JOINT MEETING OF THE PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE (PADAC) AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE (DSaRM)

FDA Briefing Document

March 19, 2015

sNDA 204-275: fluticasone furoate and vilanterol inhalation powder for the maintenance treatment of asthma in patients 12 years of age and older

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the supplemental new drug application (sNDA) 204-275, fluticasone furoate and vilanterol inhalation powder, for the maintenance treatment of asthma in patients 12 years of age and older, to this joint Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package

DIVISION MEMORANDUM

Date: March 19, 2015

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Sally Seymour, MD
Deputy Director for Safety, DPARP

To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC) and Drug Safety and Risk Management Advisory Committee (DSaRM)

Subject: Overview of the FDA background materials for Supplemental New Drug Application (sNDA) 204275-S001, for Breo Ellipta 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder) and 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder) for the once daily treatment of asthma in patients 12 years of age and older

I. Introduction

Thank you for your participation in the upcoming joint Pulmonary Allergy Drugs and Drug Safety and Risk Management Advisory Committee (PADAC and DSaRM) meeting to be held on March 19, 2015. As members of FDA Advisory Committees (AC), we consider your expert scientific advice and recommendations to the FDA very important to our regulatory decision making processes. The objective of the upcoming meeting is to discuss the supplemental new drug application (sNDA) 204275-S001 for Breo Ellipta 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder) and 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder) submitted by GlaxoSmithKline (GSK) for the once daily treatment of asthma in patients 12 years of age and older. While the discussion will include efficacy data, the focus of the meeting will be safety, including the adequacy of the safety database to support approval and whether a large safety trial to evaluate serious asthma outcomes is necessary.

Breo Ellipta is a combination inhalation product comprised of an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA). Breo Ellipta was approved on May 10, 2013, for the long-term, once daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, and to reduce exacerbations of COPD in patients with a history of exacerbations. Breo Ellipta is available as a dry powder inhaler and the approved dose is 100 mcg fluticasone furoate and 25 mcg vilanterol once daily. In this supplemental NDA, GSK proposes Breo Ellipta for the treatment of asthma. GSK proposes two doses of Breo Ellipta - 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder) and 200/25 (fluticasone furoate 200 mcg and vilanterol 25 mcg inhalation powder), with once-daily dosing regimen.

There have been longstanding safety concerns of serious asthma exacerbations, including asthma-related death with the use of long-acting beta agonists (LABA) for asthma. The safety concerns have led to a number of regulatory actions, including multiple advisory committee meetings, Boxed Warning on all LABA products, and more recently a post-marketing requirement (PMR) for large safety trials to determine the safety of LABAs added to inhaled corticosteroids (ICS) compared to ICS alone for the treatment of asthma.

The safety concerns with LABAs in asthma patients and the requirement for large safety trials for LABAs have had an impact on LABA development for asthma. Currently there are two LABAs, salmeterol and formoterol, which are approved as single ingredients or in combination with ICS in inhalation products for the treatment of asthma. Historically, LABA products were developed for patients with asthma and later developed for patients with COPD. Recently, new LABAs, such as indacaterol and vilanterol, have been developed for use in COPD patients, but not for asthma. Breo Ellipta is the first inhalation product with a new LABA (vilanterol) proposed for asthma in over a decade and would be the first once daily LABA containing product for asthma.

To support the proposed asthma indication, GSK submitted data from a clinical program that included multiple studies (discussed later in this document). GSK has a substantial safety database for Breo Ellipta for asthma. This memo will summarize regulatory history of the LABA safety issue and the asthma clinical program for Breo Ellipta. Given the LABA safety issues, the adequacy of the safety database to support approval is one of the issues for advisory committee discussion. Another major issue is whether a large safety trial to evaluate serious asthma outcomes is necessary and if so, whether the trial should be conducted pre or post-approval.

The content of this document and the materials prepared by the Agency reflect the preliminary findings and opinions based on reviews of the information submitted by GSK. These materials do not represent the final position of the Agency. The opinions and insights provided by you at this advisory committee meeting will be an important factor in our decision on this application. Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Clinical Briefing Document, Statistical Briefing Document (safety), review of LABA use data from the Office of Surveillance and Epidemiology, and a memo from the Office of Pediatric Therapeutics.

II. Regulatory History of LABA Safety

Short acting beta agonists (SABA) are the mainstay of therapy for acute treatment of bronchospasm and the duration of action is generally 6 hours. Albuterol and levalbuterol are the approved SABA in the US. Inhaled LABAs have a duration of bronchodilation of at least 12 hours after dosing resulting in improved pulmonary function, and decreased need for rescue short-acting bronchodilator use. They have adverse effects that are typical of beta-adrenergic agonists. In addition, an important adverse effect that has been observed with these drugs in patients with asthma is the occurrence of serious asthma exacerbations, including asthma-related death.

As noted above, there are currently two LABAs (salmeterol and formoterol), which are approved as single ingredients or in combination with ICS in inhalation products for the treatment of asthma. Table 1 shows the LABA products approved for asthma in the US.

Table 1. LABA Products Approved for Asthma in the United States

Product/Dosage Strength	Sponsor	Approval Date for Asthma	Approved Age Range	Dosing Regimen
Serevent Diskus (salmeterol xinafoate inhalation powder) • 50 mcg	GSK	September 1997	4 years of age and older	One inhalation BID
Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder) • 100 mcg FP/50 mcg salm • 250 mcg FP/50 mcg salm • 500 mcg FP/50 mcg salm	GSK	August 2000	4 years of age and older	One inhalation BID
Foradil Aerolizer (formoterol fumarate inhalation powder) • 12 mcg	Novartis	February 2001	5 years of age and older	One inhalation BID
Advair HFA (fluticasone propionate and salmeterol xinafoate) Inhalation Aerosol • 45 mcg FP/21 mcg salm • 115 mcg FP/21 mcg salm • 230 mcg FP/21mcg salm	GSK	June 2006	12 years of age and older	Two inhalations BID
Symbicort (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol • 80 mcg bud/4.5 mcg formoterol • 160 mcg bud/4.5mcg formoterol	Astra-Zeneca	July 2006	12 years of age and older	Two inhalations BID
Dulera (mometasone furoate and formoterol fumarate dihydrate) Inhalation Aerosol • 100 mcg mom/4.5 mcg formoterol • 200 mcg mom/4.5 mcg formoterol	Merck	June 2010	12 years of age and older	Two inhalations BID

A. Salmeterol

1. Salmeterol Nationwide Surveillance (SNS) Study

Salmeterol was the first LABA approved in the U.S as Serevent Inhalation Aerosol in 1994 (no longer marketed due to the phase out of the CFC propellant). Around the time of approval of Serevent Inhalation Aerosol, the findings from the Salmeterol Nationwide Surveillance (SNS) study were available. The SNS study was conducted in the United Kingdom in the mid 1990s and it compared salmeterol twice daily with salbutamol (albuterol in the U.S.) administered four times daily for 16 weeks in approximately 25,000 patients who were considered to need regular $beta_2$-agonist therapy. The SNS study showed a non-significant (p=0.105) 3-fold increase in respiratory and asthma-related death in patients taking salmeterol (0.07%) vs. scheduled salbutamol (0.02%).[1]

[1] Castle W, Fuller R, et al. BMJ 1993: 306: 1034-7.

2. Salmeterol Multicenter Asthma Research Trial (SMART)

Following the approval of salmeterol, GSK initiated a large safety study, the Salmeterol Multicenter Asthma Research Trial (SMART) in 1996. SMART was conducted at the Agency's request and was prompted by reports of serious asthma exacerbations and deaths in patients treated with salmeterol soon after its approval, and, by the results of the SNS study.

SMART was a randomized, double-blind study that enrolled patients 12 years of age and older with asthma not currently using a LABA and randomized them to salmeterol (Serevent Inhalation Aerosol) or placebo twice daily added to usual asthma therapy.[2] There was one baseline study visit, and inhaled corticosteroid as baseline asthma therapy was not mandated. The proposed treatment duration was 28 weeks with a revised target sample size from 30,000 to 60,000 patients. SMART was prematurely halted in 2003 after a planned interim analysis suggested that salmeterol may be associated with an increased risk of serious asthma exacerbations including asthma-related death. GSK submitted preliminary summary results of the SMART to the Agency in February 2003, which led to labeling changes, including the addition of a boxed warning cautioning the use of salmeterol in patients with asthma.

Following submission of the final SMART study report, the results were discussed at a 2005 PADAC meeting.[3] The results of SMART for the 28-week treatment period showed a 4-fold increase in asthma related deaths in patients treated with salmeterol compared to placebo (Table 2).

Table 2 Primary Endpoint and asthma related death in SMART for 28 week treatment period

	Serevent Inhalation Aerosol n=13,176	**Placebo n=13,179**	**Relative Risk (95% CI)**
Primary Endpoint: Respiratory-related deaths or life-threatening experiences			
Total	50 (0.3%)	36 (0.3%)	1.4 (0.9, 2.1)
Caucasians [salm n=9281, pbo n=9361]	29 (0.3%)	28 (0.2%)	1.1 (0.6, 1.8)
African American [salm n=2366, pbo n=2319]	20 (0.8%)	5 (0.2%)	4.1 (1.5, 10.9)
Secondary Endpoint: Asthma-related death			
Total	13 (0.1%)	3 (0.02%)	4.4 (1.3, 15.3)
Caucasians [salm n=9281, pbo n=9361]	6 (0.06%)	1 (0.01%)	5.8 (0.7, 48.4)
African Americans [salm n=2366, pbo n=2319]	7 (0.3%)	1 (0.04%)	7.3 (0.9, 58.9)

B. Formoterol

1. Formoterol Clinical Program

Formoterol was the second LABA approved for asthma in the US approved as a dry powder inhaler, Foradil Aerolizer, in 2001. There are now several formoterol containing products approved for asthma in the US (Table 1). The clinical development program conducted by Novartis to support the asthma indication for Foradil Aerolizer evaluated two doses, 12 mcg

[2] Nelson HS, Weiss ST, et al. Chest 2006; 129: 15-26.
[3] July 13-14, 2005, FDA PADAC Mtg [http://www.fda.gov/ohrms/dockets/ac/cder05 html#PulmonaryAllergy]

and 24 mcg. Review of the safety data from the development program showed a numerical increase in serious asthma exacerbations with the higher dose as shown in the table below.[4]

Table 3 Serious asthma exacerbations* in Foradil Aerolizer clinical development program

	Placebo	Albuterol 180 mcg BID	Formoterol 12 mcg BID	Formoterol 24 mcg BID
12-wk study in adults and adolescents (study 040)	0/136 (0%)	2/134 (1.5%)	0/136 (0%)	4/135† (3%)
12-wk study in adults and adolescents (study 041)	2/141 (1.4%)	0/138 (0%)	1/139 (0.7%)	4/136‡ (3.7%)
1-yr study in 5-12 year old children (study 049)	0/176 (0%)	NA	8/171 (4.7%)	11/171 (6.4%)

* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death
† 1 patient required intubation
‡ 2 patients had respiratory arrest, 1of the patients died

Based upon these safety findings, the higher dose of formoterol (24 mcg) was not approved. As a result of concerns arising from the possibility of acute exacerbation and worsening of asthma with the use of salmeterol, and the findings in the formoterol phase 3 studies, the Agency asked Novartis to perform a phase 4 clinical study to further investigate the relative safety of the two different doses of formoterol. The study was started in 2002 and completed in 2004. The study is briefly described below.

2. Formoterol Phase 4 Study[5]

The formoterol phase 4 study was a randomized, blinded, placebo-controlled study of 16 weeks duration in 2,307 patients 12 years of age and older with mild-to-moderate persistent asthma. The study consisted of one baseline visit and subsequent visits in weeks 1, 4, 8, 12, and 16. This study allowed liberal use of anti-inflammatory medications. More patients enrolled in this phase 4 study received ICS during the study than those in the phase 3 studies (58% vs. 47%). Patients were randomized approximately equally to receive Foradil Aerolizer 12 mcg BID, Foradil Aerolizer 24 mcg BID, Foradil 12 mcg BID with up to two additional on-demand 12 mcg doses per day, and placebo. The Foradil fixed-dose groups and placebo group were treated in double-blind fashion, and the Foradil on-demand group was open-label. There were no deaths in this study. The overall rates of events of interest in this study were too low to draw any firm conclusion, although the trends showed a numerical increase in serious asthma exacerbations compared to placebo.

Table 4 Asthma exacerbations in Foradil Aerolizer Phase 4 safety study

	Formoterol 12 mcg BID (n=527)	Formoterol 24 mcg BID (n=527)	Placebo (n=514)	Formoterol Open-label (n=517)
Serious asthma-related adverse events	5 (0.9%)	2 (0.4%)	1 (0.2%)	1 (0.2%)
Serious asthma exacerbations *	3 (0.6%)	2 (0.4%)†	1 (0.2%)	1 (0.2%)

* Life-threatening experience, hospitalization, prolongation of hospitalization, persistent disability, or death
† 1 patient required intubation

[4] Mann M, Chowdhury B, et al. Chest 2003; 124:70-74.
[5] July 13-14, 2005, FDA PADAC Mtg [http://www.fda.gov/ohrms/dockets/ac/cder05 html#PulmonaryAllergy]

C. July 13, 2005, PADAC Meeting[6]

A PADAC meeting was held in July 2005, to discuss the results of SMART and the formoterol phase 4 study results. After review of the data presented above, the panel recommended via unanimous vote that formoterol-containing product labels should include warning statements similar to salmeterol. This recommendation was made because both salmeterol and formoterol belong to the same class of drugs, and without convincing reassuring safety data with formoterol, the safety finding seen with salmeterol should be applied to formoterol. Furthermore, the signal of serious asthma exacerbations seen with formoterol in considerably smaller studies was concerning. Following the PADAC recommendation, the labels for all formoterol-containing products were changed to include a boxed warning regarding asthma- related death.

D. December 10-11, 2008 PADAC/PAC/DSaRM Meeting[7]

A joint PADAC, DSaRM, and Pediatric (PAC) Advisory Committee (AC) meeting was held in December 2008, to revisit the safety of LABA and to assess the risk-benefit of this class of drugs for the treatment of asthma in the adult and pediatric populations. This AC meeting was prompted by a recommendation from a PAC meeting in November 2007. During the AC meeting, the FDA presented the results of a meta-analysis of available patient level data from randomized parallel controlled clinical trials submitted by the sponsors of LABA products. The objective of the meta-analysis was to evaluate if LABA were associated with increased risk of serious asthma outcomes (death, intubation, hospitalization). One hundred and ten trials, with almost 61,000 patients were included. The analysis showed a risk difference (per 1000 patients) of 2.8 [95% CI 1.1, 4.5] for serious asthma outcomes in patients treated with LABA vs. No LABA. One of the subgroup analyses based upon age suggested an increase in risk for lower age groups (Figure 1). For details of the meta-analysis, refer to the FDA briefing package available at http://www.fda.gov/ohrms/dockets/ac/cder08.html#PulmonaryAllergy.

[6] Ibid.
[7] December 10-11, 2008, FDA PADAC/PAC/DSaRM Mtg [http://www fda.gov/ohrms/dockets/ac/cder08 html#PulmonaryAllergy]

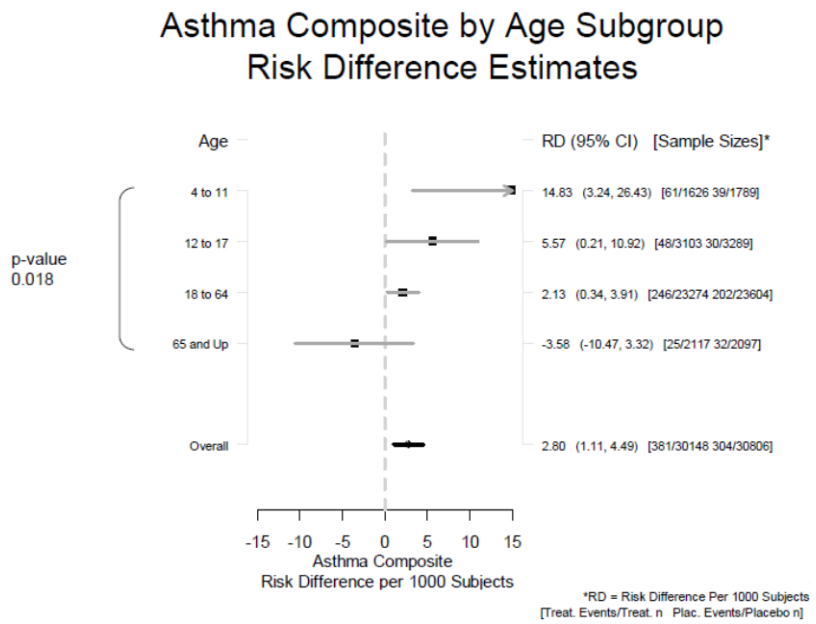

Figure 1. Risk difference estimates – age subgroup analysis
Source: http://www.fda.gov/ohrms/dockets/ac/cder08.html#PulmonaryAllergy

At the December AC meeting, the committee stressed the appropriate use of LABAs (e.g. not as monotherapy), and the need for more safety data, especially in the adolescent and pediatric population where the data were very limited. Following this 2008 AC meeting, on February 18, 2010, the Agency required further labeling changes including the following: contraindication of use of LABA without an asthma control medication; recommendation to use fixed dose ICS+LABA combination in pediatric and adolescent patients; and to assess asthma control and consider step down therapy (e.g. discontinue LABA).[8] The Agency also required post-marketing controlled safety trials (discussed below).

E. Ongoing LABA Safety Trials[9]

To evaluate the safety of LABA when added to ICS, the Agency issued a post-marketing requirement (PMR) for safety trials for each of the sponsors of LABA products marketed in the US for asthma. The design of the trials was discussed at a March 10-11, 2010, PADAC meeting, and was finalized in 2011. The final PMR for the sponsors of Advair Diskus, Dulera, Foradil Aerolizer, and Symbicort is shown below.

> ***A randomized, double-blind, 26-week, active-controlled clinical trial comparing ICS/LABA and ICS to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 11,700 adult and adolescent patients 12 years of age and older with persistent asthma. Final Study Report Submission: June 2017***

GSK also has an additional requirement for a pediatric safety trial because it is the only ICS+LABA combination product approved for asthma in children 4 to 11 years of age.

[8] Chowdhury BA, DalPan G. New Eng J Med 2010; 362:1169-1171.
[9] Chowdhury BA, Seymour SM, Levenson MS. New Eng J Med 2011;364:2473-5

A randomized, double-blind, 26-week, active-controlled clinical trial comparing Advair Diskus and Flovent Diskus to evaluate the risk of serious asthma outcomes (hospitalizations, intubation, death) in 6,200 pediatric patients 4 to 11 years of age with persistent asthma.
Final Study Report Submission: June 2017

The ongoing trials are multi-national, randomized, double-blind, parallel group, active-controlled design in which asthma patients are randomized to an ICS+LABA or an ICS for 26 weeks. Three of the trials are with ICS+LABA combination products (Advair, Dulera, and Symbicort) compared to their respective ICS monotherapy. Given that Foradil Aerolizer is a LABA single ingredient product, the Foradil Aerolizer trial requires participants to use two devices – Foradil Aerolizer + fluticasone propionate or placebo + fluticasone propionate. In each of the 4 adult and adolescent trials, 11,700 patients 12 years and older will be enrolled and in the single pediatric trial 6200 children 4 to 11 years of age will be enrolled. Because the strategy is to mimic a real-world scenario, patients may be eligible regardless of their current asthma therapy if their asthma severity warrants treatment with an ICS and LABA.

The primary endpoint is the number of patients experiencing the composite endpoint of serious asthma outcomes (asthma related hospitalization, asthma-related intubation, or asthma-related death). The trials are non-inferiority design. Based upon an estimated background rate of 1.5% per year, the adult and adolescent trials have 90% power to rule out a 2.0 fold increase in event rate (87 composite events) and the pediatric trial has 90% power to rule out a 2.7 fold increase in event rate (43 composite events). It is expected that the primary endpoint will be driven by hospitalizations, given the rarity of asthma intubations and death.

Each of the sponsors is conducting a separate LABA safety trial independently, but the trial designs are harmonized and there is a shared Joint Oversight Steering Committee and a shared Data Monitoring Committee. The idea is that the results of the trials can be reviewed independently as well as jointly with a total of 46,800 patients in order to evaluate the results for the rare events of intubations and death.

In terms of timing, the agreed upon final report submission date is June 2017. However, there is some variability in study progress and projected final report submission dates. GSK has provided an update on the status of their ongoing trials in their briefing document.

III. Regulatory History of Breo Ellipta

The sequence and scale of the fluticasone furoate plus vilanterol development program differ from prior precedent. Previous ICS+LABA development programs were based on the initial development of the individual ICS and LABA monotherapies followed by the combination product in asthmatics. In contrast, the program for fluticasone furoate plus vilanterol was conducted concurrently with the development of the individual monocomponents in both COPD and asthma followed by submission and approval of the NDA for Breo Ellipta for patients with COPD. This shift in focus to development of ICS+LABA combination products for patients with COPD is in part due to the concerns

about the need for a large amount of safety data to support approval of a new LABA in patients with asthma. With the PMR requirements for marketed LABA products, there is a question about how much safety data would be necessary for a new LABA for asthma and whether a large safety trial would be necessary and if so, pre- or post-approval. This is the main issue for discussion at this advisory committee meeting.

The clinical development for Breo Ellipta and single ingredient fluticasone furoate and vilanterol started in the late 2000s with early interaction between FDA and GSK occurring at a pre-IND meeting for vilanterol in 2007 and at a pre-IND meeting for Breo Ellipta occurring in 2008. An end-of-phase-2 meeting for Breo Ellipta for asthma was held in March 2009, and one for COPD was held in June 2009. The pre-NDA meeting for Breo Ellipta for COPD was held in July 2011, and the one for asthma was held in October 2011. The NDA for Breo Ellipta for COPD was submitted in July 2012, and the NDA was approved in May 2013. For COPD, the approved product was Breo Ellipta 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg) and the recommended dose is 1 inhalation once daily.

IV. Product Information

Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) is a fixed-dose combination product administered by oral inhalation. In this sNDA GSK is proposing marketing of Breo Ellipta at two dosage strengths for use in asthma – Breo Ellipta 100/25 that is already marketing for COPD, and a higher strength Breo Ellipta 200/25. The recommended dose is 1 inhalation once daily of Breo Ellipta 100/25 or Breo Ellipta 200/25 based on patients' asthma severity.

Fluticasone furoate is currently available in two dosage strengths as an inhalation monotherapy for asthma, marketed as Arnuity Ellipta (fluticasone furoate inhalation powder) 100 mcg and 200 mcg. The recommended dose is one inhalation once daily of Arnuity Ellipta 100 or Arnuity Ellipta 200 based on patients' asthma severity.

Vilanterol is not currently available as a monotherapy (b) (4) . In addition to Breo Ellipta, vilanterol is available in another combination product, Anoro Ellipta (umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder) for use as maintenance treatment of airflow obstruction in patients with COPD. Umeclidinium is an anticholinergic.

Ellipta inhaler, the delivery device for the products mentioned above, is a dry powder inhaler device. The Ellipta inhaler is a plastic inhaler with dose counter. The device contains two separate, double-foil, laminate blister strips that are activated in parallel and provide a total of 30 doses. For Breo Ellipta, one strip contains micronized fluticasone furoate and lactose. The second strip contains micronized vilanterol, magnesium stearate, and lactose. The device is designed to deliver the contents from a single blister from each of the two blister strips simultaneously. In the 100/25 strength, each inhalation contains 100 mcg of fluticasone furoate and 25 mcg of vilanterol and in the 200/25 strength, each inhalation contains 200 mcg of fluticasone furoate and 25 mcg of vilanterol.

V. Overview of the Breo Ellipta clinical program

The development of an ICS+ LABA combination product relies on the development of the single-ingredient ICS and LABA components. The selection of an appropriate dose and dosing frequency for each component was included in the Breo Ellipta development program. GSK was asked to provide data to support the nominal dose and dosing frequency for each of the components, as well as efficacy and safety data to support the use of fluticasone furoate alone in asthma. These data were viewed as necessary for evaluating the fluticasone furoate plus vilanterol combination, in addition to data to support the efficacy (contribution) of vilanterol in the fluticasone furoate plus vilanterol combination.

Dose ranging for fluticasone furoate in asthma and vilanterol in asthma and COPD have already been reviewed under the original Breo Ellipta development program for COPD (NDA 204275) and discussed at an April 17, 2013, PADAC meeting,[10] and fluticasone furoate 100 mcg and 200 mcg have already been approved for asthma as Arnuity Ellipta (NDA 205625). In the following sections, dose-ranging studies for fluticasone furoate and vilanterol in asthma are discussed, followed by discussion of the Breo Ellipta clinical program for asthma.

Fluticasone furoate dose ranging and dose regimen:

Selection of appropriate dose and dosing regimen is an important consideration for the development of ICSs. GSK conducted adequate exploration of dose ranging and dose regimen for fluticasone furoate (Table 5)

Table 5. Relevant dose-ranging and dose-regimen selection studies for fluticasone furoate in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
109684 [2007-2008]	- 12 to 78 yr - Asthma - Parallel arm, DB - 8 weeks	FF 200 mg QD PM FF 400 mcg QD PM FF 600 QD PM FF 800 mcg QD PM FP 500 mcg BID Placebo	99 101 107 102 110 103	FEV_1 trough at week 8	US, Canada, Mexico, W Eur, E Eur, S Africa, Australia, Thailand
109685 [2007-2008]	- 12 to 80 yr - Asthma - Parallel arm, DB - 8 weeks	FF 100 mcg QD PM FF 200 mg QD PM FF 300 mcg QD PM FF 400 mcg QD PM FP 250 mcg BID Placebo	105 101 103 99 100 107	FEV_1 trough at week 8	US, Canada, Mexico, W Eur, E Eur, S Korea, Philippines
109687 [2007-2008]	- 12 to 78 yr - Asthma - Parallel arm, DB - 8 weeks	FF 25 mcg QD PM FF 50 mcg QD PM FF 100 mcg QD PM FF 200 mcg QD PM FP 10 mcg BID Placebo	97 100 110 95 102 94	FEV_1 trough at week 8	US, Canada, EU, EU, S Africa, Other
112202	- 12 to 76 yr	FF 200 mcg QD PM	140	FEV_1 trough at the	US

[10] April 17, 2013, FDA PADAC Mtg
[http://www fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm329187 htm]

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //
[2007-2008]	- Asthma - Cross over, DB - 28 days	FF 100 mcg BID FP 200 mcg QD PM FP 100 mcg BID Placebo	142 42 43 187	end of 28-day treatment period	

* Study ID shown (top to bottom) as GSK's study number, and [year study started-completed]
† DB=double blind
‡ FF=fluticasone furoate in Ellipta device; FP=fluticasone propionate;
§ Intent to treat
¶ Primary efficacy variables and selected secondary efficacy variables are shown. The efficacy analysis for the pivotal 48 week studies and profiling 6 week studies were performed using analysis of covariance (ANCOVA).
// EU included UK, Germany, Italy, Netherlands, Sweden, Denmark, Spain, Estonia, Poland, Czech Republic, Romania; Other included Chile, Argentina, Peru, Mexico, Philippines, Thailand, Japan, S Korea, Russia, Ukraine

In dose ranging studies, trough FEV_1 responses showed efficacy of fluticasone furoate 100 mcg once daily near the maximal efficacy with fluticasone furoate 200 mcg once daily (Figure 2). Efficacy was also demonstrated with fluticasone furoate 50 mcg once daily, but the difference compared to placebo and compared to other doses was less. Results of the dose regimen study showed numerically similar changes in trough FEV_1 from baseline compared to placebo for fluticasone furoate 200 mcg once daily and fluticasone furoate 100 mcg twice daily, which support a once-daily dosing regimen for fluticasone furoate. The study had sensitivity to detect a difference between once- and twice-daily ICS dosing, since a numerically superior improvement in FEV_1 compared to placebo was seen for the twice-daily comparator, fluticasone propionate (Figure 3). These data and other data supported approval of Arnuity Ellipta (fluticasone furoate inhalation powder) with recommended doses of 100 mcg and 200 mcg once daily.

