indication in the following underlined subsections:

- Subsection: Dose Selection for Vilanterol (Trial B2C109575)
  - Include Dose Ranging Figures on Days 1 and 28, similar to COPD.
- Subsection: Dose Selection for FF (Trials 87, 85, 84, and 112202)
  - Include Dose Ranging Figures from Arnuity Label.
- Subsection: Confirmatory Trials (This subsection should include 5 trials: 29, 63, 27, 91, and 37)
  - Describe the demographics and relevant baseline characteristics of this asthma patient population. Create a table to include age, asthma duration, smoking status, post-bronchodilator FEV1, and absolute reversibility.

- Demographic information should include patients 12 to 17 years old, but clarify that Breo Ellipta is not indicated for these patients with references to the appropriate sections of the package insert (e.g. Sections 1.2, 6.2, and 8.4).
  - Provide a description of the design and results of Trials 29, 63, and 27:
    - Construct one table with weighted mean and trough FEV1 results for all three trials
    - Choose a representative trial and display three figures:
      - Mean change from baseline in individual serial FEV1 (mL) assessments over 24 hours on Day 1
      - Mean change from baseline in individual serial FEV1 (mL) assessments over 24 hours at study endpoint
      - Mean change from baseline in WM FEV1 at various timepoints throughout the trial duration
  - Provide a description of the design and results of Trial 91.

Provide a description of the design and results Trial 37.

9.3 Advisory Committee Meeting

As vilanterol is the first LABA brought forth for approval since the black box warning was placed on this class of medication warning of an increase in asthma-related death, this application was discussed at a joint meeting of the Pulmonary Allergy Drugs and the Drug Safety and Risk Management Advisory Committees on March 19, 2015. The committee members were asked to consider the efficacy, safety, and approvability for Breo Ellipta divided by age groups (12 to 17 years vs. 18 years of age).

Given the historical safety concern in pediatric patients, and the findings of the meta-analysis conducted by the Agency for this application,
the committee expressed concern over the lack of consistent treatment effect in the adolescent population. Likewise, the committee members cited that although once daily doing provides an advantage for patients, there are other highly effective medications already on the market to offer adolescents with asthma. In addition, there was concern that given the known difficulty with compliance in the adolescent population, this subgroup would likely be prescribed FF/VI most frequently.

Given all of these concerns, the committee voted in favor of approving Breo Ellipta for patients $\geq$ 18 years of age (16 yes, 4 no) but against approval for patients 12-17 years of age (1 yes, 19 no). The committee cited various possibilities of how the 12-17 year old population could further be studied to provide data for approval, such as another randomized controlled trial similar in design to HZA106837. The voting regarding the need for a large LABA safety trial in ≥18 years of age was more mixed, in that 13 members voted in favor of conducting a trial, and 7 voted that a large-safety trial was not needed. Many of the members, despite their vote of yes or no, voiced that these studies could be conducted pending the results of the on-going LABA safety trials, while two members stated that the studies should be conducted regardless of the outcomes of the ongoing trials. The committee also raised the possibility of pragmatic trials as an alternative to the traditional randomized controlled trials.

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/s/

TRACY L KRUZICK
03/27/2015

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03/27/2015