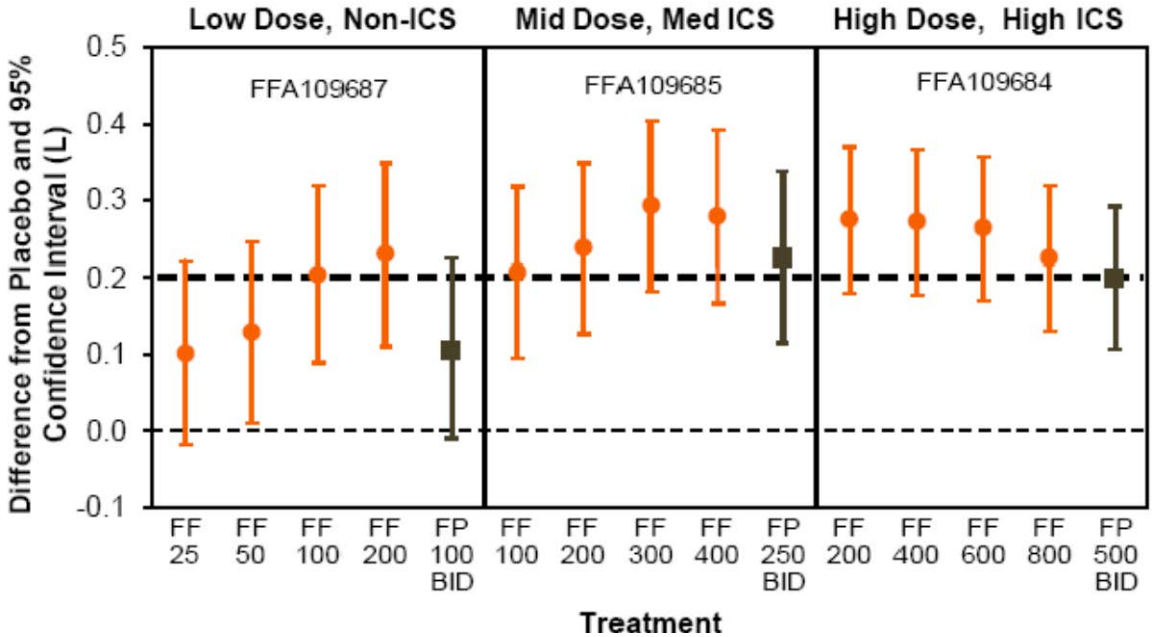

Figure 2. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at week 8 from three dose ranging studies in asthma (FF=fluticasone furoate, FP=fluticasone propionate).
Source: Summary of Clinical Efficacy, Figure 49, p. 97

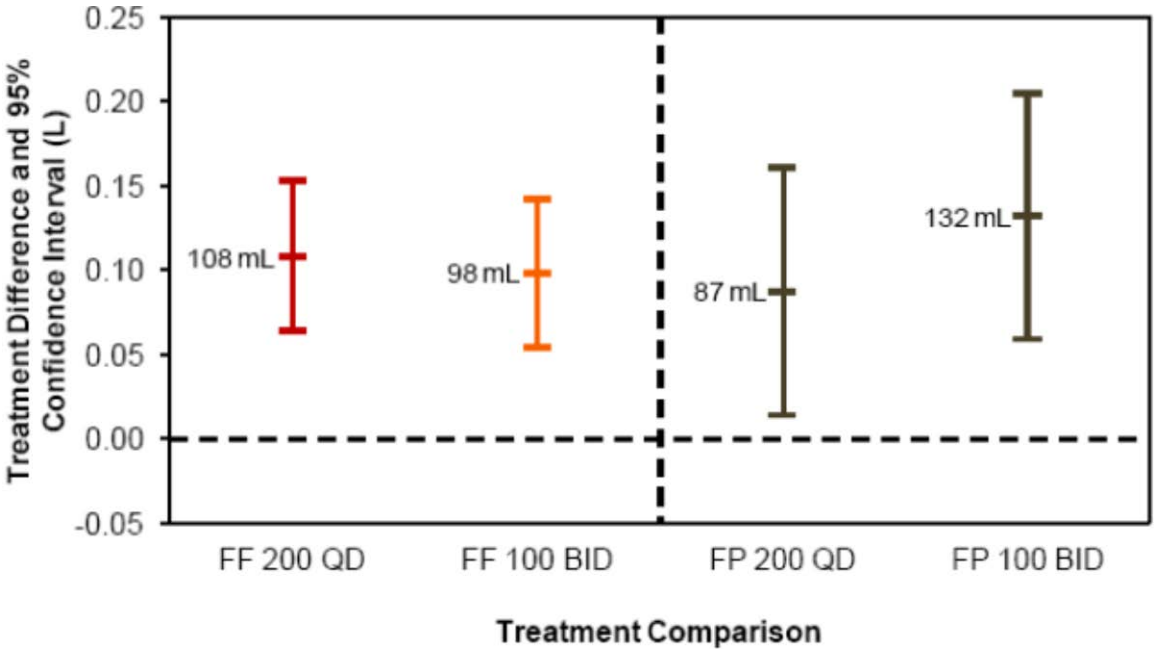

Figure 3. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at day 28 from dose regimen study in asthma (FF=fluticasone furoate, FP=fluticasone propionate).
Source: Module 5.3.5, CSR FFA112202

Vilanterol dose ranging and dose regimen:

Selection of an appropriate dose and dosing regimen is an important consideration for development of LABAs, particularly given the safety concerns in asthma that may be dose related. GSK conducted adequate exploration of dose ranging and dose regimen for vilanterol (Table 6).

Table 6. Relevant dose-ranging and dose-regimen studies for vilanterol in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
109575 [2007-2008]	- 12 to 80 yr - Asthma - Parallel arm, DB - 28 days	VI 3 mcg QD PM VI 6.25 mcg QD PM VI 12.5 mcg QD PM VI 25 mcg QD PM VI 50 mcg QD PM Placebo	101 101 100 101 102 102	FEV_1 trough at day 28	US, EU, Canada, S Africa, Other
113310 [2009-2010]	- 18 to 71 yr - Asthma - Cross over, DB - 7 days	VI 6.25 mcg QD PM VI 6.25 mcg BID VI 12.5 mcg QD PM VI 25 mcg QD PM Placebo	75	FEV_1 trough at the end of 7-day treatment period	US
112060 [2010-2011]	- 12 to 79 yr - Asthma - Parallel arm, DB, DD	VI 25 mcg QD PM Sal 50 mcg BID Placebo	115 116 116	FEV_1 (0-24h) at end of 12 week treatment period	US, EU, Other

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //
	- 28 days				

* Study ID shown (top to bottom) as GSK's study number, and [year study started-completed]
† DB=double blind, DD=double dummy
‡ VI=vilanterol in Ellipta device; Sal=salmeterol xinafoate;
§ Intent to treat
¶ Primary efficacy variables and selected secondary efficacy variables are shown. The efficacy analysis for the pivotal 48 week studies and profiling 6 week studies were performed using analysis of covariance (ANCOVA).
// EU included UK, Germany, Italy, Netherlands, Sweden, Denmark, Spain, Estonia, Poland, Czech Republic, Romania; Other included Chile, Argentina, Peru, Mexico, Philippines, Thailand, Japan, S Korea, Russia, Ukraine

In the dose ranging study, vilanterol 3 mcg and 6.25 mcg once daily were not statistically significantly different from placebo for the primary endpoint of trough FEV_1; vilanterol 12.5 mcg, 25 mcg, and 50 mcg once daily resulted in similar level of improvement in the primary endpoint of trough FEV_1 that were all statistically significantly greater than that observed with placebo (Figure 4). The vilanterol dose regimen study compared once- and twice-daily dosing of 12.5 mcg nominal dose (12.5 mcg once daily compared to 6.25 mcg twice daily), which is expected to be at the steep part of the dose-response curve. Mean change in trough FEV_1 on day 7 is shown on Figure 5. This analysis along with other analyses support once-daily dosing frequency for vilanterol and support GSK's decision to select vilanterol 25 mcg nominal once-daily in combination with fluticasone furoate for confirmatory COPD and asthma studies. In the COPD confirmatory studies, vilanterol 25 mcg in combination with fluticasone furoate 50, 100, and 200 mcg once daily doses were studied. Breo Ellipta 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder) is approved for use in patients with COPD with recommended dose of 1 inhalation once daily.

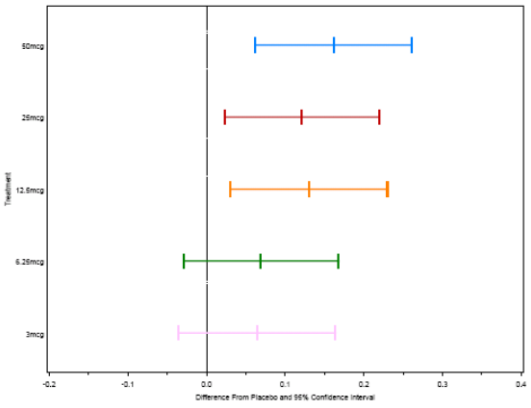

Figure 4. Adjusted treatment difference from placebo change from baseline in trough FEV1 in liters at day 28 in patients with asthma (study 9575).
Source: Module 2.7.3, Summary of Clinical Efficacy, pg. 101.

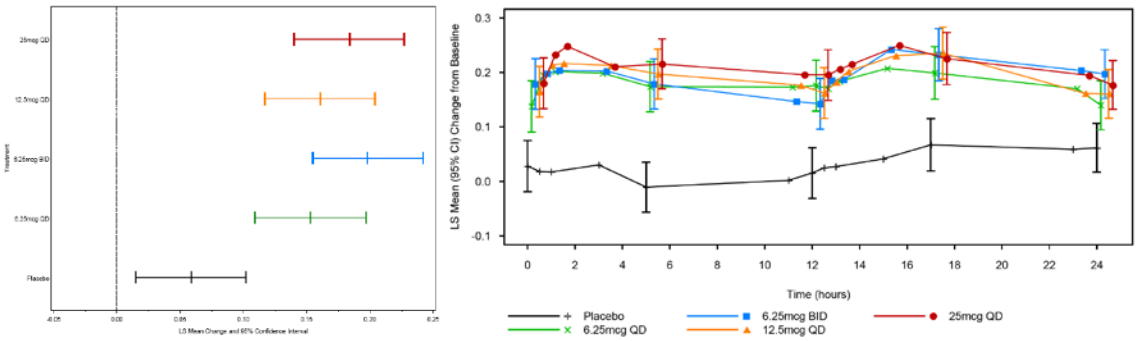

Figure 5. LS mean change in trough FEV1 on day 7 (left panel) and repeated measure adjusted mean change without placebo correction (right panel) on day 7 in patients with asthma, (vilanterol dose regimen study 3310 in asthma).
Source: Module 5.3.5 CSR HZA113310

Breo Ellipta Clinical Studies:

Although GSK conducted programs for fluticasone furoate and vilanterol that were largely concurrent for the individual components and the combination product, this application for Breo Ellipta 100/25 mcg and 200/25 mcg for asthma follows the applications and approval of Breo Ellipta 100/25 mcg for COPD, and the single ingredient Arnuity Ellipta (fluticasone furoate inhalation powder) 100 and 200 mcg for asthma. As mentioned earlier, Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) is approved for use in patients with COPD with recommended dose of fluticasone furoate 100 mcg and vilanterol 25 mcg once daily; and, Arnuity Ellipta (fluticasone furoate inhalation powder) is approved for use in patients with asthma with recommended doses of 100 mcg and 200 mcg once daily. This current application proposes to add vilanterol 25 mcg to the approved fluticasone furoate 100 mcg and 200 mcg as fixed dose combination products. Both drug formulations are in the same Breo Ellipta device, have the same lactose base formulation except the different active ingredients, and do not have drug-drug interactions in the device, delivery path of the drug product, and in vivo in the body. The essence of the clinical development program, therefore, is to demonstrate added clinical benefit of vilanterol to fluticasone furoate, and demonstrate balancing safety. Safety, particularly serious asthma exacerbation, is an important component of demonstration of safety given the known risk of LABA in patients with asthma.

Some characteristics of relevant confirmatory clinical studies that form the basis of this application are shown in Table 7. The design and conduct of these studies are briefly described below, followed by review of the efficacy findings, and review of the safety findings. For brevity, the studies are referenced in subsequent sections of this document by the last four digits of the study number.

Table 7. Relevant clinical studies with Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) in patients with asthma

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy Variables ¶**	**Regions and Countries //**
Pivotal bronchodilator (or lung function) efficacy and safety studies					
106827 [2010-2011]	- ≥ 12 yr - Asthma, FEV1 40-90% - Parallel arm, DB - 12 weeks	FF/VI 100/25 mcg QD FF 100 mcg QD Placebo	201 205 203	1^o: FEV_1 0-24 hr on day 84 in a subset 1^o: ΔFEV_1 trough baseline to day 84	US, EU, Other (32% US)
106829 [2010-2011]	- ≥ 12 yr - Asthma, FEV1 40-90% - Parallel arm, DB - 24 weeks	FF/VI 200/25 mcg QD FF 200 mcg QD FP 500 mcg BID	197 194 195	1^o: FEV_1 0-24 hr on day 168 in a subset 1^o: ΔFEV_1 trough baseline to day 168	US, EU, Other (24% US)
116863 [2012-2013]	- ≥ 12 yr - Asthma, FEV1 40-80% - Parallel arm, DB - 12 weeks	FF/VI 100/25 mcg QD FF/VI 200/25 mcg QD FF 100 mcg QD	346 346 347	1^o: FEV_1 0-24 hr on day 84 in a subset 2^o: ΔFEV_1 trough baseline to day 84	US, EU, Other (24% US)
Asthma exacerbation study					
106837 [2010-2011]	- ≥ 12 yr - Asthma, FEV1 ≥60% - Parallel arm, DB - Up to 76 weeks	FF/VI 100/25 mcg QD FF 100 mcg QD	1009 1010	1^o: Time to first asthma exacerbation ** 2^o: Rate of asthma exacerbation	US, EU, Australia, Other (18% US)
Long-term safety study					
106839 [2009-2011]	- ≥ 12 yr - Asthma, FEV1 ≥50% - Parallel arm, DB - 52 weeks	FF/VI 100/25 mcg QD FF/VI 200/25 mcg QD FP 500 mcg BID	201 202 100	-	US, EU, Other (35% US)
Supportive comparative bronchodilator (or lung function) efficacy and safety study					
113091 [2010-2011]	- ≥ 12 yr - Asthma, FEV1 40-85% - Parallel arm, DB, DD - 24 weeks	FF/VI 100/25 mcg QD FP/Sal 500/50 mcg BID	403 403	1^o: FEV_1 0-24 hr on day 168 2^o: ΔFEV_1 trough baseline to day 168	EU, EU, Other (30% US)

* Study ID shown (top to bottom) as GSK's study number, and [year study started-completed]
† DB = double blind, DD = double dummy
‡ FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF = fluticasone furoate in Ellipta device; FP = fluticasone propionate; VI = vilanterol in Ellipta; FP/Sal = Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder); FF/VI and FF dosed in the evening
§ Intent to treat (ITT)
¶ Primary and secondary efficacy variables for studies 6827, 6829, 6863, and 3091 were analyzed using Analysis of Covariance (ANCOVA) model in the ITT population. Primary efficacy variable for study 6837 was analyzed using negative binomial regression model with log time on treatment as an offset variable in the ITT population.
// EU included Germany, Netherlands, Sweden, Poland, Romania; Other included Chile, Argentina, Mexico, Philippines, Thailand, Japan, S Korea, Russia, Ukraine
** Asthma exacerbation defined as deterioration of asthma requiring the use of systemic corticosteroid (tablets, suspensions, or injection) for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

Design and conduct of the studies:

The bronchodilator (or lung function) studies 6827, 6829, and 6863, were similar in design with differences in study treatment arms, duration of treatment, and minor difference of disease severity. Patients eligible for the studies were required to have a diagnosis of asthma per standard and accepted definition with predefined FEV_1 bounds, demonstrated bronchodilator reversibility of at least 12% and 200 mL of FEV_1, on a stable dose of ICS or LABA or both ICA and LABA prior to entry, and no history of life-threatening asthma in

the past (5 or 10 years). Eligible patients entered a 4-week run-in period when baseline ICS was allowed, and at the end of run-in period patients were stratified based on asthma severity (prior use of ICS or ICS+LABA in studies 6827 and 6829, FEV1 greater than or less than 65% in study 6863) and randomized to different treatment arms as shown in Table 7. On randomization, the baseline ICS was discontinued and replaced by study treatment. Study treatment arms and primary efficacy variables are shown in Table 7. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and 24-hour urinary cortisol excretion.

Asthma exacerbation study 6837 enrolled patients with asthma severity that was higher than the bronchodilator studies. Eligible patients had a lower cut-off of FEV_1, were on mid-to-high dose of ICS or ICS+LABA combination, and history of one or more asthma exacerbation that required treatment with systemic corticosteroids, emergency department visits, or in-patient hospitalization within 12 months prior to study entry. Eligible patients entered a 2-week run-in period when baseline ICS was allowed, and at the end of run-in period patients were randomized to one of the two treatment arms as shown in Table 7. The study was event driven and continued until 330 asthma exacerbation events occurred. Treatment duration for patients was at least 26 weeks and did not exceed 76 weeks for any completed subject. Primary efficacy variable was time to first asthma exacerbation. Asthma exacerbation was defined as deterioration of asthma requiring the use of systemic corticosteroid (tablets, suspensions, or injection) for at least 3 days or an in-patient hospitalization (as defined in the protocol by GSK, hospitalization for any duration would count as an event) or emergency department visit due to asthma that required systemic corticosteroids. All asthma exacerbation events were adjudicated. Safety endpoints included intubation, hospitalization, emergency department visit, unscheduled health care provider visits due to asthma exacerbation, and physical examination, vital signs, clinical chemistry and hematology measures.

Long-term safety study 6839 enrolled patients with asthma similar in characteristics to the bronchodilator (lung-function) studies, but required patients to be on mid-to-high dose ICS or ICS+LABA, and no history of life-threatening asthma. Eligible patients entered a 2-week run-in period when baseline ICS was allowed, and at the end of run-in period patients were randomized to one of the three treatment arms as shown in Table 7. Safety endpoints included serious asthma exacerbations, adverse events, vital signs, physical examination, ophthalmic assessments, clinical laboratory and hematology measures, ECGs, and 24-hour urinary cortisol excretion.

Active comparator study 3091 enrolled patients with asthma similar in characteristics to the bronchodilator (lung-function) studies, with slightly lower FEV_1 cut-off, and on stable dose of ICS. Eligible patients entered a 2-week run-in period when baseline ICS was allowed, and at the end of run-in period patients were randomized to one of the two treatment arms as shown in Table 7. On randomization the baseline ICS was discontinued. Study treatment arms and primary efficacy variables are shown in Table 7. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and 24-hour urinary cortisol excretion.

Breo Ellipta Review of Efficacy:

The demonstration of efficacy of Breo Ellipta builds on the selection of appropriate dose and dosing regimen of fluticasone furoate and vilanterol (as discussed above and not discussed any further in this section), and demonstration of benefit of Breo Ellipta over the single ingredients, which in essence for this specific scenario is the demonstration of added clinical benefit of vilanterol to fluticasone furoate. Since two doses of Breo Ellipta are proposed for approval, assessment of benefit of the higher dose over the lower dose is also relevant. The efficacy parameters of interest are bronchodilation and reduction in exacerbation.

Breo Ellipta, bronchodilator effects:

Studies 6827, 6829, and 6863 are the primary studies designed to support the bronchodilator efficacy for Breo Ellipta.

Studies conducted to support combination products typically compare the combination to each active component to show the contribution of each component present in the combination, and also to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination to justify the use of the combination product by patients. Studies 6827, 6829, and 6863 compared Breo Ellipta to fluticasone furoate, and also compared two doses of Breo Ellipta. For a combination product such as Breo Ellipta, the peak bronchodilation effect is expected to be primarily from vilanterol.

The primary efficacy variable of FEV_1 0-24 hours is intended to show the benefit of Breo Ellipta over fluticasone furoate alone (show contribution of vilanterol in the combination). Results from the analysis of this efficacy variable are shown in Table 8.

Table 8. Bronchodilator studies 106827, 106829, and 116863; Mean change from baseline in weighted mean FEV_1 0-24 hour (ITT population)

Treatment *	N	Change (mL)	Diff from Placebo (95% CI)	P value	Diff from FF (95% CI)	P value
Study 106827, on day 84						
FF/VI 100/25	108	513	302 (178, 426)	<0.001	116 (-5, 236)	0.060
FF 100	106	398	186 (62, 310)	0.003	-	-
Placebo	95	212	-	-	-	-
Study 106829, on day 168						
FF/VI 200/25	89	464	-	-	136 (1, 270)	0.048
FF 200	83	328	-	-	-	-
FP 500	86	258	-	-	-	-
Study 116863, on day 84 †						
FF/VI 200/25	312	499	-	-	-	-
FF/VI 100/25	312	474	-	-	108 (45, 171)	<0.001
FF 100	288	366	-	-	-	-

* FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF = fluticasone furoate in Ellipta device; FP =fluticasone propionate

† Primary comparison is with FF/VI 100/25 to FF 100. No formal inferential comparison was planned for the two FF/VI doses.

The primary efficacy variable of change in trough FEV_1 is intended to show the benefit of Breo Ellipta over vilanterol alone (show contribution of fluticasone furoate in the combination). Results from the analysis of this efficacy variable are shown in Table 9. The studies understandably do not have vilanterol alone treatment arm because of the safety risk of serious asthma exacerbation with LABA monotherapy. Such direct comparison between Breo Ellipta and vilanterol is also not necessary (to show contribution of fluticasone furoate) because efficacy of fluticasone furoate in Ellipta device for patients with asthma is already established.

Table 9. Bronchodilator studies 106827, 106829, and 116863; Mean change from baseline in trough FEV_1 (ITT population)

Treatment *	N	Change (mL)	Diff from Placebo (95% CI)	P value	Diff from FF (95% CI)	P value
Study 106827, on day 84						
FF/VI 100/25	200	368	172 (87, 258)	<0.001	36 (-48, 120)	0.405
FF 100	203	332	136 (51, 222)	0.002	-	-
Placebo	193	196	-	-	-	-
Study 106829, on day 168						
FF/VI 200/25	187	394	-	-	193 (108, 277)	<0.001
FF 200	186	201	-	-	-	-
FP 500	190	183	-	-	-	-
Study 116863, on day 84 †						
FF/VI 200/25	337	457	-	-	-	-
FF/VI 100/25	334	441	-	-	77 (16, 138)	0.014
FF 100	336	365	-	-	-	-

* FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF = fluticasone furoate in Ellipta device; VI = vilanterol in Ellipta; FP = fluticasone propionate
† Nominal p-value for study 116863. Trough FEV1 was a secondary efficacy variable. No formal inferential comparison was planned for the two FF/VI doses.

The two doses of Breo were numerically separated, although small, for both FEV_1 0-24 hour and FEV_1 trough (Table 8 and Table 9). The differences between the two doses of Breo Ellipta for trough FEV_1 was not large suggestive of vilanterol bronchodilation lasting through to the next dose, thus blunting the separation of fluticasone furoate trough FEV_1 response.

Breo Ellipta, exacerbation effects:

Studies conducted to support a combination product typically compare the combination to each active component to show the contribution of each component present in the combination, and also to show that the combination provides clinically meaningful benefit over single ingredient to justify the use of the combination product. Study 6837 compared Breo Ellipta to fluticasone furoate to assess the additional benefit of the vilanterol component on asthma exacerbation. Results from the analysis of exacerbations for all patients are shown in Table 10 and Figure 6. The exacerbation data help to place the FEV_1 data discussed above in context. FEV_1 is generally considered to be a surrogate measure of efficacy, and probably reflects benefit on reductions in asthma exacerbations.

Table 10. Results from the asthma exacerbation study 106837, all patients (ITT)

	FF 100 (n=1010)	FF/VI 100/25 (n=1009)
Time to first asthma exacerbation		
Number of patients with at least 1 event (n)%)	186 (18%)	154 (15%)
Probability of at least 1 event by 52 wks, % (95% CI)	15.9 (13.5, 18.2)	12.8 (10.7, 14.9)
FF/VI vs FF, Hazard ratio (95% CI), p-value		0.80 (0.64, 0.99), 0.04
Rate of asthma exacerbation		
Mean rate of events	0.19	0.14
FF/VI vs FF, Ratio (95% CI), p-value		0.76 (0.60, 0.95), 0.01
* FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF=fluticasone furoate in Ellipta device		

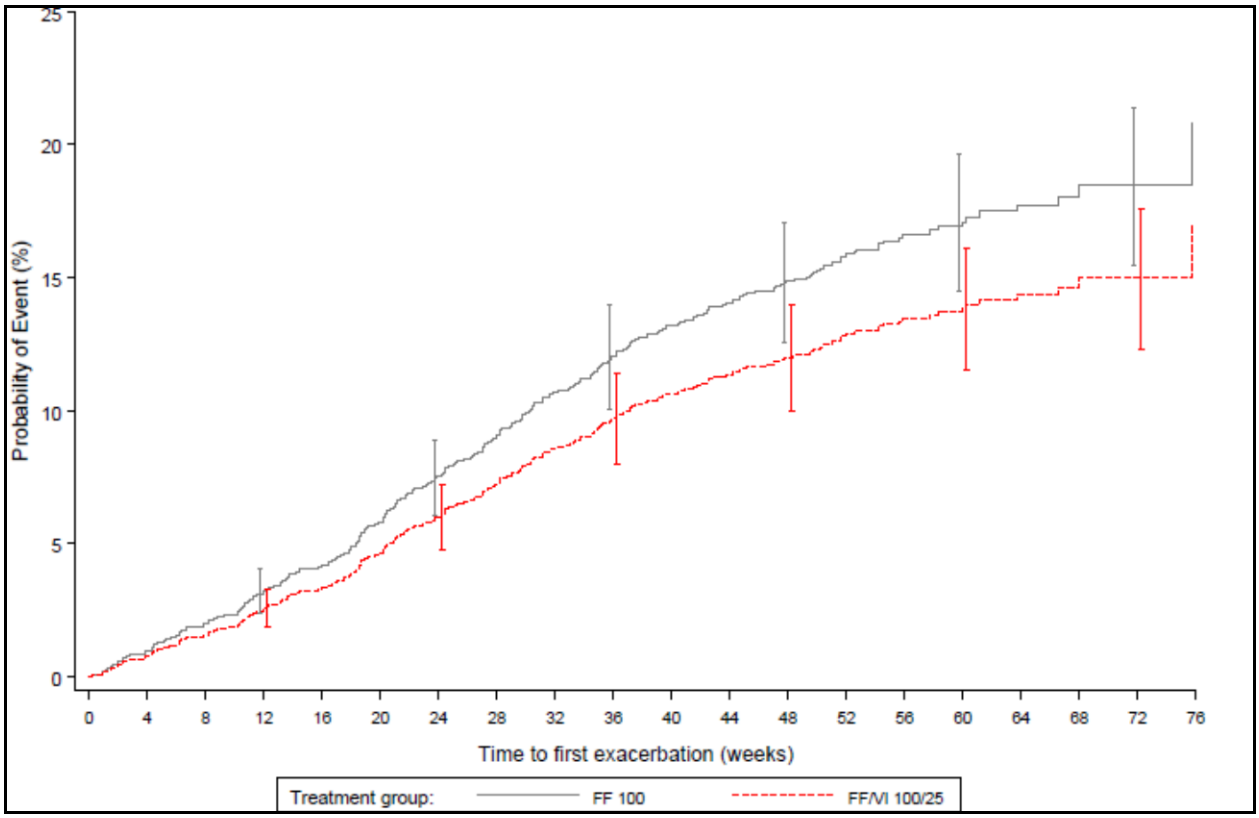

Figure 6. Cox Proportional Hazards model cumulative incidence curve for time to first asthma exacerbation (ITT) in study 106837. Vertical bars represent 95% CI.
Source: Module 5.3.5, CSR HZA106837, Figure 1, pg. 48.

Efficacy Subgroup Analyses

Efficacy was analyzed in various sub-groups in the individual trials and the results are described in the clinical briefing document. As discussed in the background section, increased risk of serious asthma exacerbations has been noted in African Americans and pediatric patients, so the efficacy of these two subgroups are of interest, although the number of patients in these subgroups is limited. In African American patients, there was no clear trend in efficacy difference compared to the overall population. In pediatric

patients, there was a more consistent efficacy (and safety) trend that differed from the overall population, favoring the fluticasone treatment arm over the Breo Ellipta treatment arm. Thus, the results in pediatric patients are summarized briefly below.

Results for patients 12 to 17 years old are shown in Table 11. The FEV_1 response was less apparent for the Breo Ellipta treatment groups in patients 12 to 17 years of age. Although the number of patients in this sub-group was small, there was consistency of low response of Breo Ellipta on FEV_1. The fluticasone treatment arms also had smaller number of patients, but had consistent favorable response. The apparent lack of consistent FEV_1 response for patients 12 to 17 years old from Breo Ellipta raises questions on the contribution (efficacy) of vilanterol in younger patients with asthma.

Table 11. Bronchodilator studies 106827, 106829, and 116863; Patients 12 to 17 years of age; Mean change from baseline in weighted mean FEV_1 0-24 hour and trough FEV_1

Treatment *	FEV_1 0-24 hour			Trough FEV_1		
	N	Change (mL)	Difference from FF (95% CI) †	N	Change (mL)	Difference from FF (95% CI) †
Study 106827, on day 84						
FF/VI 100/25	14	675	27 (-347, 400)	21	526	6 (-286, 300)
FF 100	19	648		28	520	
Placebo	24	442		33	365	
Study 106829, on day 168						
FF/VI 200/25	5	644	-51 (-993, 891)	6	1043	207 (-773, 1186)
FF 200	4	695		5	836	
FP 500	5	1084		8	648	
Study 116863, on day 84						
FF/VI 200/25	13	985		14	854	
FF/VI 100/25	21	770	-190 (-496, 115)	21	758	-196 (-498, 105)
FF 100	21	967		23	954	

* FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF = fluticasone furoate in Ellipta device; FP = fluticasone propionate
† Descriptive, not for formal inferential comparison.

The bronchodilator study 3091 compared Breo Ellipta 100/25 (fluticasone furoate 100 mcg and vilanterol 25 mcg) to Advair 500/50 (fluticasone propionate 500 mcg and salmeterol 50 mcg) over 24 weeks of treatment. Results of the study for all patients and for patients 12 to 17 years of age are shown in Table 12. Breo Ellipta 100/25 tended to show numerically smaller response compared to Advair 500/50, more so in patients 12 to 17 years of age. The FEV_1 0-24 hour is more reflective of the LABA effect than the ICS effect.

Table 12. Comparative bronchodilator study 113091; Mean change from baseline in weighted mean FEV_1 0-24 hour

	All patients		Patients 12 to 17 years of age	
	Advair (n=403)	**Breo (n=403)**	**Advair (n=38)**	**Breo (n=29)**
LS mean change from baseline in mL Difference, (95% CI)	377	341 -37 (-88, 15)	691	488 -203 (-478, 71)
Nominal p-value. Not for formal inferential comparison.				

As with the FEV_1 bronchodilator response data, the exacerbation data were also assessed in various sub-groups. Results for patients 12 to 17 years of age are shown in Table 13. Similar to the lack of consistent FEV_1 response in patients 12 to 17 years of age, the exacerbation response was also not consistent with the response in the total study population. The numerical trend was against Breo Ellipta compared to fluticasone furoate.

Table 13. Results from the asthma exacerbation study 106837, patients 12 to 17 years of age

	FF 100 (n=130)	**FF/VI 100/25 (n=151)**
Time to first asthma exacerbation		
Number of patients with at least 1 event (n)%)	9 (7%)	15 (10%)
Probability of at least 1 event by 52 wks, % (95% CI)	8.7 (3.0, 14.0)	12.0 (6.0, 17.6)
FF/VI vs FF, Hazard ratio (95% CI), p-value		1.41 (0.61, 3.21), 0.42
Rate of asthma exacerbation		
Mean rate of events	0.00098	0.0015
FF/VI vs FF, Ratio (95% CI), p-value		1.59 (0.70, 3.60), 0.27
FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF=fluticasone furoate in Ellipta device; VI=vilanterol in Ellipta P-values are descriptive, not for inferential comparison		

Breo Ellipta Review of Safety:

The safety assessment of Breo Ellipta is based on studies shown in Tables 5, 6, and 7, and various other studies. The overall safety database contains a large number of studies including those with single ingredient fluticasone furoate, single ingredient vilanterol, and the combination product in patients with asthma and also with COPD. The studies that are discussed in this section are studies that used Breo Ellipta in patients with asthma, particularly chronic dosing studies. Given the LABA related safety concerns, studies that compare Breo Ellipta to fluticasone furoate in patients with asthma are of particular interest. The asthma exacerbation study 6837 (Table 7) that compares Breo Ellipta to fluticasone furoate for treatment duration up to 76 weeks provides very relevant safety data.

Safety assessment in the clinical studies included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and 24-hour urinary cortisol excretion. Events related to ICS, such as pneumonia, bone disorder, ocular disorders, and local and systemic corticosteroid effects were of interest. Events related to LABA, such as ECG parameters, adrenergic and metabolic effects, and serious asthma

exacerbations resulting in asthma-related deaths, intubations, and hospitalizations were of interest.

Deaths, SAEs, dropouts and discontinuations:

Death was rare in the clinical program. There were three deaths in the pertinent clinical studies, and none were deemed to be related to the study drugs. A 68-year-old patient receiving Breo Ellipta (in study 6837) died in a car accident. A 65-year-old patient receiving fluticasone furoate (in study 6837) was diagnosed with late stage lung cancer. A 62-year old patient receiving fluticasone furoate (in study 6837) developed pneumonia and sepsis. There were no asthma-related deaths in the clinical program.

Serious adverse events (SAEs) occurred with low frequencies in the clinical studies. There was no new safety signal identified based on evaluation of these SAEs. There were no asthma-related intubations in the clinical program.

Dropouts and discontinuations were also low in the clinical studies. Events leading to dropouts and discontinuations were typical of events seen in asthma development programs and did not reveal any new safety signal.

Common adverse events:

Common adverse events seen in the program were typical of asthma studies, and studies using ICS, and LABAs. Events that were seen in drug treatment groups included oropharyngeal pain, oral candidiasis, dysphonia, and tremor.

Laboratory findings and ECGs:

No clinically meaningful effects on hematologic or chemistry parameters were noted in the clinical program. There were some reports of elevated glucose and potassium that are known effects of drugs used in the studies. HPA axis assessment by serum cortisol assessment did not show negative adrenal axis effect. Assessments of ECGs were also uneventful.

Asthma exacerbation:

Since asthma exacerbation leading to death, intubation, and hospitalization has been reported with LABAs, the review of asthma exacerbation safety was of interest. As mentioned above, there were no asthma-related deaths or intubations in the clinical program. Therefore, the event of interest was asthma-related hospitalization.

The studies relevant for assessment of asthma exacerbation as those that compared Breo Ellipta to fluticasone as chronic dosing. There were four such studies (6837, 6863, 6827, and 6829), of which the major contribution is from the exacerbation study 6837 (Table 7).

The FDA analyzed the clinical data for serious asthma outcomes and the results are described in detail in the FDA statistical briefing document and summarized here. There were a total of 18 asthma-related hospitalization events (as defined in the protocol by GSK, hospitalization for at least one full day was required to count as an event) in the four relevant studies (6837, 6863, 6827, and 6829), 17 occurring in study 6837 (10 in Breo

Ellipta treatment arm, and 7 in fluticasone treatment arm) and 1 occurring in study 6829 (in fluticasone treatment arm). Of the 18 asthma-related hospitalization events, 10 were in the Breo Ellipta treatment arm (incidence rate of 0.7 per 100 person-years), and 8 were in the fluticasone treatment arm (incidence rate of 0.6 per 100 person-years).

Analyses of hospitalization data for study 6837, which had 17 of the 18 events, are shown in Figure 7 and Figure 8. The incidence of asthma-related hospitalization (shown in Figure 7) was generally higher in Breo Ellipta treatment arm patients compared to fluticasone furoate treatment arm. The results for subgroup analyses (shown in Figure 8) are based on very few events within subgroup levels. There were 4 hospitalizations in patients 12 to 17 years of age in study 6837, all occurring in the Breo Ellipta treatment arm. Only one event was in non-white patients.

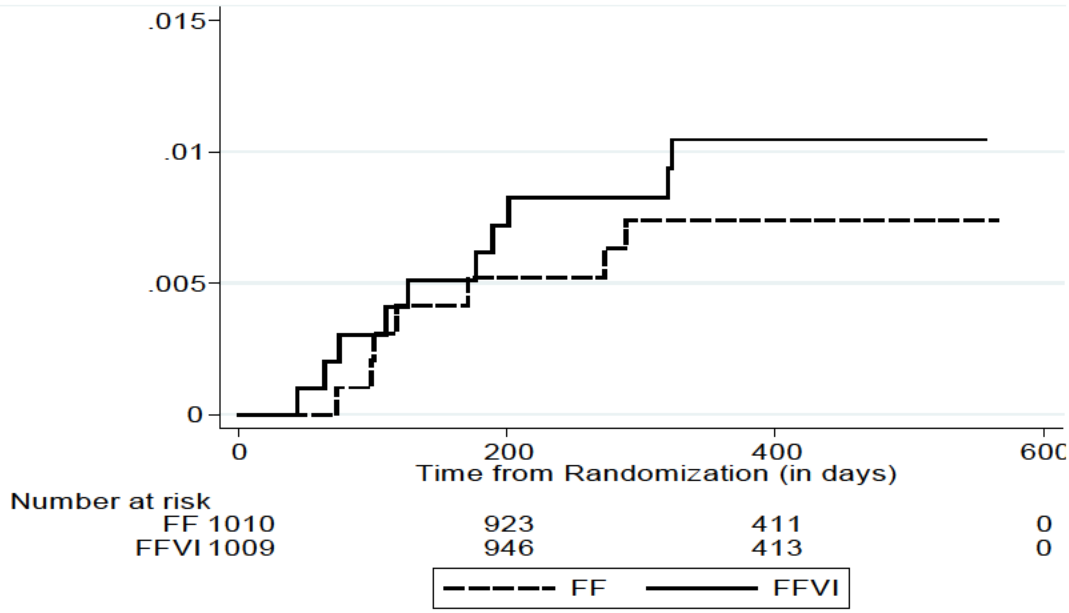

Figure 7. Kaplan-Meyer cumulative incidence plot of time to first asthma-related hospitalization in study 106837 (created by FDA statistical reviewer).

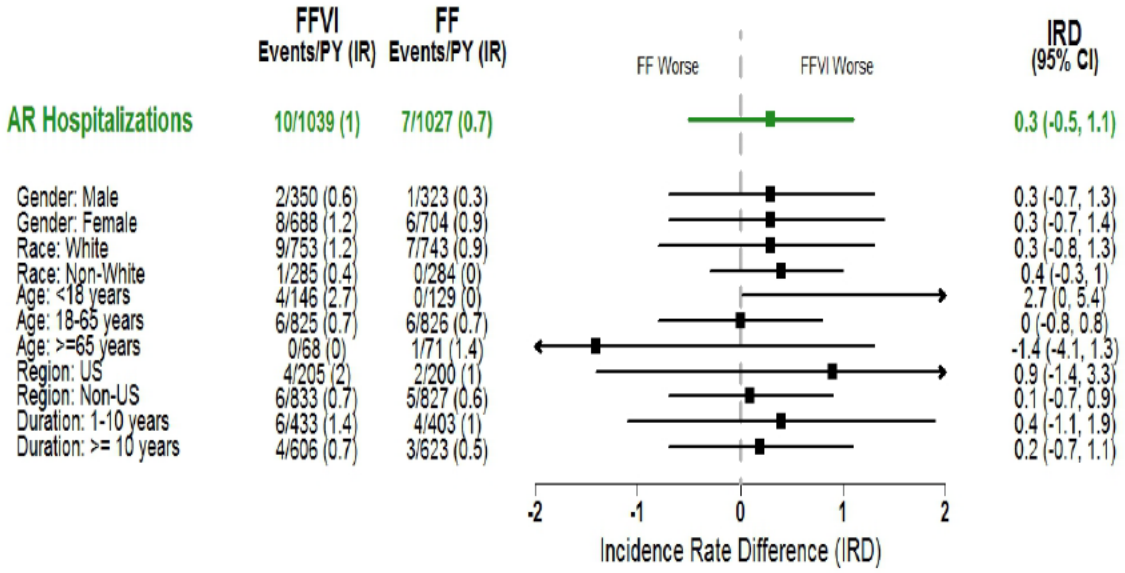

Figure 8. Plot of subgroup results from study 106837 (created by FDA statistical reviewer). Notations: IR is incidence rate per 100 patient-year, IRD is incidence rate difference per 100 patient-year, AR is asthma-related

Risk-benefit of Breo Ellipta in Asthma:

The discussion at the advisory committee meeting will include review of the efficacy data and the safety data, including review of subgroups, particularly by age. One important issue for discussion at the meeting will be safety of Breo Ellipta in asthma, particularly serious asthma exacerbation because of ongoing concerns with LABAs. It is worth noting that serious asthma exacerbation as a safety concern is at the end of the spectrum of asthma exacerbation as a potential benefit of a drug. Adrenergic agonists, including LABAs are expected to demonstrate FEV_1 improvement over the dosing interval, which is expected to translate to clinically meaningful benefits, such as reduced asthma exacerbation. ICSs are also expected to improve FEV_1, mostly demonstrated as trough FEV_1 improvement, which is expected to reflect clinically meaningful benefits, such as reduced asthma exacerbation. The issues for consideration for the advisory committee are whether the clinical program for Breo Ellipta in patients with asthma age 12 years and older has demonstrated that Breo Ellipta has efficacy benefit over fluticasone furoate, and how does the efficacy data balance with the safety data. An important consideration is the assessment of efficacy, safety, and risk-benefit in patients of all age groups studied, particularly in the younger patients.

Draft Topics for Discussion:

1. Discuss the efficacy data for fluticasone furoate/vilanterol (FF/VI) 100/25 and 200/25 to support the proposed indication of the once daily maintenance treatment of asthma in patients 12 years of age and older. Include a discussion of the efficacy findings in children 12-17 years of age.

2. Do the efficacy data provide substantial evidence of a clinically meaningful benefit of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma

    a. in adults 18 years of age and older?
        - *If no, what further data should be obtained?*

    b. in children 12-17 years of age?
        - *If no, what further data should be obtained?*

3. Discuss the safety data for FF/VI 100/25 and 200/25 once daily. Include the following in your discussion: size of overall database, and findings in children 12-17 years of age.

4. Has the safety of FF/VI 100/25 and 200/25 once daily been adequately demonstrated for the proposed indication

    a. in adults 18 years and older?
        - *If not, what further data should be obtained?*

    b. in children 12-17 years of age?
        - *If not, what further data should be obtained?*

5. Do the efficacy and safety data provide substantial evidence to support approval of FF/VI 100/25 and 200/25 for the once daily maintenance treatment of asthma

    a. in adults 18 years and older?
        - *If not, what further data should be obtained?*

    b. in children 12-17 years of age?
        - *If not, what further data should be obtained?*

6. Do you recommend a large LABA safety trial with FF/VI similar to the ongoing LABA safety trials

    a. in adults 18 years and older?
        - *If yes, comment on the timing of the trial, e.g. pre-approval, post-approval or pending results of ongoing LABA safety trials*

    b. in children 12-17 years of age?
        - *If yes, comment on the timing of the trial, e.g. pre-approval, post-approval or pending results of ongoing LABA safety trials*

Clinical Review for the Joint Meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) and the Drug Safety and Risk Management Advisory Committee

March 19, 2015

Fluticasone furoate/Vilanterol
inhalation powder
sNDA 204-275

Dose: 100/25 mcg (1 inhalation) once daily and 200/25 mcg (1 inhalation) once daily

Proposed indications:
Maintenance treatment of asthma
in patients 12 years of age and older

Team Leader: Banu Karimi-Shah, MD

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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List of Commonly Used Abbreviations

AE	Adverse Event
BID	Twice daily
CMC	Chemistry, manufacturing, and controls
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
ECG	electrocardiogram
FEV1	Forced expiratory volume in 1 second
FF	Fluticasone furoate
FP	Fluticasone propionate
HPA	Hypothalamic pituitary axis
ICS	Inhaled corticosteroid
LABA	Long-acting-beta-agonist
MDI	Metered dose inhaler
Mcg	Microgram
NDA	New drug application
OTC	Over-the-counter
PD	Pharmacodynamic
PK	Pharmacokinetic
PRN	As needed
QD	Once daily
SABA	Short-acting beta-agonist
SAE	Serious Adverse Event
Salm	Salmeterol
VI	Vilanterol
WM	Weighted mean

1 Executive Summary

Background

GlaxoSmithKline (GSK) 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 maintenance 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.

Breo Ellipta® 100/25 mcg was approved on May 10, 2013, for the once daily treatment of chronic obstructive pulmonary disease (COPD), including both maintenance treatment of airflow obstruction and for reducing COPD exacerbations. As was discussed at the Pulmonary-Allergy Drugs Advisory Committee (PADAC) on April 17, 2013, during which the COPD indication was addressed, the sequence and scale of the FF/VI development program differ from prior precedent. Previous ICS/ LABA development programs were based on the initial development of the individual ICS and LABA monotherapies followed by the combination product in asthmatics, a patient population that is presumably more sensitive to both bronchodilators and inhaled corticosteroids. While there are distinct clinical differences between asthma and COPD, the similarities between these two obstructive lung diseases have formed the basis for extrapolation of dose selection of other ICS/LABA products from asthma to COPD in the past.

In contrast, the program for FF/VI was approved for patients with COPD first. In many respects, the COPD development program encompassed the individual development programs for FF and VI and spanned two disease indications (both asthma and COPD). While GSK does not intend to market the VI monotherapy, Arnuity Ellipta® (FF monotherapy) was approved on August 20, 2014 for the once-daily maintenance treatment of asthma in subjects 12 years of age and older. The approved doses are one inhalation of either FF 100 mcg or FF 200 mcg once daily.

Based on the dose ranging data that has already been reviewed as part of the Breo Ellipta® in COPD (NDA 204275) and the Arnuity Ellipta in asthma programs (NDA 205625), and the efficacy data from the Arnuity Ellipta® asthma development program, the Applicant now seeks registration of Breo Ellipta® 100/25 and 200/25 mcg for the once-daily maintenance treatment of asthma in patients 12 years of age and older.

While the discussion at the advisory committee meeting will include an overview of the efficacy data, the focus of the meeting will be safety, specifically whether the submitted safety database is adequate to support the approval of FF/VI in asthma, or whether a large safety trial to evaluate serious asthma outcomes is recommended. As there has been greater concern regarding the risk of LABA-associated serious asthma-related events in the pediatric population, the risk-benefit assessment in the pediatric subgroup of patients 12 to <18 years of age will be a key issue for discussion.

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 maintenance 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 200/25) over the lower dose (FF 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 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.

From the perspective of this review, there is no standardized definition of a severe exacerbation, and as the reader will take note later in this review, most exacerbations

were defined by use of oral corticosteroids, rather than 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 timepoints. 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.

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 using the primary endpoint in this trial which was the time to first asthma exacerbation. It is important to note that the trials were not powered to detect differences based on subgroup analysis. Subgroups were examined by age (12 to 17 years vs. ≥ 18 years), gender, race (African American vs. other), and geographical region (US. vs. non-US). 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. Analysis of this subpopulation is ongoing, and further information will be added in an addendum as it becomes available. The data that is available at the present time is summarized here.

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 the subgroup analyses from the Arnuity Ellipta (FF monotherapy) clinical development program are examined, the treatment effect of FF is comparable between the younger age group and the adult population. 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 an issue that warrants discussion.

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, there is a numerical trend towards increased risk of asthma exacerbation with FF/VI compared to FF. The results of the analysis show that about 10% of adolescents on FF/VI had at least 1 asthma exacerbation compared with 7% in the FF treatment group. This represents a hazard ratio of 1.4 (0.6, 3.2), which is numerically in favor of FF, although not statistically significant. This trend is further supported by the analysis of the rate of asthma exacerbations, which shows that there may be an increase in the rate of asthma exacerbation in this subgroup with a ratio of 1.6 (0.7, 3.6), which indicates an increase of 60% in the FF/VI subgroup compared to FF alone. In the case of the rate of asthma exacerbations, the test for the interaction was statistically significant, indicating that either the magnitude of the treatment effect ratio of rates between the two age subgroups was different or the direction of the ratio was different. For adults the rate ratio was 0.72, which was consistent with the overall rate ratio of 0.76 indicating the FF/VI was better than FF. The treatment difference in the ≥18 year old subgroup was statistically significant. However, for patients between the ages of 12 and 17, the rate ratio was 1.6 (95% CI: 0.7, 3.6) indicating that FF/VI was worse than FF, but this difference was not statistically significant. The numerical trend in the exacerbation data which is in favor of FF over FF/VI is an issue that requires further consideration.

Consideration of the efficacy information, including the efficacy in the 12 to 17 year old subgroup with respect to lung function and asthma exacerbation, will be important in the risk-benefit evaluation as the advisory committee discusses the issues related to the adequacy of the safety database to assess for the LABA-associated serious asthma outcomes of hospitalization, intubation, and death.

Safety Summary

The background regarding the history of the known safety concerns, including asthma-related death, with the use of LABA for asthma, is discussed in the Division Memorandum preceding this review. In addition to the analysis the Applicant will present, the Agency has 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 Agency's statistical briefing document. Therefore, the safety review in this clinical briefing document will focus on safety findings unrelated to serious asthma-related outcomes with the exception of asthma exacerbations which were examined as an efficacy endpoint in Trial HZA106837.

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 of FF/VI is similar to that for other ICS/LABA products in asthma, and current product labeling contains warning language regarding these risks.

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, one strip contains 100 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 maintenance treatment of asthma in patients 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, DPI	Flovent HVA Flovent Diskus
	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) 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. Details regarding the history of LABA safety in asthma can be found in the Division Memorandum preceding this review.

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 Other Relevant Background Information

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

Table 2. Milestone Interactions Between the Agency and the Sponsor		
Date	Interaction	Highlights
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
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

Table 2. Milestone Interactions Between the Agency and the Sponsor		
Date	Interaction	Highlights
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 of 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 and that extrapolation from 12-17 yo is not acceptable • 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, but would be a review issue
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		

3 Overview of the Clinical Program

This review focuses on the clinical development program conducted in support of FF/VI in asthma. 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 will be summarized in Section 4. The primary efficacy and safety data to support FF/VI in asthma are discussed in Sections 6 and 7, respectively.

The FF dose-ranging trials are summarized in Table 3. The VI dose-ranging trials are summarized in Table 4. The FF/VI dose regimen trial is summarized in Table 5. The results of these trials are summarized in Section 4.

Table 3. 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 low 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, Philippines)*
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)*
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 4. 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	102 102 102 103 102 103	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=M salt 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 maintenance 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 5 summarizes the efficacy trials. The protocols for the efficacy/safety trials are reviewed in Section 5. The results of the efficacy/safety trials and the active comparator trials are reviewed in Section 6. The long-term safety trial is reviewed in Section 7.

Table 5. 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 $\geq$ 60%	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							
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 40-90%	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

4 Dose Selection

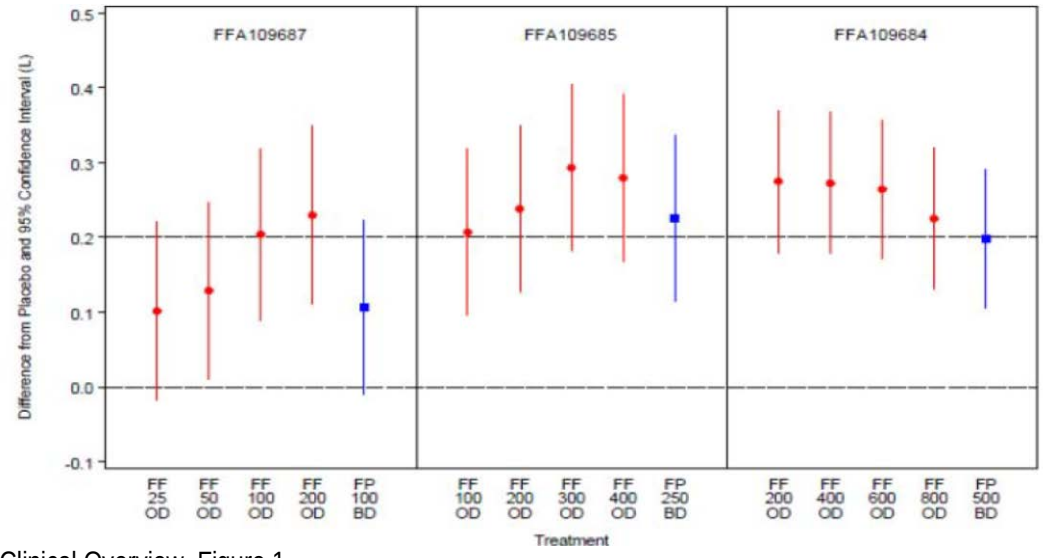
The dose ranging/regimen studies for the individual components FF and VI have been reviewed as part of the Breo Ellipta COPD (NDA 204-275) and Arnuity Ellipta asthma development programs (NDA 205-625). The results of these studies are summarized here.

4.1 Fluticasone Furoate (FF) Dose Selection

- Nominal dose selection

The results of three dose-ranging trials in asthma are summarized in Figure 1. The trials were similarly designed and were randomized, double-blind, placebo-controlled, 8-week trials that included an approved dose for fluticasone propionate as a benchmark. A relative dose response was observed for FF doses ranging from FF 25 mcg to 200 mcg. There did not appear to be a consistent additive benefit for FF doses above 200 mcg. Fluticasone propionate (FP) was included as active control in the dose ranging studies as a means of providing a benchmark. The efficacy of the 100 and 200 mcg doses of FF appear numerical comparable to the efficacy of FP 250 mcg BID. The results of these three trials in asthma were the basis for the selection of FF 50, 100, and 200 mcg for further evaluation in confirmatory trials and the subsequent approval for Arnuity Ellipta 100 and 200 mcg doses for the maintenance treatment of asthma.

Figure 1: Trials FFA109687, FFA109685, and 109684: Adjusted treatment differences from placebo of change from baseline in trough FEV1 (L) at Week 8



Source: Clinical Overview, Figure 1

- Dosing frequency

GSK conducted Trial FFA112202, a randomized, double-blind, placebo-controlled, cross-over trial in 190 adults and adolescents with asthma to compare FF 200 mcg QD (PM), FF 100 mcg BID, FP 200 mcg QD (PM), and FP 100 mcg BID. Based on trough

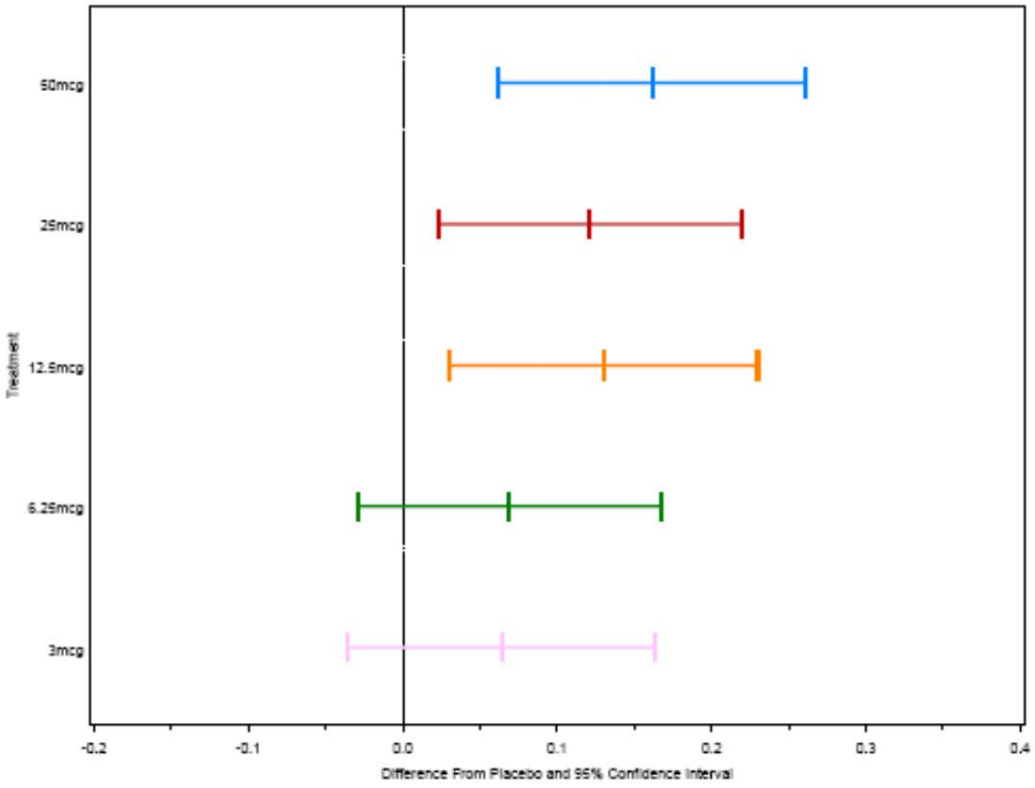
FEV1, FF 200 mcg QD versus FF 100 mcg BID appeared similar, whereas FP 100 mcg BID dosing resulted in a numerically higher trough FEV1 compared to FP 200 mcg QD. These results supported the selection of the QD regimen for further evaluation.

4.2 Vilanterol (VI) Dose Selection

- Nominal dose selection

GSK explored a range of nominal doses for the VI component in both asthma and COPD. Trial BC 109575 was a randomized, double-blind, placebo-controlled, parallel group, 28-day trial that evaluated five doses of VI (3, 6.25, 12.5, 25, and 50 mcg) administered once daily in the evening in 614 adults and adolescents with persistent asthma. Trough FEV1 results demonstrated an approximate dose-response between the lowest and highest doses, although the point estimate for the 25 mcg dose was slighter lower than for the 12.5 mcg dose (Figure 3). The 6.25 mcg dose clearly had a lower effect on FEV1.

Figure 2. Trial B2C109575: Vilanterol Dose Ranging Adjusted treatment differences of change from baseline in trough FEV1 (LOCF) at Day 28

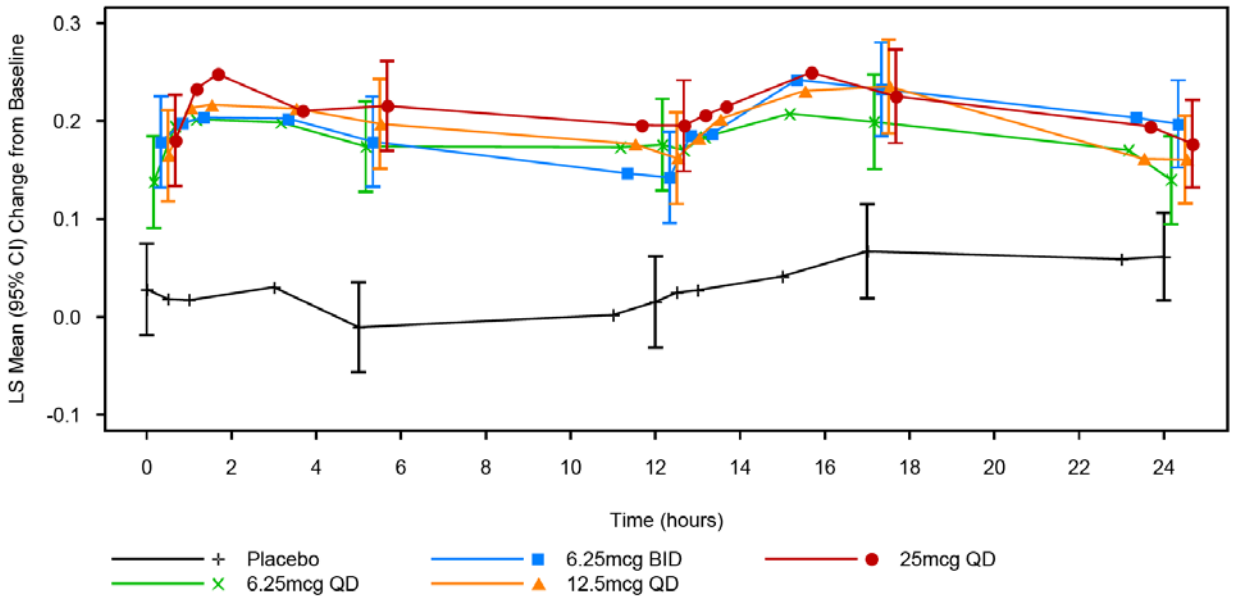


Source: Module 5.3.5.4, CSR, Figure 7.1

- Dosing frequency

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 (Figure 3). 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. Another trial, HZA114624, indicated that once-daily dosing with FF/VI 100/25 in the PM was similar to AM dosing (results not shown).

Figure 3. Vilanterol Dose Ranging and Frequency- Repeated measures adjusted mean change from period baseline in FEV1 (L) over time at Day 7



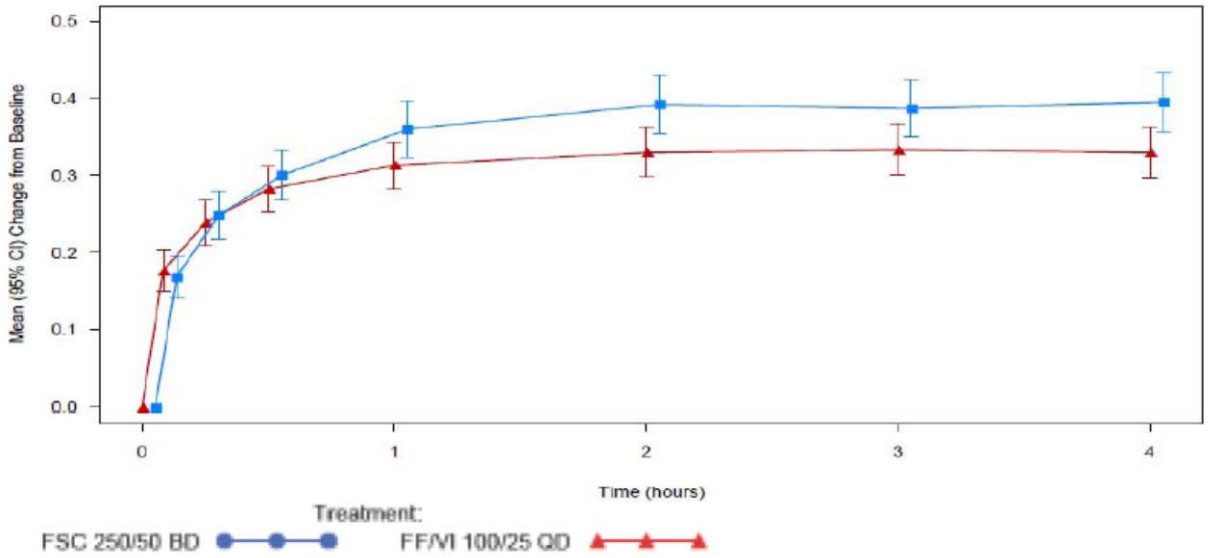
Source: CSR HZA113310 Figure 6.12

- 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 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 $FEV1_{(0\text{-}4h)}$ 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 Figure 4 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 4. Trial HZA 113091: LS mean change from baseline in FEV1 (0-4h) at Day 1



Source: Module 5.3.5, Complete Study Report Figure 3

5 Clinical Development Program – Trial Design

5.1 Efficacy and Safety Trials

5.1.1 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: August 20, 2010 to October 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 6.

Table 6: Study Assessments: Study 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								

Table 6: Study Assessments: Study 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
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 Sampling (one visit only)				X[6]					
Serum pregnancy test	X						X	X	
Urine Pregnancy			X						X

Table 6: Study Assessments: Study 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
test									
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/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 4 weeks of visit 1 and during the study:
        - Inhaled, oral, or transdermal long-acting beta 2-agonists
        - Combination therapy containing long-acting beta 2-agonists and ICS for asthma
    - Following the morning of visit 1 and during the study:
        - 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 9 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-day 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 Amendments

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

5.1.2 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: September 20, 2012 to October 15, 2013
- 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 or less than 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 7.

Table 7. Study Assessments: Study HZA116863

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								

Table 7. Study Assessments: Study HZA116863									
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
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 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[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	

Table 7. Study Assessments: Study HZA116863									
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
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				

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

Primary Endpoint
- 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 Amendments

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

5.1.3 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: June 10, 2010 to October 18, 2011
- Study Sites: Russia (163), US (143), Romania (117), Germany (66), Poland (61), Japan (36)
- Study Report Date: April 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 8. Schedule of Assessments: Trial HZA106829

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												
Spirometry Pulmonary Function	X		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	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

Table 8. Schedule of Assessments: Trial HZA106829

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
12-lead EKG		X	Xc							X	X	
Laboratory Assessments												
Hematology	X											
Chemistry (includes liver safety testing)	X						Xe			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							Xh			Xh		
HBsAg and hepatitis C antibody screening	X											
Questionnaires												
ACT	X		X				X			X	X	
AQLQ 12+			X				X			X	X	
Unscheduled Healthcare contact/Resource Utilization9			Xi	Xi	Xi	Xi	Xi	Xi	Xi	Xi	Xi	
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

Table 8. Schedule of Assessments: Trial HZA106829												
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

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 Amendments

There were no protocol amendments to this study.

5.1.4 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: February 22, 2010 to September 15, 2011
- 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 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

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.

From the perspective of this review, there is no standardized definition of a severe exacerbations, and as the reader will take note later in this review, most exacerbations were defined by use of oral corticosteroids, rather than inpatient hospitalization or ED visits. 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.

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 mcg once-daily in the evening
• FF 100 mcg 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 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 9. 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
Asthma Exacerbation		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory Assessments															
Clinical Laboratory	X														

Table 9. 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
Assessment[6]															
Liver Safety Assessment					X		X			X			X	X	
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 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 following exceptions:

- 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 those for the aforementioned studies, 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 described above.

Randomization Criteria
Randomization criteria were similar to the studies described 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 described above with the exception that subjects were not required to be withdrawn for asthma exacerbations until he/she experienced 3 protocol defined asthma exacerbations within any 6 month treatment period or 4 asthma exacerbations during the double-blind treatment period.

Permitted medications
Permitted medications were similar to the studies described 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 asthma exacerbation

Secondary Efficacy Endpoints

- Rate of 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 asthma exacerbations through exploration of use of rescue medication ±14 days around the onset of an 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 asthma exacerbations
- Number of emergency department/urgent care clinic visits due to asthma exacerbations
- Number of unscheduled health care provider visits due to asthma exacerbations
- Number of intubations due to 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

This was an event-driven study, designed to have 90% power to detect the following reductions in the risk of experiencing an asthma exacerbation for FF/VI compared with FF.

Two-Sided Significance Level	Hazard Ratio	Corresponding Reduction	Number of Events[1] Required
0.05	0.70	30%	330
0.01	0.65	35%	321
0.001	0.60	40%	321

1. An "event" is a subject with one or more severe asthma exacerbations

Source: Study HZA106837 synopsis, pg. 4.

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 asthma exacerbations. A total sample size of 2000 (1000 per arm) would provide 90% power based on the above assumptions.

One interim analysis was planned for efficacy and to assess safety. At this interim, an analysis of the time to first asthma exacerbation was performed. In addition, tabulation of SAEs and most frequent (≥3%) on-treatment AEs were provided to the Independent Data Monitoring Committee. For the final analysis, an adjusted p-value and the median unbiased estimate of the hazard ration with its associated confidence intervals was calculated using discrete stagewise ordering.

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 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 secondary endpoint was rate of asthma exacerbations per subject year over the treatment period. This endpoint was analyzed using a negative binomial regression model with log-time on treatment as an offset variable. The response variable was the number of on-treatment asthma exacerbations experienced per subject. The model included adjustment for effects due to baseline disease severity (FEV1 measured at randomization), sex, age, and region.

The analysis was repeated for the ITT population excluding all data from Investigator 171806 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 040688), 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 171806 and Investigator 040688. 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 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 Amendments

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

5.2 Long-term Safety Trials

5.2.1 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: October 19, 2009 to May 12, 2011
- Study Sites: US (17), German (14), Ukraine (10), Thailand (4)
- Study Report Date: May 12, 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 2-week run-in period 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 10. 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														

Table 10. 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
Therapy History	X														
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
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				

Table 10. 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
PGx Sampling			X												
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 following exception:

- Subjects were to be on a dose of ICS equivalent to FP 200-1000 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 as described for the aforementioned studies.

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 asthma exacerbations throughout the 52-week treatment period
- Laboratory assessments
- 24-hour urinary cortisol excretion
- Oropharyngeal examinations
- Vital signs
- ECG assessments
- Ophthalmic assessments

Protocol Amendments

There were no amendments to the protocol.

5.3 Active Comparator Trials

5.3.1 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: June 16, 2010 to July 27, 2011
- 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 11.

Table 11. 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 Informed Consent	X							
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 FEV_1 (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]				
Serum	X					X	X	

Table 11. 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
pregnancy test								
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 could be collected at any one visit after the PGx consent had been signed and the subject had been randomized
7. In subset of subjects
8. To be completed associated with an asthma exacerbation and 'other' unscheduled asthma-related health care

Study Population

Inclusion Criteria

These were similar to the above studies with the following exceptions:

- 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 following exceptions:

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

Withdrawal Criteria and Permitted Medications

- These were similar to those already described for the aforementioned 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 asthma exacerbations and other asthma-related health care)

Safety Endpoints

- Incidence of AEs throughout the 24-week treatment period
- Incidence of asthma 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 Amendments

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 maintenance 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 200/25) over the lower dose (FF 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 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.

From the perspective of this review, there is no standardized definition of a severe exacerbation, and as the reader will take note later in this review, most exacerbations were defined by use of oral corticosteroids, rather than 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 timepoints. 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.

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 using the primary endpoint in this trial which was the time to first asthma exacerbation. It is important to note that the trials were not powered to detect differences based on subgroup analysis. Subgroups were examined by age (12 to 17 years vs. ≥ 18 years), gender, race (African American vs. other), and geographical region (US. vs. non-US). 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. Analysis of this subpopulation is ongoing, and further information will be added in an addendum as it becomes available. The data that is available at the present time is summarized here.

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 the subgroup analyses from the Arnuity Ellipta (FF monotherapy) clinical development program are examined, the treatment effect of FF is comparable between the younger age group and the adult population. 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 an issue that warrants discussion.

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, there is a numerical trend towards increased risk of asthma exacerbation with FF/VI compared to FF. The results of the analysis show that about 10% of adolescents on FF/VI had at least 1 asthma exacerbation compared with 7% in the FF treatment group. This represents a hazard ratio of 1.4 (0.6, 3.2), which is numerically in favor of FF, although not statistically significant. This trend is further supported by the analysis of the rate of asthma exacerbations, which shows that there may be an increase in the rate of asthma exacerbation in this subgroup with a ratio of 1.6 (0.7, 3.6), which indicates an increase of 60% in the FF/VI subgroup compared to FF alone. In the case of the rate of asthma exacerbations, the test for the interaction was statistically significant, indicating that either the magnitude of the treatment effect ratio of rates between the two age subgroups was different or the direction of the ratio was different. For adults the rate ratio was 0.72, which was consistent with the overall rate ratio of 0.76 indicating the FF/VI was better than FF. The treatment difference in the ≥18 year old subgroup was statistically significant. However, for patients between the ages of 12 and 17, the rate ratio was 1.6 (95% CI: 0.7, 3.6) indicating that FF/VI was worse than FF, but this difference was not statistically significant. The numerical trend in the exacerbation data which is in favor of FF over FF/VI is an issue that requires further consideration.

Consideration of the efficacy information, including the efficacy in the 12 to 17 year old subgroup with respect to lung function and asthma exacerbation, will be important in the risk-benefit evaluation as the advisory committee discusses the issues related to the adequacy of the safety database to assess for the LABA-associated serious asthma outcomes of hospitalization, intubation, and death.

6.1 Indication: Once daily maintenance treatment of asthma

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 maintenance 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 similar across treatment groups within 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.

See Table 12, Table 13, Table 14, Table 15, and Table 16 for the demographic and baseline characteristics of subjects in each of the trials.

Table 12. Demographic and Baseline Characteristics: HZA106827 (ITT Population)				
	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	19 (9)	16 (8)	16 (8)	51 (8)
White	169 (83)	171 (83)	172 (86)	512 (84)
Duration of Asthma, n (%)				
<6 months	5 (2)	1 (<1)	5 (2)	11 (2)
≥6 months 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)	47 (23)	127 (21)
≥10 years	99 (49)	107 (52)	83 (41)	289 (47)
Baseline Lung Function (Mean)				
Pre-bronchodilator FEV1 (L)	2.277	2.174	2.227	2.226
Percent predicted FEV1 (L)	68.47	67.04	67.25	67.59
Reversibility (Mean)				
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 (41)	81 (40)	248 (41)
Source: CSR HZA 106827 Tables 5.15, 10, 13, 14, 18, 29				

Table 13. Demographic and Baseline Characteristics: HZA116863 (ITT Population)				
	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	78	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)

Table 13. Demographic and Baseline Characteristics: HZA116863 (ITT Population)				
	FF 100 N=347	FF/VI 100/25 N=346	FF/VI 200/25 N=346	Total N=1039
Duration of Asthma, n (%)				
<6 months	5 (1)	4 (1)	1 (<1)	10 (<1)
≥6 months 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)
Baseline 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 (Mean)				
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 14. Demographics and Baseline Characteristics: HZA106829				
	FF 200 N=194	FF 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	81 (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 months	2 (1)	1 (<1)	1 (<1)	4 (<1)
≥6 months 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 (250	35 (18)	45 (23)	129 (22)
≥10 years	112 (58)	129 (65)	112 (57)	353 (60)
Baseline 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 (Mean)				
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)

Table 14. Demographics and Baseline Characteristics: HZA106829				
	FF 200 N=194	FF 200/25 N=197	FP 500 BID N=195	Total N=586
On ICS+LABA	150 (78)	150 (76)	146 (75)	446 (76)
Source: CSR HZA 106829 Table 5, 6, 7, 9				

Table 15. Demographic and Baseline Characteristics: HZA106837			
	FF 100 N=1010	FF/VI 100/25 N=1009	Total N=2019
Age			
Mean Min Max	42.3 12 79	41.1 12 82	41.7 12 82
Sex, n (%)			
Female Male	689 (68) 321 (32)	661 (66) 348 (34)	1350 (67) 669 (33)
Race, n (%)			
African Heritage Other[1] Asian White	47 (5) 110 (11) 110 (11) 743 (74)	40 (4) 117 (12) 112 (11) 740 (73)	87 (4) 227 (11) 222 (11) 1483 (73)
Duration of Asthma, n (%)			
<6 months ≥6 months to <1 year ≥1 to < 5 years ≥5 to <10 years ≥10 years	0 0 208 (21) 195 (19) 607 (60)	0 0 212 (21) 216 (21) 581 (58)	0 0 420 (21) 411 (20) 1188 (59)
Baseline Lung Function (Mean)			
Pre-bronchodilator FEV1 (L) Percent predicted	2.101 69.0	2.144 68.8	2.108 68.9
Reversibility (Mean)			
Absolute FEV1 reversibility (mL) Percent reversibility FEV1 (%)	500.0 24.3	499.1 24.4	499.6 24.4
Concomitant Medications			
On any asthma medication	188 (19)	157 (16)	345 (17)
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 16. Demographic and Baseline Characteristics: HZA113901 (ITT Population)			
	FF/VI 100/25 N=403	FP/salmeterol N=403	Total N=806
Age			
Mean Min Max	43.8 12 79	41.9 12 80	42.8 12 80
Sex, n (%)			
Female Male	244 (61) 159 (39)	245 (61) 158 (39)	489 (61) 317 (39)
Race, n (%)			
African Heritage Amer. Indian or Alaska Native Asian White	36(9) 1 (<1) 124 (31) 242 (60)	43 (11) 1 (<1) 125 (31) 232 (58)	79 (10) 2 (<1) 249 (31) 474 (59)
Duration of Asthma, n (%)			
<6 mo ≥6 mo to <1 year ≥1 to < 5 years ≥5 to <10 years ≥10 years	3 (<1) 2 (<1) 32 (8) 67 (17) 299 (74)	5 (<1) 3 (<1) 34 (8) 58 (14) 303 (75)	8 (<1) 5 (<1) 66 (8) 125 (16) 602 (75)
Baseline Lung Function			
Mean pre-bronchodilator FEV1 (L) Percent predicted	1.885 63.7	1.930 64.4	1.907 64.2
Reversibility			
Absolute FEV1 reversibility (mL) Percent reversibility FEV1 (%)	487.1 26.4	536.3 29.0	511.7 27.7
Concomitant Medications			
ICS alone ICS/LABA	125 (31) 279 (69)	123 (31) 279 (69)	248 (31) 558 (69)
Source: CSR HZA113901, tables 5, 6, 7, 8			

6.1.3 Patient 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 17, Table 18, Table 19, Table 20, and Table 21 depict patient disposition for these five trials. Treatment compliance is summarized under the table for each trial.

Table 17. 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				
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				

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 18. 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 19. Patient Disposition: HZA106829				
	FF 200 N=194	FF/VI 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	1 (<1)	3 (<1)
Source: CSR HZA106829 table 3				

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 20. 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	3 (<1)	2 (<1)	5 (<1)
Protocol Deviation	26 (3)	17 (2)	43 (2)
Lost to Follow-up	11 (1)	9 (<1)	20 (<1)
Source: CSR 106837 table 5			

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 21. Patient Disposition: HZA113901			
	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)
Source: CSR 113901 table 3			

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 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 22.

Table 22. 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

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 23.

Table 23. 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 24.

Table 24. 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 (95% CI) p-value		193 (108, 277) <0.001			136 (1,270) 0.048	
Difference vs. FP500 BID (95% CI) p-value	18 (-66, 102) 0.676	210 (127, 294) <0.001		7 (-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).

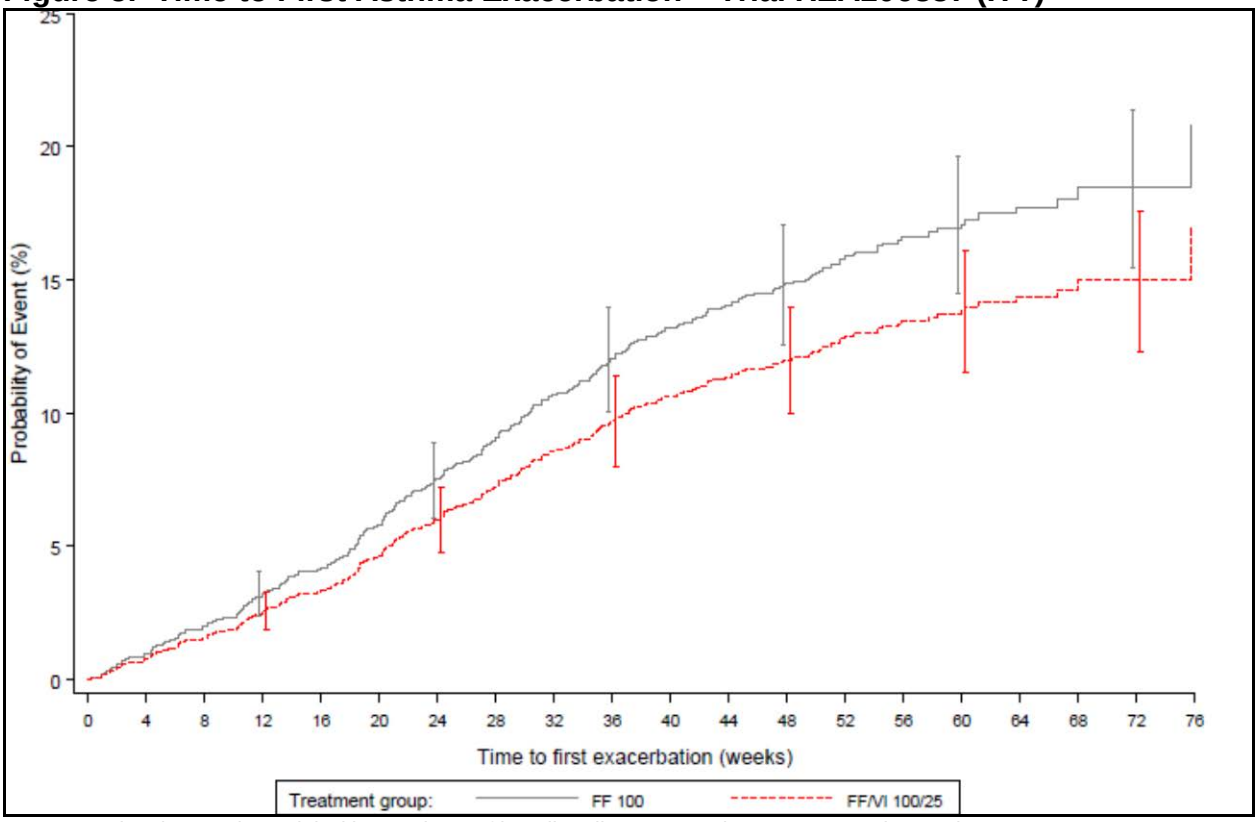
The time to first asthma exacerbation is presented in Table 25 and Figure 5.

Table 25. 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)
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.

Table 26. Hospitalizations and ED Visits due to Asthma Exacerbations: Trial HZA106837 (by number of subjects)		
	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

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. No subjects in either treatment group died or were intubated due to asthma exacerbations.

Table 27. Hospitalizations and ED Visits due to Asthma Exacerbations: Trial HZA106837 (by number of exacerbations)		
	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

When examined by the number of severe asthma exacerbations, the profile of asthma exacerbations between the two treatment groups also appears to be similar. 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.

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 28.

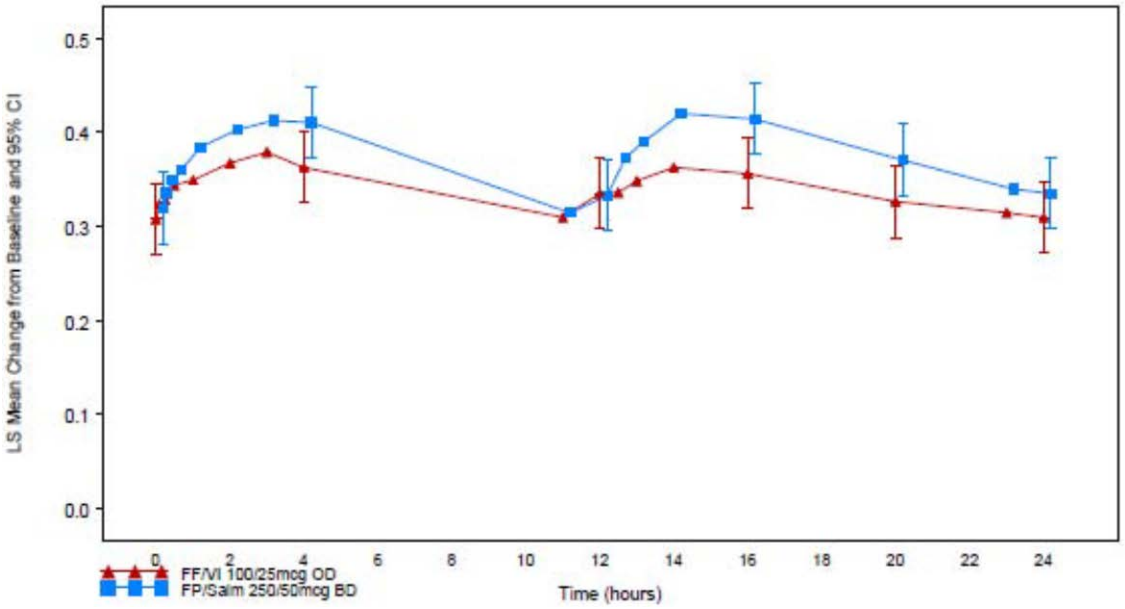
Table 28. Summary of Reasons that Led to the Diagnosis of an Asthma Exacerbation: Trial HZA106837		
	FF 100 N=1010	FF/VI 100/25 N=1009
Number of Asthma Exacerbations	271	200
Worsening daytime symptoms	188 (69)	133 (67)
Worsening nighttime symptoms	124 (46)	79 (40)
Decreasing peak flow	17 (6)	20 (10)
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 29 and Figure 6.

Table 29. Trial HZA113091: Weighted Mean Serial FEV1 (0-24h) at Week 24 (ITT)		
	FF/VI 100/25 N = 403	FP/Sal 250/50 BID N = 403
n	352	347
LS Mean Change from Baseline (mL)	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, S=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).

As the FF dose ranging data showed comparability of treatment effect between FF 100 and FP 250 BID (Figure 1), the differential treatment response between Advair and FF/VI is likely due to vilanterol, as demonstrate here.

6.1.5 Analysis of Secondary Endpoints(s)

The following section contains a discussion of important secondary endpoints (if evaluated in the trial) and supportive endpoints including rescue-free 24 hour periods, symptom free 24 hour periods, AM and PM peak expiratory flow (PEF), AQLQ, and ACT scores. These data are summarized in Table 34.

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 HZA113091. The results from this analysis are presented in Table 30.

Table 30. 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 200/25 vs FF 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 200/25 over FF 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 31. The number and rate of multiple exacerbations per subject is displayed in Table 32.

Table 31. 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 32. 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 33.

Table 33. 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) (95% CI) p-value	-19 (-73,34) 0.485	

Source: CSR 113091 table 6.18, pg. 282
ANCOVA with covariates of baseline FEV1, region, sex, age, and treatment
FP=fluticasone propionate, S=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 34.

Table 34. 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 100/25 (95% CI)		0.9 (-4.2,6.1)			

Table 34. 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 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 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 100/25 (95% CI)		2.0 (-4.2, 8.2)			
AQLQ, units					
Difference vs FF 100	0.08 p=0.303				
Difference s FF 100/25 (95% CI)		0.14 (-0.01, 0.28)			
ACT, units					
Difference vs FF 100	0.9 p=0.002				
Difference s FF 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 34. 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 Subpopulations

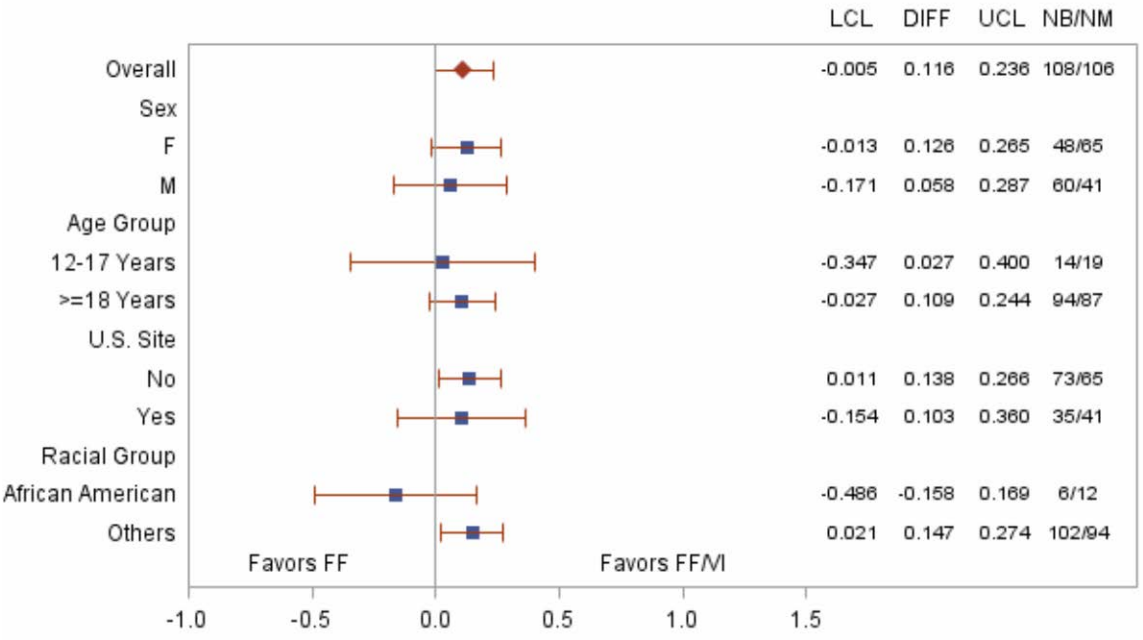
The Agency conducted subgroup analyses for weighted mean serial FEV1 and trough FEV1 for trials HZA106827, HZA116863, HZA106289, and HZA1131091. In addition, subgroup analyses were conducted for HZA106837, for the time to first exacerbation. As FF monotherapy (Arnuity Ellipta, NDA 205625) is already 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 for this comparison:

- age (12 to 17 years old vs. ≥ 18 years old)
- gender
- race (African Americans vs. Other)
- geographical region (US vs. Non-US)

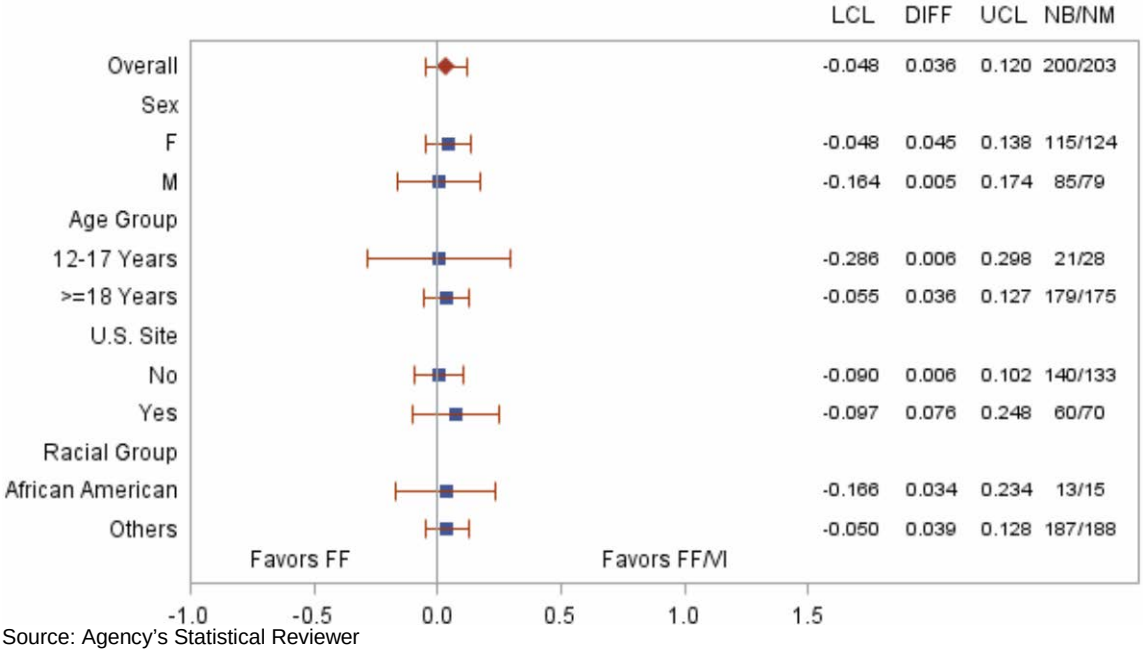
The forest plots for the overall subgroup analyses for each of the studies are presented in this section in the following order: HZA106827, HZA116863, HZA106829, HZA113091, and HZA106837. It is important to note that the trials were not powered to detect differences based on subgroup analysis.

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



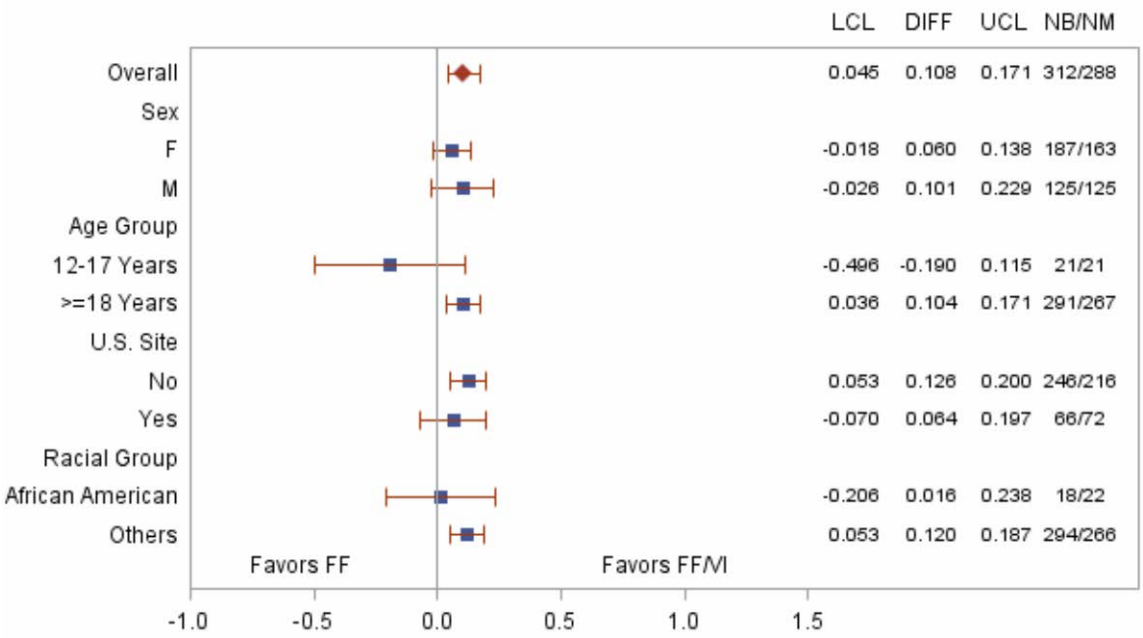
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Combination)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



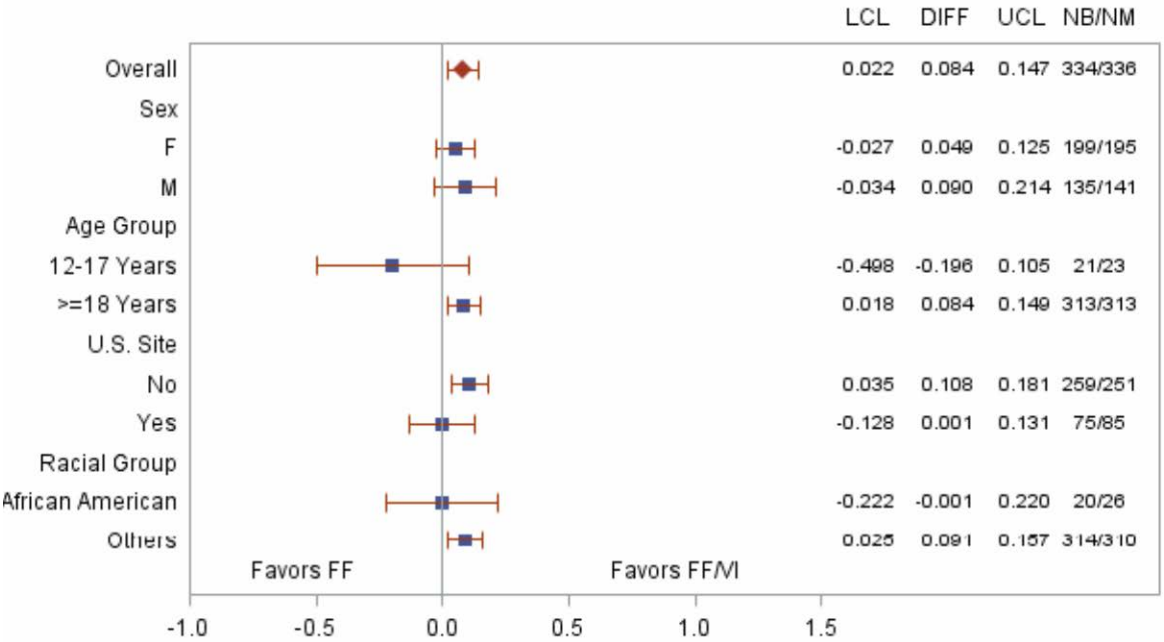
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Combination) 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 200/25 vs. FF200 with 95% CI



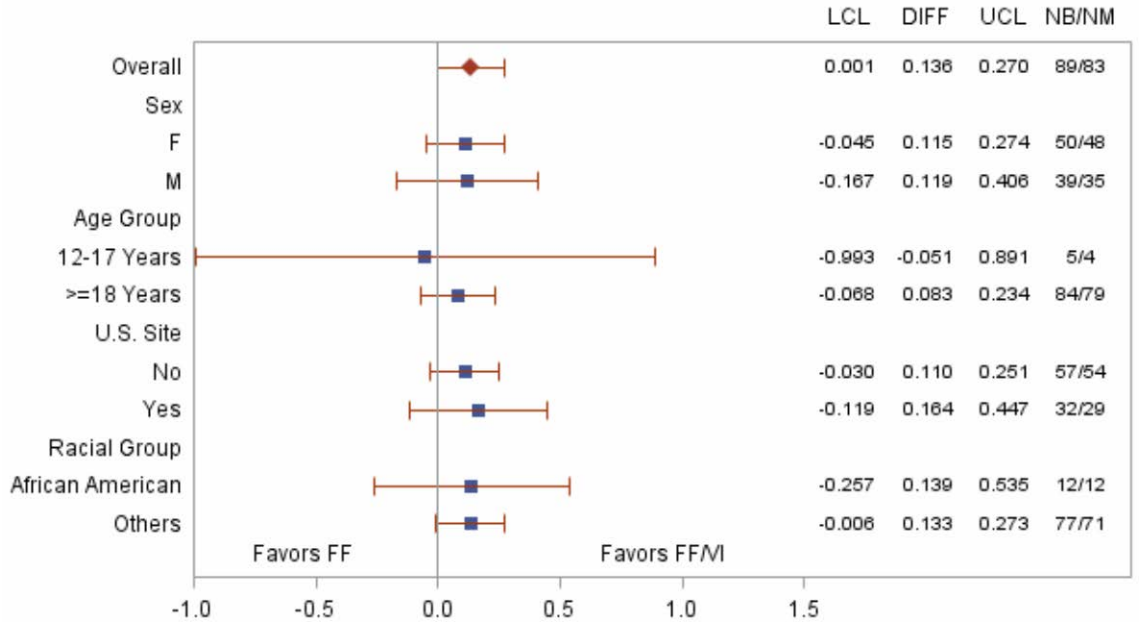
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Combination) 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 200/25 vs. FF200 with 95% CI



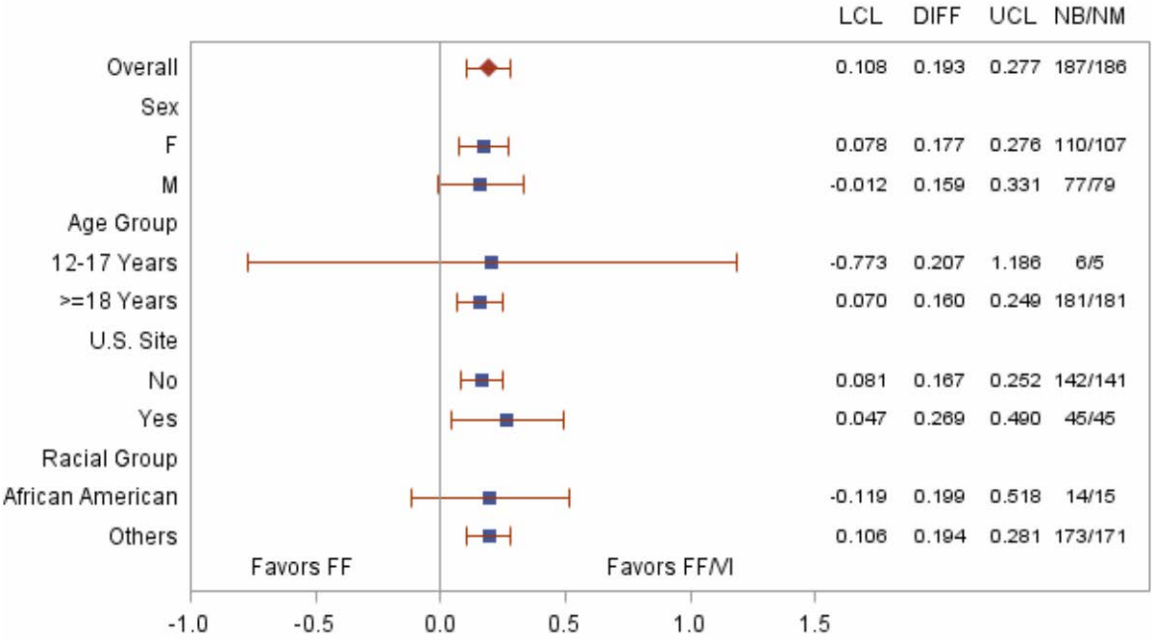
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Combination)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

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



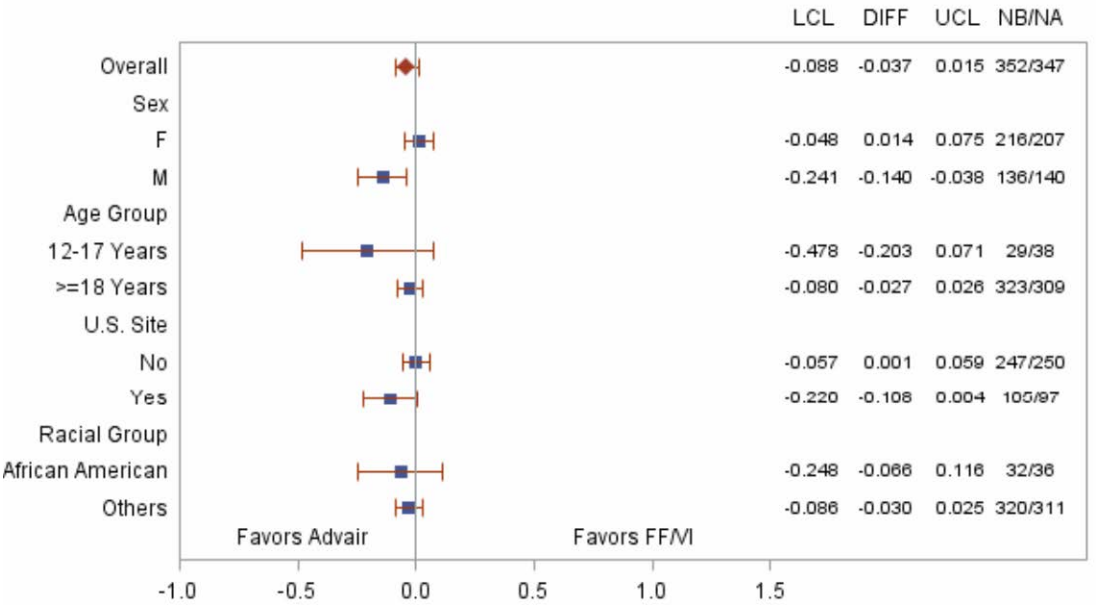
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Combination)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

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



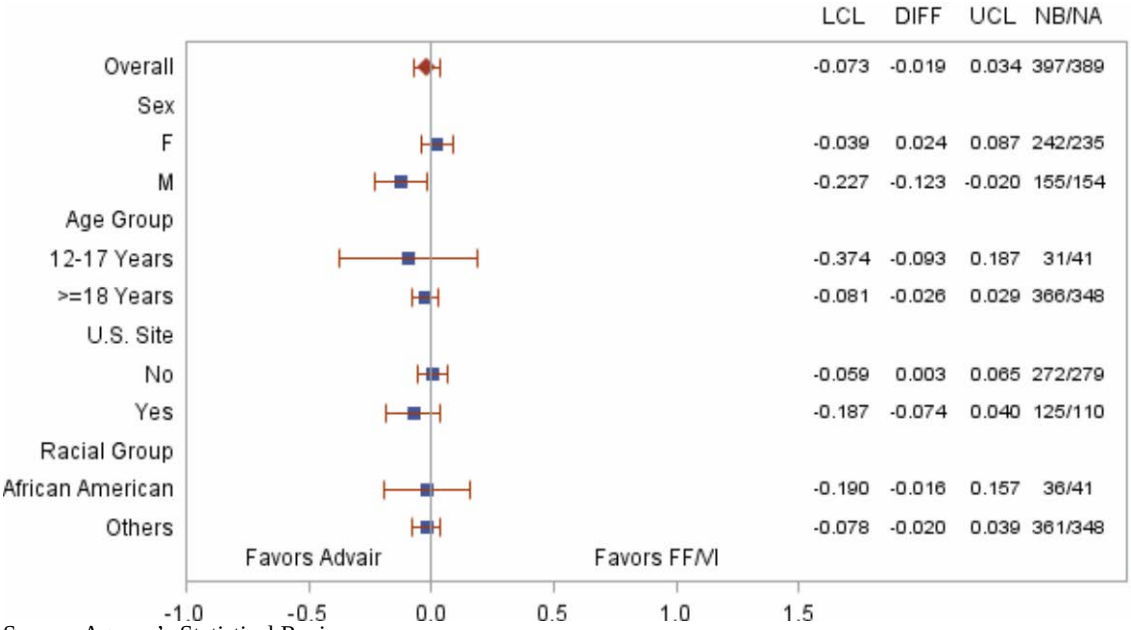
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI and FF under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NC/NM: Number of patients under the FF/VI (Combination)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

Figure 13. Subgroup Analysis of Trial HZA113091 for Weighted Mean FEV1: Estimated Difference of FF/VI 100/25 vs. Advair 250/50 BID with 95% CI



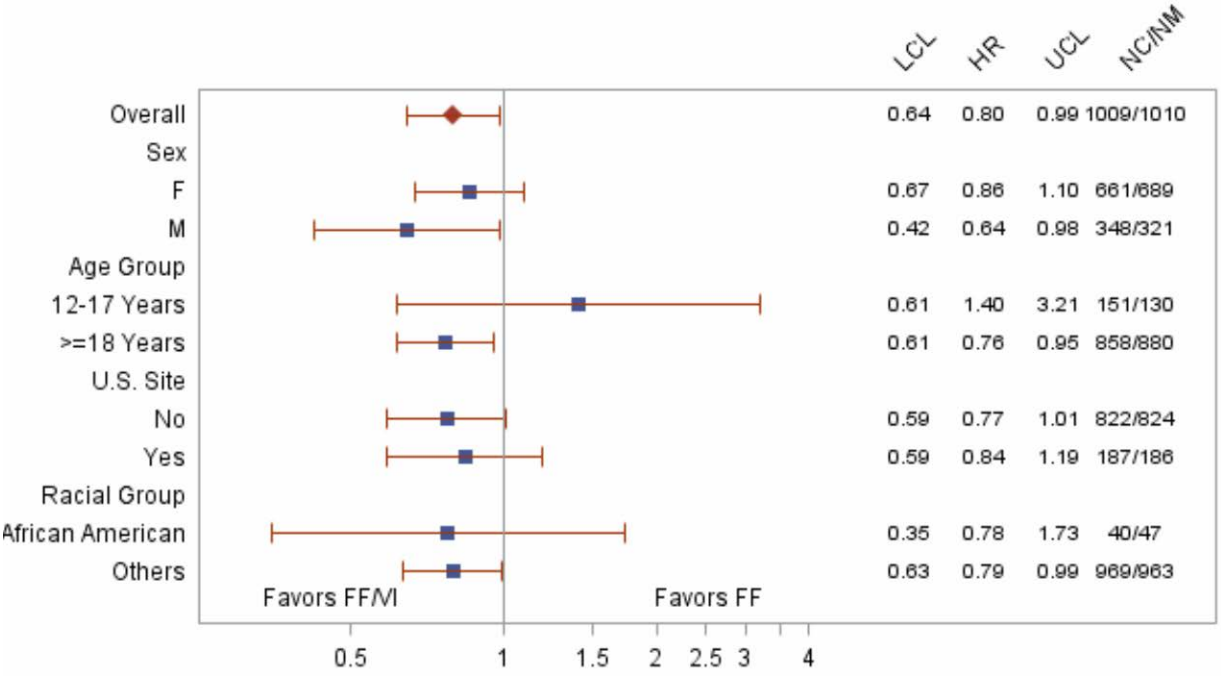
Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI 100/25 and FP/Salm 250/50 under each subgroup.
LCL: Lower limit of the confidence interval of the mean difference;
UCL: Upper limit of the confidence interval of the mean difference
NB/NA: Number of patients under Breo Ellipta (FF/VI 100/25 QD) arm versus number of patients under the Advair (FP/Salm 250/50 BID) arm.

Figure 14. Subgroup Analysis of Trial HZA113091 for Trough FEV1: Estimated Difference of FF/VI 100/25 vs. Advair 250/50 BID with 95% CI



Source: Agency's Statistical Reviewer
DIFF: Estimated mean difference between the FF/VI 100/25 and FP/Salm 250/50 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/NA: Number of patients under Breo Ellipta (FF/VI 100/25 QD) arm versus number of patients under the Advair (FP/Salm 250/50 BID) arm.

Figure 15. Subgroup Analysis of Trial HZA106837 for Time to First Asthma Exacerbation: Estimated Hazard Ratio and 95% CI



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.

6.1.6.1 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. Analysis of this subpopulation is ongoing, and further information will be added in an addendum as it becomes available. The data that is available at the present time is displayed in the following sections.

Section 6.1.6.1.1 describes the weighted mean serial FEV1 response in trials HZA106827, HZA116863, and HZA106829. Section 6.1.6.1.2 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 6.1.6.3 includes a subgroup 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 6.1.6.4 includes a subgroup analysis in the same age group in Trial HZA106837, examining time to first asthma exacerbation. .

6.1.6.1.1 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 HZA106828 who were 12 to 17 years old versus those who were ≥ 18 years of age. 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 35: 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

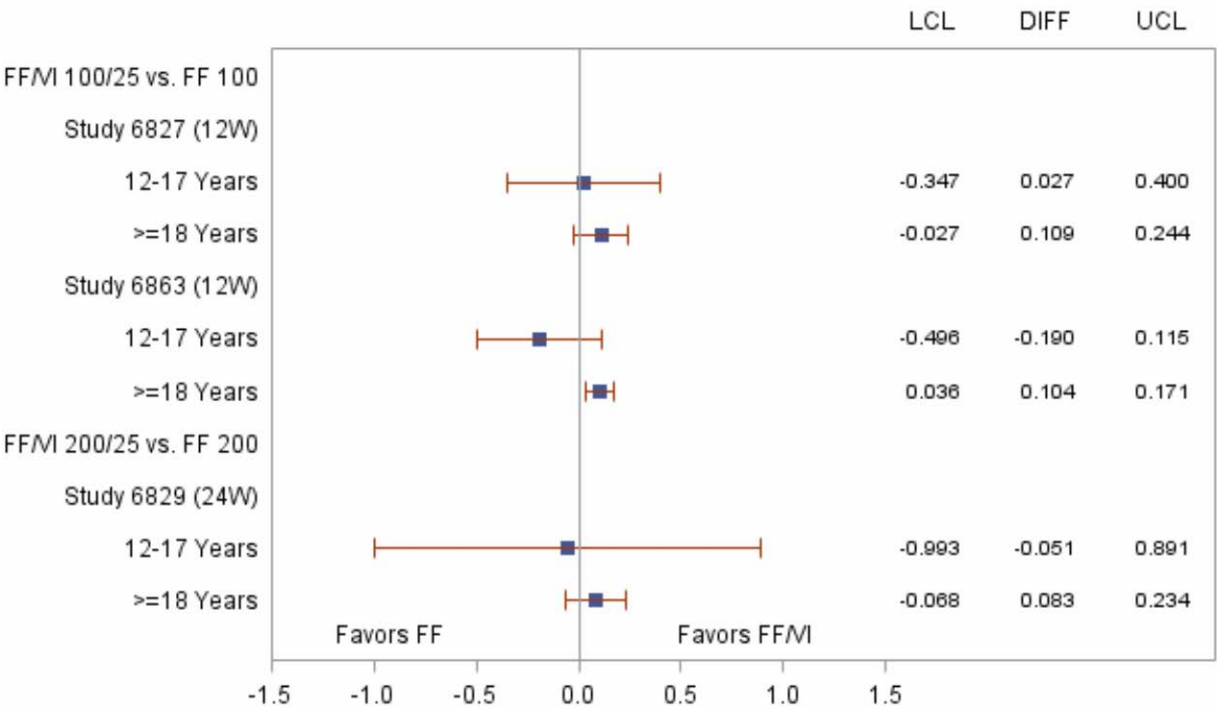
Source: Agency's Statistical Reviewer, LOCF, ITT; ANCOVA model including treatment, baseline FEV1, region, sex, age group, and age group * treatment interaction as covariates
Interaction test: p=0.80

Table 36: 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)	961	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 37: 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
Difference vs. FF200 (mL) 95%CI p-value			-51 (-993, 891) 0.90			83 (-68, 234) 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 16. 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 (12 to 17 years old vs. ≥ 18 years old)



Source: Agency's Statistical Reviewer

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 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).

6.1.6.1.2 Trough FEV1 – 12 to 17 year olds

The following section shows the subgroup analyses change from baseline in trough FEV1 for the subgroup of patients included in studies HZA106827, HZA116863, and HZA106828 who were 12 to 17 years old versus those who were ≥ 18 years of age. The primary efficacy variable of trough FEV1 is intended to show the benefit of FF/VI over vilanterol (i.e. the contribution of FF to the combination). However, the studies do not have a vilanterol alone treatment arm because of the safety risk of serious asthma exacerbations with LABA monotherapy. Also, such direct comparison between Breo Ellipta and vilanterol is less necessary (to show contribution of fluticasone furoate) because efficacy of fluticasone furoate for patients has already been established for FF in the Arnuity Ellipta development program. Some results of the pediatric subgroup analysis in the FF program are shown in this section as a means of reference.

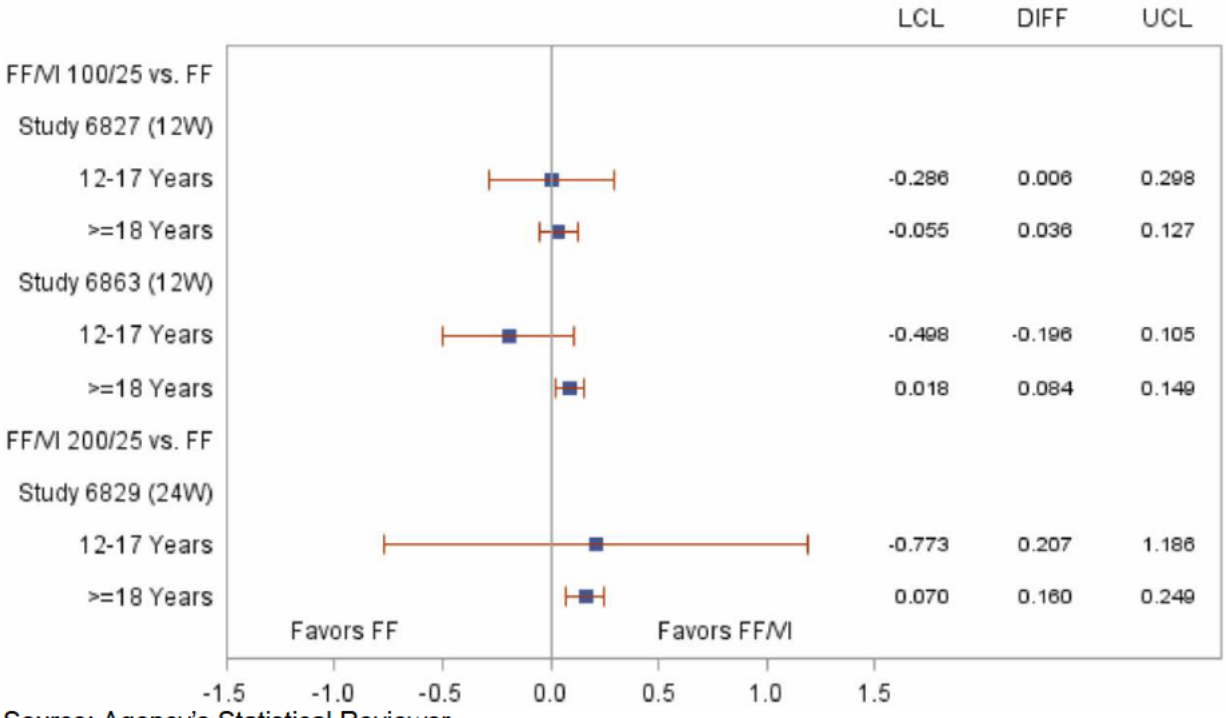
Table 38: Trial HZA106827: Change from Baseline in Trough FEV1 at Week 12						
	Patients 12 to 17 years of age			Patients ≥ 18 years of age		
	Placebo N=33	FF100 N=28	FF/VI 100/25 N=21	Placebo N=160	FF100 N=175	FF/VI 100/25 N=179
LS Mean Change from Baseline (mL)	365	520	526	197	292	327
Difference vs. 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 39: 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 40: 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 17. Estimated Treatment Difference of FF/VI vs. FF for Change from Baseline in Trough FEV1 in Trials HZA106827, 116863, and 106829 for Subgroups of Patients by Age (12 to 17 years old vs. ≥ 18 years old)

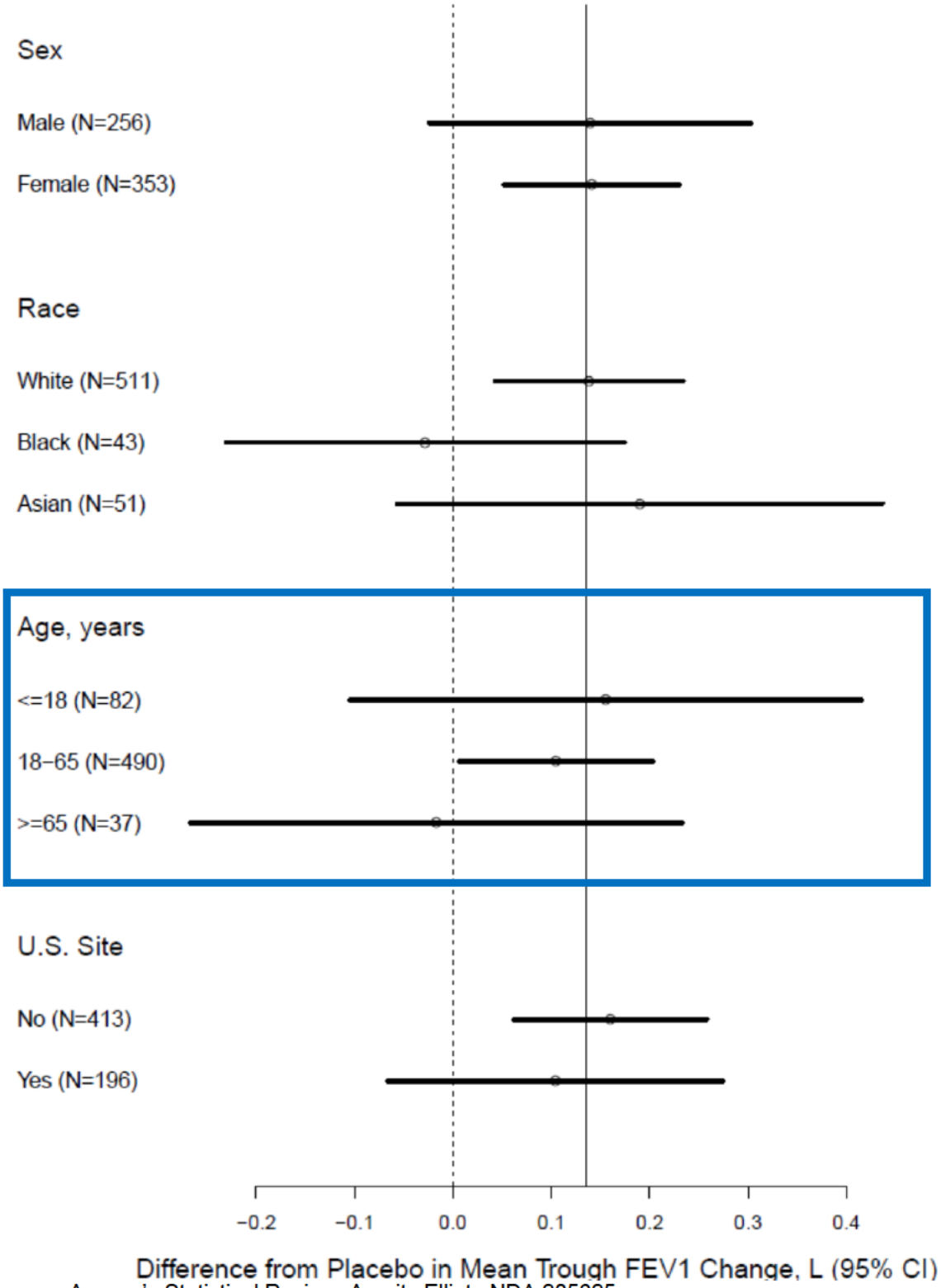


Source: Agency's Statistical Reviewer

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).

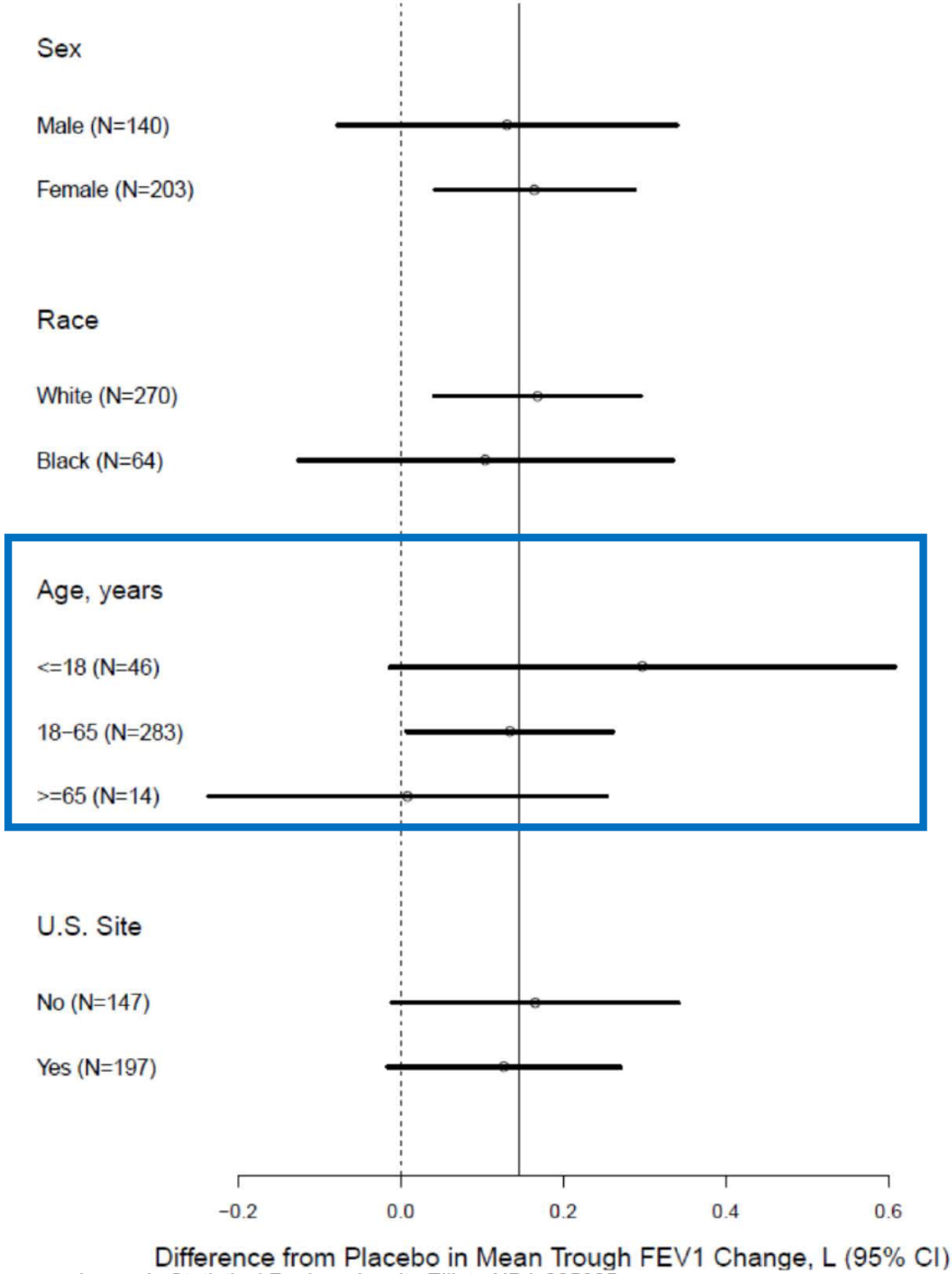
The objective of using the trough FEV1 is to examine the contribution of FF to the combination FF/VI. The relevant comparison in order to achieve this objective would be FF/VI versus VI. However, VI alone treatment arms are not practical for the reasons already mentioned above. Therefore, the next most direct method is to examine the efficacy of FF in asthma. 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 18 and Figure 19 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 18. 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 19. 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

6.1.6.1.3 Comparison to Advair – Trial 113091 – 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 in Trial 113091 who were 12 to 17 years old versus those who were ≥ 18 years of age. The weighted mean serial FEV1 is more reflective of the LABA effect.

Table 41. Mean Change from Baseline in Weighted Mean Serial FEV1 at Week 24: Trial HZA113091

	Patients 12 to 17 years of age		Patients ≥ 18 years of age	
	Advair 250/50 BID N=38	**FF/VI 100/25 N=29**	**Advair 250/50 BID N=309**	**FF/VI 100/25 N=323**
LS Mean Change from Baseline (mL)	691	488	347	320
Difference vs. Fp/Salm 250/50 BID (mL) 95% CI p-value		-203 (-478,71) 0.14		-27 (-80, 26) 0.32

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 41, 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 29), 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. This result is supported numerically by the trough FEV1 data in Table 42 as well.

Table 42. Mean Change from Baseline in Trough FEV1 at Week 24: Trial HZA113091

	Patients 12 to 17 years of age		Patients ≥ 18 years of age	
	Advair 250/50 BID N=41	**FF/VI 100/25 N=31**	**Advair 250/50 BID N=348**	**FF/VI 100/25 N=366**
LS Mean Change from Baseline (mL)	526	432	284	258
Difference vs. Fp/Salm 250/50 BID (mL) 95% CI p-value		-93 (-374, 187) 0.51		-26 (-81, 27) 0.35

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=0.90

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

In Trial HZA106837, the primary endpoint was time to first asthma exacerbation. The results for the ITT population and by subgroups (12 to <18 years old and ≥ 18 years old) are presented in Table 43 and Table 44.

Table 43. 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
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
nteraction 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 44. Rate of 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
Mean asthma exacerbation rate per subject year	0.19	0.14	0.00098	0.0015	0.2117	0.1516
FF/VI 100/25 vs. FF 100 **Ratio** **95% CI** **p-value**		0.755 (0.603, 0.945) 0.04		1.589 (0.700, 3.606) 0.27		0.716 (0.567, 0.906) 0.01

Source: Agency's Statistical Reviewer
Interaction analysis performed with a negative binomial regression model. The model to test interaction includes Treatment, Baseline FEV_1 score, Region, Sex, Age Group and Age Group * Treatment interaction as covariates.
Interaction test: p=0.02

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, there is a numerical trend towards increased risk of asthma exacerbation with FF/VI compared to FF. The results of the analysis show that about 10% of adolescents on FF/VI had at least 1 asthma exacerbation compared with 7% in the FF treatment group. This represents a hazard ratio of 1.4 (0.6, 3.2), which is numerically in favor of FF, although not statistically significant.

This trend is further supported by the analysis of the rate of asthma exacerbations, which shows that there may be an increase in the rate of asthma exacerbation in this subgroup with a ratio of 1.6 (0.7, 3.6), which indicates an increase of 60% in the FF/VI subgroup compared to FF alone. In the case of the rate of asthma exacerbations, the test for the interaction was statistically significant, indicating that either the magnitude of the treatment effect ratio of rates between the two age groups was different or the direction of the ratio was different. For adults the rate ratio was 0.72, which was consistent with the overall rate ratio of 0.76 indicating the FF/VI was better than FF. The treatment difference in the ≥18 year old subgroup was statistically significant. However, for patients between the ages of 12 and 17, the rate ratio was 1.6 (95% CI: 0.7, 3.6) indicating that FF/VI was worse than FF, but this difference was not statistically significant. The numerical trend in the exacerbation data which is in favor of FF over FF/VI is an issue that requires further consideration.

As shown in Table 45, 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.

Table 45. 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. These efficacy analyses in patients 12 to 17 years old will be an important issue for the committee's discussion.

Analysis of the pediatric subpopulation is ongoing, and further information will be provided in an addendum to this document as it becomes available.

7 Review of Safety

Safety Summary

The background regarding the history of the known safety concerns, including asthma-related death, with the use of LABA for asthma, is discussed in the Division Memorandum preceding this review. In addition to the analysis the Applicant will present, the Agency has 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 Agency's statistical briefing document. Therefore, the safety review in this clinical briefing document will focus on safety findings unrelated to serious asthma-related outcomes with the exception of asthma exacerbations which were examined as an efficacy endpoint in Trial HZA106837.

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 of FF/VI is similar to that for other ICS/LABA products in asthma, and current product labeling contains warning language regarding these risks.

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 Applicant 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 Applicant are listed below:

Table 46. 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

Study	Phase	Study Design	Run-in (weeks)	Treatment (weeks)	Follow-up (weeks)	Treatment details (mcg; OD unless otherwise noted)	Total # of Subjects Randomized[1]
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

As described in the Executive Summary, 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 (See Table 33). 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) and will be summarized in Section 7.4.5. As a result, this clinical review focuses on the safety information for FF/VI in trials HZA106827, HZA116863, HZA106829, HZA106837, and HZA106839, as listed in Table 5 and shown below in Table 33, 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 individually. Patient disposition and demographic information for each of these studies is presented in Section 6, with the exception of Study HZA106839, which is included in Section 7.7.1 Safety Results from Long-Term Trials. Summary data of the Applicant'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

[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.

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 47.

Table 47. 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	Pneumonia
	LRTI (Excluding Pneumonia)
Systemic Corticosteroid Effects – Effect on HPA-Axis	Systemic Corticosteroid Effects – Effect
Tremor	Tremor

7.2 Adequacy of Safety Assessments

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

Extent of Exposure

From the pooled safety database provided by the Applicant, 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 48).

Table 48. Total Subjects Treated in the FF/VI Asthma Clinical Program (ITT)

Study Grouping	Total Subjects Treated[1]			
	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

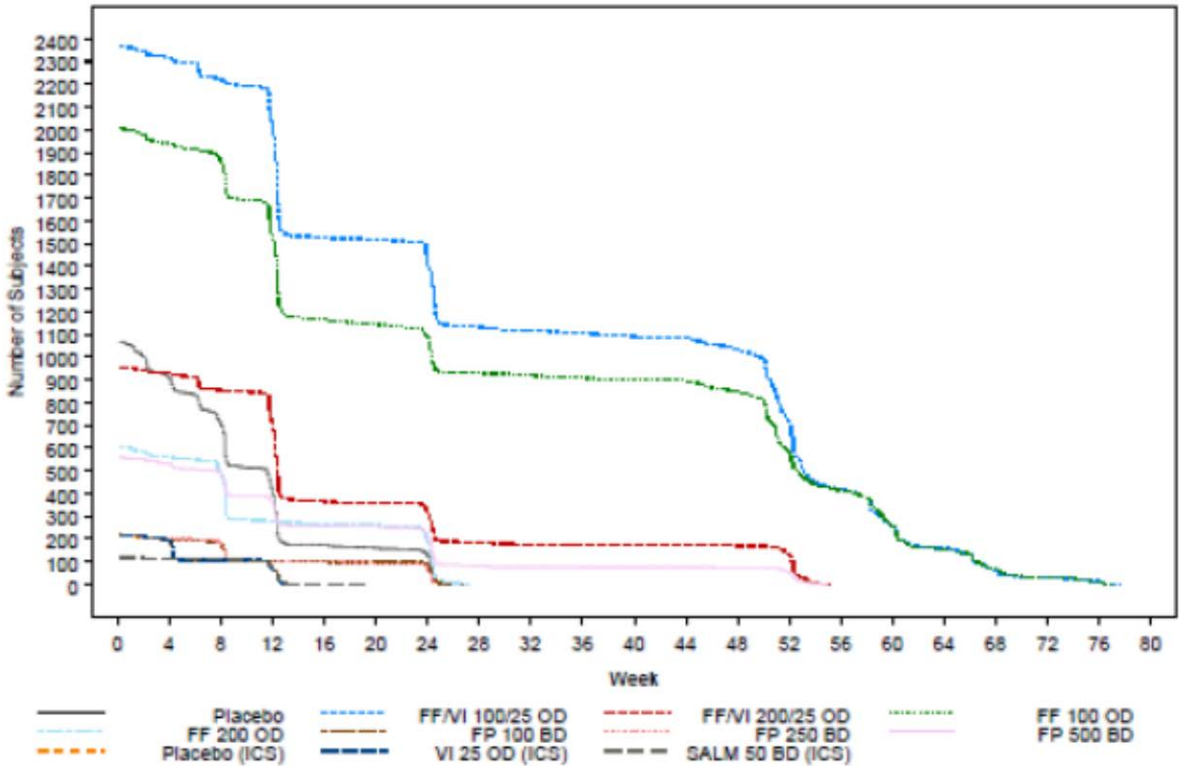
1. Numbers provided are not unique subjects (i.e., subjects who participated in more than one study or subjects in the Clinical Pharmacology Program who participated in multiple periods in crossover design studies are counted more than once).
2. Includes subjects treated with at least one dose of any 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 H-salt 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 Figure 7).

Figure 20. 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 49.

Table 49. 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 50 displays the total number of subjects exposed in the clinical trials that contained a FF/VI treatment arm.

Table 50. Number of Subjects Exposed in Trials Including an FF/VI Treatment Group

		FF (mc) QD		FP 500 mcg BID	FP/Salm 250/50 BID	FF/VI (mcg) once a day	
	Placebo	100	200			100/25	200/25
Total	430	1562	194	254	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				197
52 weeks							
HZA106839				100		201	202
Up to 76 weeks							
HZA106837		1010				1009	

Source: Module 5.3.5.3, ISS, Table 2, p.30
*Includes placebo and placebo+prednisolone groups
Italicized/boldstudiesare reviewed individually in Section 7.

A total of 2,396 subjects were exposed to FF 100/25 mcg, and 956 subjects to FF 200/25 mcg. A total of 201 subjects were exposed to FF 100/25 for at least six months, and 399 subjects to FF/VI 200/25 for at least six months. A total of at least 201 subjects were exposed to FF/ VI 100/25 for one year, and a total of 202 subjects were exposed to FF/VI 200/25 for 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. Those studies in italics will be reviewed further in Section 7 as described in Section 7.1. Methods.

Table 51 depicts the extent of exposure to both doses of FF/VI. The mean exposure for FF 100/25 was 237 days and for FF/VI 200/25 was 146.3 days.

Table 51. Extent of Exposure to FF/VI 100/25 and FF/VI 200/25		
Study drug	FF 100/25 N=2369	FF 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)
>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 52.

Table 52. 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 yrs, 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
(SD)	(49.88)	(140.55)	(139.26)	(148.47)	(54.09)	(32.14)	(25.67)
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 yrs, 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	104.7	52.8	51.9
(SD)	(46.25)	(148.26)	(107.62)	(158.35)	(59.42)	(29.90)	(29.19)
Median (days)	58.0	171.0	85.0	169.0	59.0	29.0	29.0
>52 weeks, n (%)	0	519 (27)	76 (9)	445 (27)	0	0	0
Elderly >=65 yrs, 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
(SD)	(47.47)	(150.11)	(82.89)	(156.63)	(60.50)	(28.96)	(29.36)
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 37).

Disposition

The disposition of subjects is displayed for the studies HZA106827, HZA116863, HZA106829, and HZA106837 in Section 6. Subject disposition by treatment group in the Sponsor's pooled database is shown below in Table 53.

Table 53. Subject Disposition (Sponsor's Pooled Safety Database, ITT)

Status	Number (%) of Subjects						
	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 protocol-defined stopping criteria[1]	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: Table 1.08

1. Includes pre-defined stopping criteria for abnormal ECG, Holter monitoring, liver function test, pregnancy or ophthalmologic exam.

Source: Module 5.3.5.3, ISS, Table 15, p. 61.

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.

Demographics

The demographic information of subjects is displayed in Section 6 for the individual relevant studies HZA106827, HZA116863, HZA106829, and HZA106837. The demographic information for the pooled safety database is displayed in Table 54.

Table 54. Demographics (Sponsor's Pooled Safety Database, ITT)

Demographic Parameter	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
Gender, 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)
Age (years)							
Mean	40.1	42.3	44.2	42.1	43.3	40.9	41.5
(SD)	(16.36)	(16.55)	(15.22)	(16.60)	(15.43)	(16.15)	(16.22)
Min, Max	12, 84	12, 82	12, 79	12, 84	12, 77	12, 75	12, 79
Age Category, n (%)							
12-17 yr	115 (11)	261 (11)	66 (7)	236 (12)	41 (7)	21 (10)	25 (12)
18-64 yr	890 (83)	1930 (81)	816 (85)	1630 (81)	525 (86)	184 (84)	177 (82)
≥65 yr	65 (6)	178 (8)	74 (8)	144 (7)	42 (7)	13 (6)	14 (6)
Race, n (%)							
White	610 (57)	1652 (70)	652 (68)	1550 (77)	468 (77)	149 (68)	141 (65)
Asian	216 (20)	457 (19)	224 (23)	167 (8)	57 (9)	11 (5)	9 (4)
African American	67 (6)	124 (5)	62 (6)	126 (6)	29 (5)	15 (7)	19 (9)
Mixed Race	75 (7)	125 (5)	14 (1)	151 (8)	41 (7)	3 (1)	1 (<1)
American Indian	101 (9)	9 (<1)	3 (<1)	12 (<1)	13 (2)	40 (18)	46 (21)
Hawaiian/Pacific Islander	1 (<1)	2 (<1)	0	3 (<1)	0	0	0
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 was 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.

7.2.1 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 serum IgE, 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.

7.2.2 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. The Agency's analysis of serious asthma related-outcomes are summarized in the Division Memorandum and detailed in the statistical review included in this briefing document.

7.3 Major Safety Results

For review of major safety results, this review will focus on those studies as outlined above in Table 35, as these included an FF/VI treatment arm for evaluation. Because each of these trials was either of different durations or included different treatment arms, the review examines the safety of FF/VI in asthma individually. These trials include HZA106827, HZA116863, HZA106829, and HZA106837.

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. Overall, no new safety signal was identified based on evaluation of theses SAEs.

Trial HZA106827

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

Table 55. 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 Table 56.

Table 56. 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 Table 57; a higher number of SAEs occurred in the FF 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 57. 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 70 non-fatal SAEs were reported in 68 subjects during the treatment period (29 SAEs [3%] in 28 subjects in the FF100 group and 41 SAEs [4%] in 40 subjects in the FF/VI 100/25 group). Nine (9) SAEs were reported for eight (8) subjects during the post-treatment period (5 SAEs [<1%] in 4 subjects in the FF 100 group and 4 SAEs [<1%] in 4 subjects in the FF/VI 100/25 group).

Of the 70 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 1129); and two subjects treated with FF 100 had SAEs of asthma considered not asthma-related, as they occurred in conjunction with SAEs of pneumonia (Subject 1247 and Subject 2785); and 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 5582).

Seven subjects had SAEs that resolved with sequelae: 2 subjects in the FF 100 group (Subject 2624, upper limb fracture; Subject 3079, diabetic foot) and 5 subjects in the FF/VI 100/25 group (Subject 285, asthma; Subject 1285, labyrinthitis; Subject 3016, bronchial hyper-reactivity, sepsis and anemia; Subject 6143, pneumonia; Subject 6495, nasal polyps) and 2 subjects had SAEs that were unresolved at study end: 1 subject in the FF 100 group (Subject 6927, subarachnoid hemorrhage) and 1 subject in the FF/VI 100/25 group (Subject 4233, 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 9 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.

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							
1	29/M	Pleurisy[3]	213	Severe	3	Resolved	No
		Pneumonia	213	Severe	3	Resolved	No
		Meningitis aseptic[2]	216	Severe	4	Resolved	No
87	72/M	Anaphylactic reaction	250	Severe	3	Resolved	No
225	55/F	Breast cancer	257	Moderate	57	Resolved	No
781	43/F	Asthma[3]	99	Severe	3	Resolved	No
794	47/F	Anxiety	233	Mild	2	Resolved	No
		Intervertebral disc degeneration	233	Moderate	2	Resolved	No
		Radiculopathy	233	Moderate	2	Resolved	No
828	61/F	Non-cardiac chest pain[3]	11	Severe	2	Resolved	No
1129	21/F	Asthma	221	Moderate	5	Resolved	No
		Lobar pneumonia	222	Moderate	6	Resolved	No
		Asthma	289	Severe	2	Resolved	Yes
1247	48/F	Asthma	226	Severe	32	Resolved	Yes
		Pneumonia	226	Severe	32	Resolved	No
1927	19/F	Abortion spontaneous[2]	277	Severe	1	Resolved	No
2242	40/F	Abortion spontaneous[2]	264	Moderate	2	Resolved	No
2624	52/F	Upper limb fracture	202	Moderate	52	Resolved with sequelae	No
2785	36/F	Asthma	372	Moderate	6	Resolved	Yes
		Pneumonia	372	Moderate	6	Resolved	Yes
3025	26/F	Limb traumatic amputation	115	Severe	2	Resolved	No
3079	42/F	Diabetic foot	91	Severe	49	Resolved with sequelae	No
3228	59/F	Renal cell carcinoma	224	Severe	32	Resolved	Yes
3991	51/F	Cholelithiasis	182	Mild	120	Resolved	No
4088	60/F	Intervertebral disc protrusion	72	Moderate	2	Resolved	No
4096	47/M	Pulmonary embolism	224	Severe	12	Resolved	Yes
4129	52/F	Ovarian cyst	126	Mild	192	Resolved	No
4742	20/F	Intra-uterine death[2]	50	Moderate	1	Resolved	No
4938	45/F	Osteochondroma	286	Mild	93	Resolved	No
5089	37/M	Deafness unilateral	89	Moderate	17	Resolved	No
		Otitis media	89	Moderate	17	Resolved	No
		Vertigo	89	Mild	17	Resolved	No
5482	48/F	Asthma	118	Moderate	17	Resolved	No
5491	70/F	Asthma	101	Moderate	23	Resolved	No
		Bronchitis	101	Moderate	23	Resolved	No
5522	52/M	Asthma	273	Moderate	16	Resolved	No
5533	69/F	Angioedema	206	Moderate	9	Resolved	No
5686	51/F	Hypertension	41	Moderate	11	Resolved	No
5708	73/F	Cerebrovascular accident	84	Moderate	107	Resolved	No
5811	51/F	Asthma	171	Severe	15	Resolved	No
6201	49/F	Asthma	72	Moderate	20	Resolved	No
6927	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							
41	47/F	Asthma	44	Moderate	2	Resolved	No
285	24/F	Abortion spontaneous[2]	479	Moderate	9	Resolved	No
343	54/F	Asthma	320	Severe	19	Resolved with sequelae	No
372	34/F	Asthma	75	Moderate	7	Resolved	Yes
390	29/M	Meningitis viral	73	Severe	9	Resolved	No
591	76/F	Breast cancer	205	N/A	100	Resolved	No
622	50/M	Asthma	323	Moderate	3	Resolved	Yes
1285	61/F	Labyrinthitis	51	Severe	3	Resolved	No
1286	41/F	Nausea	93	Severe	2	Resolved with sequelae	No
2305	14/M	Hand fracture	29	Moderate	28	Resolved	No
3016	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
3182	30/F	Premature labour[2]	348	Moderate	3	Resolved	No
3204	19/F	Pharyngitis	371	Moderate	14	Resolved	No
		Viral infection	371	Moderate	14	Resolved	No
3827	30/M	Fear	250	Moderate	2	Resolved	No
		Tachycardia	250	Moderate	2	Resolved	No
4082	54/F	Chronic sinusitis	283	Mild	6	Resolved	No
4095	52/M	Tachyarrhythmia[3]	105	Severe	2	Resolved	No
4230	66/F	Hypertension	276	Severe	2	Resolved	No
4233	62/F	Metastases to lung	237	Severe	N/A	Not resolved	No
4349	34/F	Subcutaneous abscess	58	Moderate	2	Resolved	No
4354	43/F	Abdominal pain	66	Mild	5	Resolved	No
		Anal abscess	169	Moderate	3	Resolved	No
		Anal fistula	234	Moderate	8	Resolved	No
4360	46/F	Osteoarthritis	183	Severe	10	Resolved	No
4370	44/F	Skin infection	22	Mild	12	Resolved	No
4733	30/M	Dermatitis allergic	134	Moderate	6	Resolved	No
4863	69/F	Acute coronary syndrome	101	Moderate	7	Resolved	No
4944	41/F	Dysfunctional uterine bleeding	422	Mild	4	Resolved	No
4945	38/F	Hydrocholecystis	27	Moderate	12	Resolved	No
4949	52/F	Coronary artery disease	266	Moderate	10	Resolved	No
5091	52/F	Pneumonia	170	Moderate	9	Resolved	No
5215	72/F	Diabetic microangiopathy	83	Mild	6	Resolved	No
5582	61/F	Tracheobronchitis	163	Moderate	15	Resolved	No
		Asthma	166	Moderate	12	Resolved	No
5743	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)							
5791	32/F	Appendicitis	189	Severe	10	Resolved	No
5798	63/F	Renal cancer stage I	171	Moderate	36	Resolved	Yes
5805	56/F	Asthma	177	Severe	11	Resolved	No
5836	56/F	Asthma	126	Moderate	22	Resolved	No
5947	22/M	Pneumonia	413	Moderate	14	Resolved	No
6039	16/M	Asthma	64	Moderate	18	Resolved	No
6040	16/F	Asthma	189	Moderate	12	Resolved	No
		Asthma	205	Severe	17	Resolved	No
		Syncope	349	Severe	5	Resolved	No
6052	16/F	Asthma	110	Moderate	29	Resolved	No
6143	56/M	Pneumonia	209	Moderate	15	Resolved with sequelae	No
6343	13/F	Asthma	201	Severe	26	Resolved	No
		Asthma	212	Severe	15	Resolved	No
6495	55/F	Nasal polyps	76	Moderate	26	Resolved with sequelae	No
6856	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 ranged from 0-<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. Eleven 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=3). The asthma events leading to discontinuation were all serious adverse events (SAEs).

7.3.4 Adverse Events of Special Interest

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 59.

Table 59. Trial HZA106827: Adverse Events of Special Interest

AE of Special Interest (Preferred Term), n (%)	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	3 (1)	4 (2)	4 (2)
Dysphonia	0	3 (1)	5 (2)
Oral candidiasis	0	2 (<1)	1 (<1)
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; more subjects in the high dose group experienced this AESI. The adverse events of special interest occurring in ≥ 2 subjects across treatment groups are summarized below in Table 60.

Table 60. 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)	0	1 (<1)
Cardiovascular effects	3 (<1)	6 (2)	1 (<1)
LRTI excluding pna	9 (3)	3 (<1)	7 (2)
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

In trial HZA106829, the sponsor did not specifically examine adverse events of special interest.

Trial HZA106837

Of the AESIs, local corticosteroid effects and lower respiratory tract infections excluding pneumonia were the most common (Table 61). 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 AESIs were included under the umbrellas of local steroid effects (oropharyngeal pain, dysphonia), LRTI excluding pneumonia (bronchitis), and cardiovascular effects (hypertension), 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 61. 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 HZA106827 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 Table 62.

Table 62. HZA106827: Most Frequent Adverse Events Occurring in ≥3% in Any Treatment Group			
	Placebo N=203	FF 100 N=205	FF/VI 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 Table 63.

Table 63. 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 Table 64. Nasopharyngitis and cough occurred more in the FP treatment group. No other AEs occurred in ≥ 3% of subjects in any treatment group.

Table 64. 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: CSR,HZA106829, 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. See Table 65.

Table 65. 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)
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

Data from the FF/VI trial HZA106851 is being used to support HPA-axis safety in this application. This 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). Additionally, a PK/PD meta-analysis of 9 studies was conducted to characterize the relationship between FF $AUC_{(0-24)}$ and 24-hour weighted mean serum cortisol. The average estimate of FF $AUC_{(0-24)}$ required to reduce cortisol by 50% (AUC_{50}) was 1,345 pg•hr/mL, which is several-fold higher than average FF $AUC_{(0-24)}$ values observed at the therapeutic dose of fluticasone furoate 100 mcg (184 pg•hr/mL) in subjects with COPD.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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 ≤ 64 and > 65 years of age. 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.

7.6 Additional Safety Evaluations

7.6.1 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 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.

7.6.2 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 Long-term Safety Study – HZA106839

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 66. Demographic and Baseline Characteristics: Trial 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 months	2 (<1)	1 (<1)	3 (3)	6 (1)
≥6 months 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)
Baseline Lung Function				
Mean pre-bronchodilator FEV1 (L)	2.305	2.290	2.353	2.308
Percent predicted	74.2	74.1	75.2	74.4
Reversibility				
Absolute FEV1 reversibility (mL)	542.4	500.9	522.9	522.1
Percent reversibility FEV1 (%)	23.6	24.0	23.8	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 67. 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)	0	2 (<1)	3 (<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				

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: 10%); 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, 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.

7.7.2 120-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

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.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL BRIEFING MATERIAL

META-ANALYSIS OF ASTHMA-RELATED SERIOUS ADVERSE EVENTS

Statistical Briefing Material for the Joint Meeting of the Pulmonary Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee on March 19, 2015

Janelle K. Charles, PhD
Mat Soukup, PhD
Mark Levenson, PhD

Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

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1 EXECUTIVE SUMMARY

1.1 Introduction

This document presents a retrospective meta-analysis conducted by the FDA to investigate the risk of asthma-related serious adverse events (SAEs) in patients treated with BREO ELLIPTA, also referred to as FFVI (fluticasone furoate and vilanterol). The risk estimates presented in this document are intended to facilitate the Committees' deliberations about the safety of BREO ELLITPA and to be considered along with the efficacy findings presented at the meeting in the Committees' discussions about the overall benefit to risk profile for this product.

The supplemental[1] New Drug Application for BREO ELLIPTA, currently under review, was submitted by the Applicant, GlaxoSmithKline (GSK), in June 2014 with the proposed indication for once-daily treatment of asthma in patients 12 years and older. Safety concerns, including increased of risks of asthma-related deaths, with the use of long-acting $beta_2$-adrenergic agonist (LABA), such as vilanterol an ingredient in BREO ELLIPTA, has prompted the FDA to include Boxed Warning of these risks for LABA products. Additionally, the FDA has required manufacturers of approved LABA products indicated for the treatment of asthma to conduct dedicated, randomized postmarketing safety trials to assess the risk of asthma-related SAEs with use of LABA product compared to treatment not containing LABA; refer to Section 2.1 for more information regarding the design parameters for such trials. At the time of this document, there has not been a requirement for GSK to conduct a dedicated randomized safety trial to assess the risk of asthma-related SAEs for BREO ELLIPTA. Therefore, the objective of the FDA meta-analysis was to assess the risks of asthma-related SAEs in patients treated with FFVI compared to patients treated with fluticasone furoate (FF) only. The trials selected for the meta-analysis were obtained from the 23 Phase 2 and 3 trials included in the asthma development program for BREO ELLIPTA; see Section 3.1 for trial selection criteria.

The primary meta-analysis set comprised patient-level data from double-blind, randomized, controlled trials in which FFVI and FF were studied in parallel. The analysis population was composed of adolescents and adults (at least 12 years old) who were randomized and received at least one dose of assigned treatment. Pediatric patients, that is, 11 years or younger, were not studied in any of the 23 Phase 2 and 3 trials submitted by the Applicant. Therefore, risks among these patients cannot be investigated in this meta-analysis. The main outcomes of interest in the meta-analysis were asthma-related deaths, asthma-related intubations, and asthma-related hospitalizations. All events included in the meta-analysis were positively adjudicated by an independent, blinded adjudication committee; refer to Section 3.2 for outcome definitions and adjudication process.

The primary meta-analysis statistic was the incidence rate difference (IRD), which was estimated by stratified analysis using Mantel-Haenszel (MH) weights to preserve the randomization for each trial included in the meta-analysis. The corresponding 95% confidence intervals (CIs) are also presented. A negative IRD suggests a lower rate of asthma-related SAEs in the FFVI arm

[1] BREO ELLIPTA was approved in the United States in 2013 for long-term maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

compared to the FF arm. A positive IRD suggests a higher rate of asthma-related SAEs in the FFVI arm compared to the FF arm. An IRD of 0 (the null value) suggests no difference in the rates between the treatment arms. There were no pre-specified statistical hypotheses for which this meta-analysis was designed to test and no adjustments were made for multiple comparisons. Therefore, all confidence intervals presented in this document are based on a two-sided alpha=0.05.

1.2 Findings and Limitations

There were no asthma-related deaths or asthma-related intubations reported in any of the 23 Phase 2 and 3 trials from which the meta-analysis trials were selected. Therefore, only analyses for the outcome of asthma-related hospitalizations are performed in the meta-analysis. This outcome occurred infrequently across the Phase 2 and 3 trials included in the asthma clinical development program of BREO ELLIPTA; refer to Appendix I.

The primary meta-analysis set comprised patient-level data from 3855 patients (2099 FFVI and 1756 FF) who were randomized in four trials meeting the trial selection criteria. The total duration of treatment exposure among these patients was 2504.5 person-years: 1301.6 in FFVI patients and 1202.9 in FF patients. The crude incidence rate of asthma-related hospitalizations for the primary meta-analysis set was 0.7 per 100 person-years (10 events) in FFVI patients and 0.6 per 100 person-years (8 events) in FF patients. The MH stratified IRD was 0.1 per 100 person-years with 95% CI (-0.5, 0.8); consistent results were obtained from sensitivity meta-analysis methods.

The majority of data for the meta-analysis were from a long-term event-driven trial of duration up to 76 weeks that enrolled patients with a history of asthma exacerbations; refer to Section 4.1 for more details about this trial. For this trial, the incidence rate was 1.0 per 100 person-years (10 events) in FFVI patients and 0.7 per 100 person-years (7 events) in FF patients resulting in an IRD estimate of 0.3 per 100 person-years and 95% CI (-0.5, 1.1).

There are limitations to be considered when interpreting the findings from the FDA meta-analysis. Firstly, the trials included in the meta-analysis were not primarily designed or powered for investigating the safety outcomes considered in this meta-analysis. Secondly, because there were no reported asthma-related deaths or asthma-related intubations, the risks of these outcomes with BREO ELLIPTA use could not be characterized from the available data. Finally, few asthma-related hospitalizations were observed in the Phase 2/3 clinical development program which resulted in imprecise estimates of the risk in the FDA meta-analysis.

2 INTRODUCTION

2.1 Background

This document presents a retrospective meta-analysis conducted by the FDA to investigate the risk of asthma-related serious adverse events (SAEs) with BREO ELLIPTA use. BREO

ELLIPTA, also referred to as FFVI, is a combination of fluticasone furoate (FF), an inhaled corticosteroid (ICS) and vilanterol (VI), a long-acting $beta_2$-adrenergic agonist (LABA) which was approved in the United States in May 2013 for long-term maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). The Applicant, GlaxoSmithKline (GSK), submitted a supplemental New Drug Application (sNDA) for BREO ELLIPTA in June 2014 that is currently under FDA review. GSK is proposing that BREO ELLIPTA be indicated for once-daily treatment of asthma in patients 12 years and older.

The asthma clinical development program included 23 Phase 2 and 3 trials composed of 12051 randomized patients, of which 3478 were randomized to FFVI and 4727[2] were randomized to FF. The trials had varying designs (e.g. with respect to blinding, randomization ratios, etc.) and treatment durations which ranged from 4 weeks up to 76 weeks. There were 8 Phase 2 trials with durations of 4-8 weeks and 15 Phase 3 trials of durations 6-76 weeks; see Table 1 for summary of trial designs and number of patients randomized to the various treatment arms for all 23 trials.

Currently the labels for LABA containing products, including the 2013 BREO ELLIPTA label for COPD, contain a Boxed Warning which states that LABAs increase the risk of asthma-related deaths. Additionally, FDA has required manufacturers of LABA containing products approved for the treatment of asthma to conduct postmarketing safety trials to evaluate the risks of serious asthma-related outcomes; namely, hospitalizations, deaths, and intubations. Generally, these trials were to be designed as 26-week randomized, double-blind, controlled trials in patients at least 12 years old treated with LABA/ICS combination or ICS alone. The primary objective of each safety trial was to rule out a relative risk of 2.0, which assuming a background rate of 0.0075 per 26-weeks and equal risk among the treatment groups, would require 87 events or approximately 12000 patients. A separate safety trial in pediatric patients, aged between 4 and 11 years, has also been required by the FDA to assess the risks of serious asthma-related outcomes in these patients. At the time of this document, there has not been a requirement for GSK to conduct a dedicated randomized safety trial to assess the risk of asthma-related SAEs for BREO ELLIPTA.

As part of the safety evaluation for the BREO ELLIPTA sNDA, FDA conducted a retrospective meta-analysis of Phase 2 and 3 trials to investigate the risk of asthma-related SAEs in FFVI patients compared to FF patients. All safety outcomes included in the FDA meta-analysis were positively adjudicated by an independent, blinded committee established by GSK to determine events that were considered asthma related. Details of the adjudication process and outcome definitions are provided in Section 3.2.

While trials Phase 2 and 3 trials collected relevant safety information for the meta-analysis, it is important to note that these trials were not primarily designed or powered for the purpose of testing differences between treatment arms for the safety outcomes of interest in this meta-analysis. The risk estimates presented in this document are intended to facilitate the Committees' deliberations about the safety of BREO ELLITPA and to be considered along with

[2] The 4727 FF patients include 95 patients who were randomized to FF during the first treatment period of crossover Trial FFA112202; see Table 1.

the efficacy findings presented at the meeting in the Committees' discussions about the overall benefit to risk profile for this product.

2.2 Objectives

The objectives of the meta-analysis were to:

1. Investigate whether FFVI is associated with an increased risk of asthma-related deaths, asthma-related intubations, or asthma-related hospitalizations.

2. Investigate the risk of the safety outcomes listed in 1. for patient subgroups defined by
    a. Demographic characteristics, namely, age, gender, race, geographic region
    b. Baseline asthma duration.

3. Investigate whether FFVI is associated with an increased risk of all-cause mortality.

Table 1 Design for 23 Phase 2 and 3 Trials in FFVI Asthma Development Program

Trial Number	Design	Treatment Arms				Total*	Treatment Duration (in weeks)	Post-treatment Follow-up (in weeks)
		FFVI	FF	PBO	Other[1]			
Phase 2 Trials								
B2C109575	R, DB, PC, PG	--	--	--	607	607	4	1
FFA20001	R, DB, PC, PG	--	432	143	--	575	4	1
FFA112202**	R, DB, PC, AC, XO	--	**	**	**	190	4	1
HZA113310***	R, DB, PC, XO	--	--	--	75***	75	1	1
FFA109687	R, DB, DD, PC, AC, PG	--	402	94	102	598	8	1
FFA109685	R, DB, DD, PC, AC, PG	--	408	107	100	615	8	1
FFA109684	R, DB, DD, PC, AC, PG	--	409	103	110	622	8	1
FFA106783	R, DB, PC, PG	--	545	101	--	646	8	1
Phase 3 Trials								
HZA106851	R, DB, PC, AC, PG	112	--	58	15	185	6	1
FFA115283	R, DB, PC, PG	--	121	121	--	242	12	1
B2C112060	R, DB, DD, PC, AC, PG	--	--	--	347	347	12	2
HZA106827	R, DB, PC, PG	201	205	203	--	609	12	2
HZA113719	R, DB, PC, PG	153	--	154	--	307	12	1
HZA116863	R, DB, PG, AC	692	347	--	--	1039	12	1
HZA113714	R, DB, DD, AC, PG	155	--	--	154	309	12	1
FFA114496	R, DB, PG	--	238	--	--	238	24	1
FFA115285	R, DB, DD, PC, AC, PG	--	117	115	115	347	24	1
FFA112059	R, DB, DD, PC, AC, PG	--	114	115	114	343	24	1
HZA106829	R, DB, DD, AC, PG	197	194	--	195	586	24	1
HZA113091	R, DB, DD, AC, PG	403	--	--	403	806	24	1
HZA106839	R, DB, DD, AC, PG	403	--	--	100	503	52	1
HZA106837	R, DB, AC, PG	1009	1010	--	--	2019	24 up to 76	1
HZA113989	NR, OL, AC, PG	153	90	--	--	243	52	1

DB=double blind, DD=double-dummy, PC=placebo-controlled, PG=parallel group, AC=active-controlled, OL=open-label, R=randomized, NR=non-randomized, XO=cross-over, FF=fluticasone furoate, FFVI=FF and vilanterol inhalation powder, PBO=placebo, ICS=inhaled corticosteroid other than FF, e.g. fluticasone propionate (FP)

-- indicates that treatment arm not studied in the trial.

* Total number of randomized patients who received at least one dose of assigned study mediation.

** Double-blind cross-over trial in which patients are randomized to one of 12 sequences comprising three treatment periods each of duration 4 weeks and separated by washout period up to 14 days.

*** Double-blind cross-over trial in which patients are randomized to one of 5 cross-over sequences comprising five treatment periods each of duration 1 week and separated by washout period up to 10 days.

[1] Other=placebo + ICS, placebo + OCS, Salmeterol + ICS, Salmeterol/FP, VI + ICS

Source: Created by the statistical reviewer using trial protocols and Integrated Summary of Safety (Table 2 and Table 4).

3 DATA SOURCES

3.1 Meta-analysis Trial Selection Process

The FDA meta-analysis was composed of Phase 2 and 3 trials selected from the BREO ELLIPTA asthma development program. The meta-analysis was conducted in accordance with a statistical analysis plan that was developed internally blinded to outcome. As shown in Table 1, trials included in the asthma clinical development program had varying designs, e.g. with respect to blinding, randomization ratios, and comparator arm. Therefore, only trials which met all the following criteria were considered for the meta-analysis:

- Randomized, double-blind, controlled
- Parallel-group or crossover trials. For cross-over trials, only the period prior to treatment cross-over was to be included.
- Trials in which at least one of the treatment arms, FFVI or FF, was studied.

The meta-analysis excludes nonrandomized, uncontrolled, open-label, or clinical pharmacology trials, as well as trials in which neither FFVI nor FF treatment arms were studied, e.g. trials comparing vilanterol to placebo.

3.2 Safety Outcomes and Adjudication

The safety outcomes considered for this meta-analysis were as follows:

- Composite endpoint comprising asthma-related death, asthma-related hospitalizations, or asthma-related intubations
- Individual components of the composite
- All-cause mortality.

All SAEs reported in the 23 Phase 2 and 3 clinical trials were retrospectively adjudicated by an independent blinded committee to determine events that were considered asthma-related. The adjudication committee comprised a group of three clinicians including the committee chair, who have expertise in treating patients with respiratory diseases. The following definitions, as documented in the guidelines provided by GSK, were used by the committee in identifying the safety outcomes assessed in this meta-analysis:

1. Hospitalizations: defined as a hospital admission or an emergency room visit greater than 24 hours in duration (± systemic corticosteroid treatment).

2. Intubation: defined as endotracheal intubation for mechanical ventilation for the treatment of acute hypoxemic or hypercapneic respiratory failure.

For all deaths, the committee determined the primary cause of death. Deaths, hospitalizations, or intubations were considered asthma-related if due to acute worsening of the patient's underlying asthma.

Each committee member independently evaluated each SAE as described in the patient narrative provided to determine if the SAE met the aforementioned definitions. For each event evaluation, once consensus was reached among the members, the evaluation was documented and recorded. When there was no unanimous agreement among the three committee members on the evaluation of a specific SAE, a meeting was held in order to reach a unanimous evaluation, after which the evaluation was documented and recorded.

NOTE: There were no reported asthma-related deaths or asthma-related intubations, and there were 4 non-asthma deaths. Therefore, the remainder of this document is dedicated to investigations of the risk of asthma-related hospitalizations.

4 STATISTICAL METHODS

This section defines the analysis sets and describes the analyses performed by the FDA for investigating risks of asthma-related hospitalizations. There was no pre-specified statistical hypothesis for which the meta-analysis was performed to test and no adjustments were made for multiple comparisons. All confidence intervals are presented based on two-sided alpha=0.05.

4.1 Analysis Sets

The analysis population for the FDA meta-analysis comprises adolescents and adults (patients at least 12 years old) who were randomized and received at least one dose of assigned treatment.

The primary meta-analysis set was composed of patients in the analysis population who were randomized in the trials that met the trial selection criteria outlined in Section 3.1 in which FFVI and FF were studied in parallel. Specifically, the trials comprising the primary meta-analysis were trials HZA106827, HZA116863, HZA106829, and HZA106837.

An additional analysis was based on patients in the analysis population who were randomized in Trial HZA106837. This trial was a large event-driven long-term trial[3] in which patients were treated for at least 24 weeks and for duration up to 76 weeks.

[3] The primary objective of HZA106837 was to demonstrate that treatment with FFVI 100/25 mcg once-daily significantly reduced the risk of severe asthma exacerbations as measured by time to first severe asthma exacerbation when compared to FF 100 mcg alone administered once-daily. A severe asthma exacerbation was defined in the trial protocol as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or an in-patient hospitalization or emergency department visit due to asthma that required systemic corticosteroids.

4.2 Analysis Methods

The primary statistic presented in this document, the incidence rate difference (IRD), is the difference between the FFVI and FF incidence rates. A negative IRD suggests a lower rate of asthma-related hospitalizations in the FFVI arm compared to the FF arm. A positive IRD suggests a higher rate of asthma-related hospitalizations in the FFVI arm compared to the FF arm. An IRD of 0 suggests no difference in the rates between the treatment arms.

4.2.1 Analysis Methods for the Primary Meta-analysis Set

For each trial in the primary meta-analysis set, the incidence rate of each treatment arm is estimated by dividing the number of patients experiencing at least one occurrence of asthma-related hospitalizations by the sum of the patient-years at risk. All asthma-related hospitalizations that occurred during trial follow-up, including those occurring after treatment discontinuation were included in the incidence rate estimates. Because the duration of post-treatment follow-up was at most 2 weeks (see Table 1), incidence rates based on on-treatment events only were not expected to yield different conclusions and therefore were not performed in this meta-analysis. Patient-years at risk was defined as the time from randomization to date of first occurrence, for patients with the outcome, or the time from randomization to last contact date for patients without the outcome.

The overall IRD estimate using the primary meta-analysis set was obtained using Mantel Haenszel (MH) weights[4] to account for the trial-level differences; the corresponding 95% confidence interval (CI) was also estimated. The trial-level and MH based confidence intervals were estimated using normal approximations. No continuity correction was used for trials with zero events in either treatment arm. Therefore, CIs for trials with no events in both treatment arms are not defined; however, data from these trials were utilized for MH weights for the overall IRD and 95% CI.

A sensitivity analysis using the primary meta-analysis set was performed using an exact meta-analysis method[5] to estimate the IRD for asthma-related hospitalizations and 95% CI to assess the robustness of the primary analysis method, which relies on normal approximations.

4.2.2 Analysis Methods for Trial HZA106837

The IRD for the analysis of Trial HZA106837 as well as the 95% confidence interval, using normal approximations, were estimated. Kaplan-Meier cumulative incidence plot of time to first asthma-related hospitalization is presented for the FFVI and FF arms.

Subgroup analyses were conducted in this trial for the following baseline (or pre-treatment) patient characteristics:

- Age: <18 years, 18-65 years, ≥ 65 years,

[4] Refer to Rothman et al. *Modern Epidemiology 3rd Edition*. Lippincott Williams & Wilkins 2008.
[5] Refer to Tian et al. Exact and efficient inference for meta-analysis. *Biostatistics* (2009), 10, 275-281.

- Gender: male, female,
- Race: white, non-white,
- Geographic region: US, non-US
- Asthma duration: 1-10 years, ≥ 10 years.

5 RESULTS

This section presents the results of analyses of asthma-related hospitalizations performed in the primary meta-analysis set and in the analysis of Trial HZA106837. Refer to Appendix I for the number of patients with asthma-related hospitalizations reported in the 23 Phase 2 and 3 clinical trials included in the asthma development program for FFVI. The baseline characteristics of these patients are also provided in this appendix.

5.1 Results for the Primary Meta-Analysis Set

A total of 3855 patients (2099 FFVI and 1756 FF) were randomized in the four trials meeting the trial selection criteria and included in the primary meta-analysis set. Appendix II shows the baseline characteristics for these patients. The total duration of treatment exposure was 2504.5 person-years, 1301.6 in FFVI patients and 1202.9 in FF patients. The observed difference in treatment exposure is due to the unequal randomization ratio (2:1 for FFVI to FF) in trial HZA116863.

The crude incidence rate of asthma-related hospitalizations in the primary meta-analysis set was 0.7 per 100 person-years (10 events) in FFVI patients and 0.6 per 100 person-years (8 events) in FF patients. There were no events reported in trials HZA106827 and HZA116863 and the majority of events were reported in trial HZA106837; see Table 2. The stratified IRD based on Mantel-Haenszel methods was 0.1 per 100 person-years with 95% CI (-0.5, 0.8). Consistent results, IRD=0.2 per 100 person-years and 95% CI (-0.6, 0.9), were obtained from the sensitivity analysis based on exact meta-analysis methods.

Table 2 Results in Primary Meta-analysis Set using Mantel-Haenszel Methods

Trial Number	**FFVI n/PY (IR)**	**FF n/PY (IR)**	**IRD** (95% CI)**
HZA106827	0/52 (0.0)	0/53 (0.0)	0.0 (-- , --)
HZA116863	0/167 (0.0)	0/82 (0.0)	0.0 (-- , --)
HZA106829	0/85 (0.0)	1/76 (1.3)	-1.3 (-3.9, 1.3)
HZA106837	10/1039 (1.0)	7/1027 (0.7)	0.3 (-0.5, 1.1)
Total	**10/1343 (0.7)**	**8/1237 (0.6)**	**0.1 (-0.5, 0.8)***

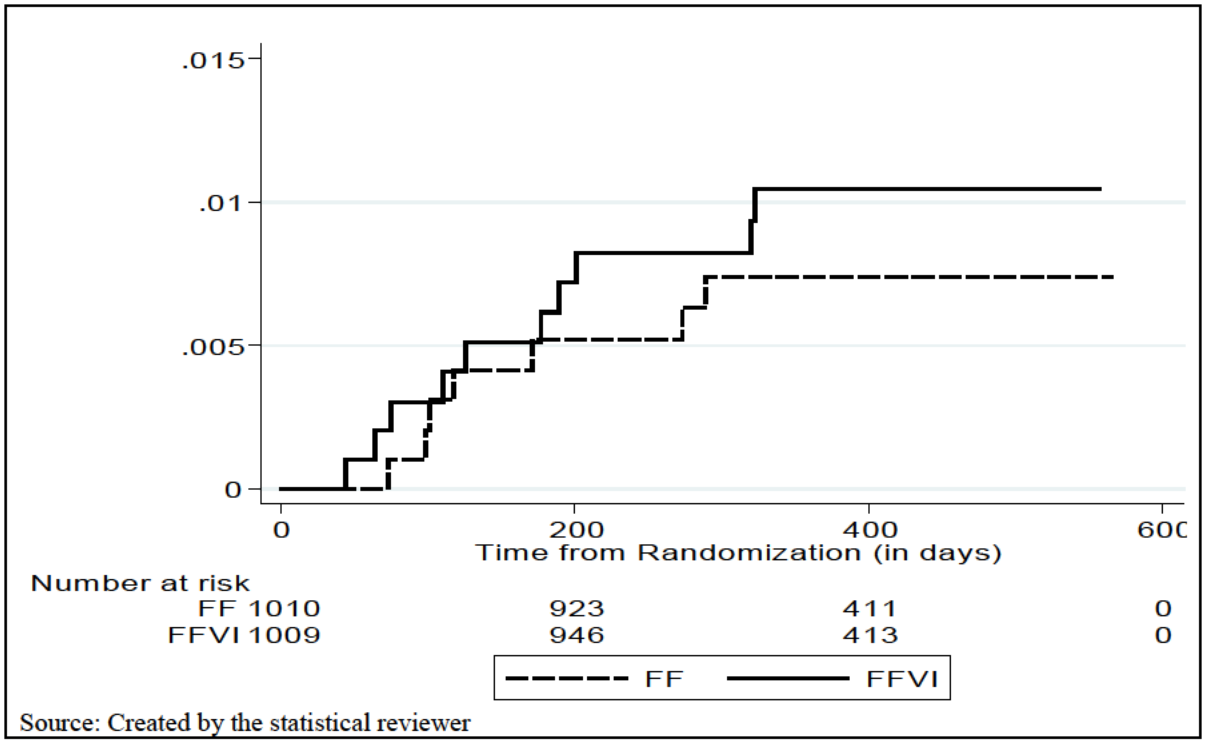
IR=incidence rate per 100 person-years, IRD=incidence rate difference per 100 person-years, PY=person-years at risk, n=number of asthma-related hospitalizations, CI=confidence interval (determined by normal approximations)
*IRD and CI based on stratified analysis, by trial, using Mantel-Haenszel weights.
**A negative IRD suggests a lower rate of asthma-related hospitalizations in the FFVI arm compared to the FF arm. A positive IRD suggests a higher rate of asthma-related hospitalizations in the FFVI arm compared to the FF arm. An IRD of 0 suggests no difference in the rates between treatment arms.
Shaded row indicates long-term trial of duration up to 76 weeks.
Source: Created by the statistical reviewer.

5.2 Results for Trial HZA106837

There were 2019 patients (1009 FFVI and 1010 FF) randomized in the long-term trial HZA106837. The total duration of treatment exposure in this trial was 2025.9 person-years, 1020.2 in FFVI patients and 1005.7 in FF patients. With the exception of one patient, all patients in this trial had a history of asthma exacerbations prior[6] to enrollment in the trial. Other baseline characteristics of the patients in this trial are shown in Appendix II.

The incidence rate for asthma-related hospitalizations was 1.0 per 100 person-years (10 events) in FFVI patients and 0.7 per 100 person-years (7 events) in FF patients, which resulted in an IRD estimate of 0.3 per 100 person-years and 95% CI (-0.5, 1.1). Figure 1 shows that the incidence rate for asthma-related hospitalizations was generally higher in FFVI patients compared to FF patients over the duration of this trial. Note that this observed trend was based on too few events to definitively conclude that FFVI was worse than FF for the duration of the trial.

Figure 1 Kaplan-Meier Cumulative Incidence Plot of Time to First Asthma-Related Hospitalizations in Trial HZA106837



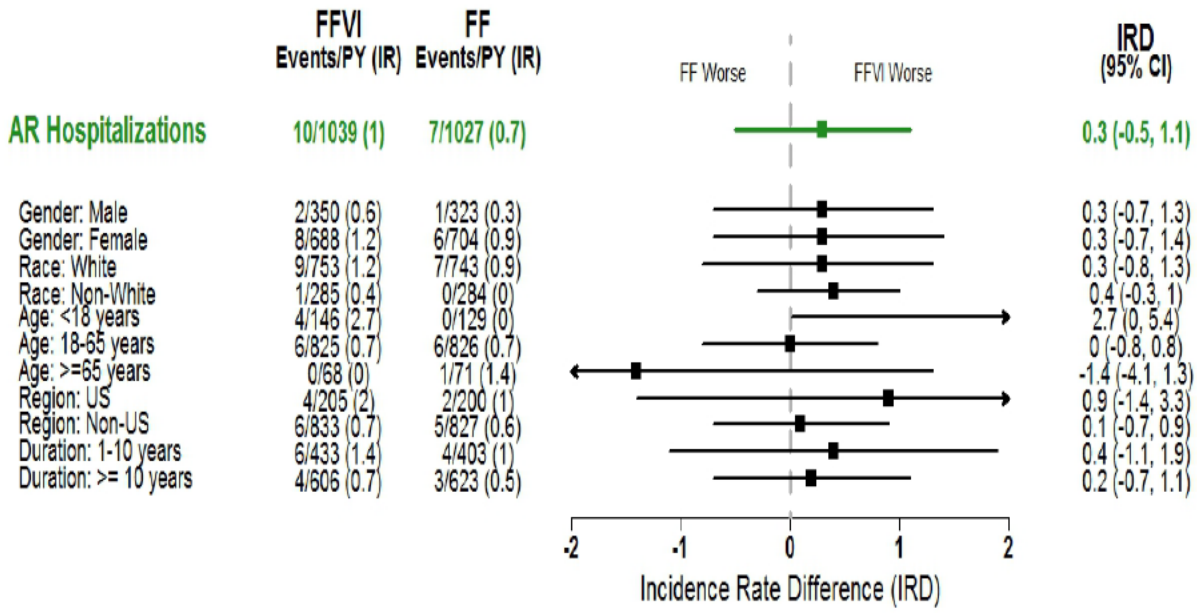
Source: Created by the statistical reviewer

The results for subgroup analyses by gender, race, age, geographic region, and asthma duration for trial HZA106837 are shown in Figure 2. Subgroup results are generally consistent with the overall trial-level findings shown in the row "AR Hospitalizations" in the figure. Note that there

[6] Per trial protocol, eligible patients had to have a history of one or more asthma exacerbations that required treatment with oral/systemic corticosteroids or emergency department visit or in-patient hospitalization for the treatment of asthma within 12 months prior to Visit 1.

are few events within subgroup levels and analyses have not been adjusted for multiple comparisons.

Figure 2 Plot of Subgroup Results in the Trial HZA106837



AR=asthma-related, PY=person-years at risk, IR=incidence rate per 100 person-years, IRD=incidence rate difference per 100 person-years.
Source: Created by the statistical reviewer

6 SUMMARY OF FINDINGS AND LIMITATIONS

This document presents a retrospective meta-analysis conducted by the FDA to investigate the risk of asthma-related SAEs in FFVI patients compared to FF patients. The trials selected for the meta-analysis were obtained from 23 Phase 2 and 3 trials included in the supplemental New Drug Application (submitted June 2014) in which GSK has proposed for BREO ELLIPTA (FFVI) to be indicated for treatment of asthma patients 12 years or older. The primary meta-analysis set comprised patient-level data from double-blind, randomized, controlled trials in which FFVI and FF were studied in parallel. The analysis population was composed of adolescents and adults (at least 12 years old) who were randomized and received at least one dose of assigned treatment. Pediatric patients, that is, 11 years or younger, were not studied in any of the 23 Phase 2 and 3 trials submitted by the Applicant. Therefore, risks in these patients cannot be investigated in this meta-analysis. All events included in the meta-analysis were positively adjudicated by an independent, blinded adjudication committee.

There were no asthma-related deaths or asthma-related intubations reported in any of the 23 Phase 2 and 3 trials from which the meta-analysis trials were selected. Therefore, only analyses for the outcome of asthma-related hospitalizations were performed in the meta-analysis. Refer to

Appendix I for the number of patients with asthma-related hospitalizations reported for each of the Phase 2 and 3 trials in the asthma clinical development program.

The primary meta-analysis set comprised patient-level data from 3855 patients (2099 FFVI and 1756 FF) who were randomized in four trials meeting the trial selection criteria. As shown in Table 3, the crude incidence rate of asthma-related hospitalizations was 0.7 per 100 person-years in FFVI patients and 0.6 per 100 person-years in FF patients, resulting in a stratified IRD estimate of 0.1 per 100 person-years with 95% CI (-0.5, 0.8); consistent results were obtained from sensitivity exact meta- analysis methods. Most of data for the meta-analysis, including the reported events, were from a long-term event-driven trial of duration up to 76 weeks that enrolled patients with a history of asthma exacerbations. The analysis findings from this trial are shown in Table 3.

Table 3 Summary of Findings in Primary Meta-analysis and Trial HZA106837

	Primary Meta-analysis Set[1]		Trial HZA106837 Analysis[2]	
	FFVI N=2099	FF N=1756	FFVI N=1009	FF N=1010
Person-years of Exposure[*]	1301.6	1202.9	1020.2	1005.7
Number of Events/PY (IR)	10/1343 (0.7)	8/1237 (0.6)	10/1039 (1.0)	7/1027 (0.7)
IRD (95% CI)	0.1 (-0.5, 0.8)		0.3 (-0.5, 1.1)	

IR=incidence rate per 100 person-years, N=number of patients in analysis population, PY=person-years at risk, IRD=incidence rate difference per 100 person-years, CI=confidence interval.
[*]Person-years of exposure determined by the sum of durations of treatment exposure for patients.
[1]The primary meta-analysis set was composed of randomized patients in HZA106827, HZA116863, HZA106829, and HZA106837. IRD and CI based on stratified analysis using MH method to account for trial.
[2] CI based on normal approximation.
Source: Created by the statistical reviewer

There are limitations to be considered when interpreting the findings from the FDA meta-analysis. Firstly, the trials included in the meta-analysis were not primarily designed or powered for investigating the safety outcomes considered in this meta-analysis. Secondly, because there were no reported asthma-related deaths or asthma-related intubations, the risks of these outcomes with BREO ELLIPTA use could not be characterized from the available data. Finally, few asthma-related hospitalizations were observed in the Phase 2/3 clinical development program which resulted in imprecise estimates of the risk in the FDA meta-analysis.

APPENDIX I Summary of Patients with Asthma-Related Hospitalizations across 23 Phase 2 and 3 Trials

Table I-1 Number of Patients with Asthma-Related Hospitalizations in 23 Phase 2 and 3 Trials

Trial Number	FFVI n	FF n	Placebo n	Other n
Phase 2 Trials				
FFA109684	--	0	1	1
FFA109685	--	1	0	0
FFA109687	--	0	0	0
B2C109575	--	--	--	0
FFA20001	--	1	1	--
FFA106783	--	0	0	--
FFA112202*	--	0	0	0
HZA113310*	--	--	--	0
Phase 3 Trials				
HZA106827	0	0	0	--
HZA116863	0	0	--	--
HZA106829	0	1	--	0
HZA106837	10	7	--	--
HZA106851	0	--	0	0
FFA115283	--	0	0	--
HZA113719	0	--	0	--
HZA113714	1	--	--	1
FFA115285	--	0	0	0
FFA112059	--	0	0	0
HZA113091	1	--	--	2
HZA106839	1	--	--	2
B2C112060	--	--	--	1
FFA114496	--	0	--	--
HZA113989	0	0	--	--
Total	**13**	**10**	**2**	**7**

-- indicates that treatment arm was not investigated in trial, n=number of patients with at least one asthma-related hospitalizations
*For cross-over trials, only events occurring during first treatment period considered.
Other=placebo + ICS, placebo + OCS, Salmeterol + ICS, Salmeterol/FP, FP, or VI + ICS
Shaded regions show trials included in primary meta-analysis set.
Source: Created by statistical reviewer.

Table I-2 Baseline Characteristics of Patients with Asthma-Related Hospitalizations in Phase 2 and 3 Trials

Patient ID	Assigned Treatment	Age*	Race	Country	Gender	Asthma Duration*
B2C112060.0020005	VI 25 OD + ICS	38	African American/African Heritage	United States	Female	1.4
FFA109684.0006071	FP 500 BD	25	White - White/Caucasian/European Heritage	South Africa	Female	14.0
FFA109684.0006123	Placebo	67	White - White/Caucasian/European Heritage	South Africa	Female	32.0
FFA109685.0012175	FF 400 OD	55	White - White/Caucasian/European Heritage	Germany	Female	33.0
FFA20001.0001131	Placebo	46	Other	Mexico	Female	--
FFA20001.0001121	FF 100 OD	49	Other	Mexico	Female	--
HZA106829.0009470	FF 200 OD	13	White - White/Caucasian/European Heritage	United States	Female	5.0
HZA106837.0006343	FF/VI 100/25 OD	13	White - White/Caucasian/European Heritage	Ukraine	Female	10.3
HZA106837.0006039	FF/VI 100/25 OD	16	White - White/Caucasian/European Heritage	Ukraine	Male	7.5
HZA106837.0006040	FF/VI 100/25 OD	16	White - White/Caucasian/European Heritage	Ukraine	Female	10.5
HZA106837.0006052	FF/VI 100/25 OD	16	White - White/Caucasian/European Heritage	Ukraine	Female	12.1
HZA106837.0001129	FF 100 OD	21	White - White/Caucasian/European Heritage	United States	Female	13.0
HZA106837.0000372	FF/VI 100/25 OD	34	White - White/Caucasian/European Heritage	United States	Female	6.3
HZA106837.0000781	FF 100 OD	43	White - White/Caucasian/European Heritage	United States	Female	43.2
HZA106837.0000041	FF/VI 100/25 OD	47	White - White/Caucasian/European Heritage	United States	Female	34.0
HZA106837.0005482	FF 100 OD	48	White - White/Caucasian/European Heritage	Russian Federation	Female	1.5
HZA106837.0006201	FF 100 OD	49	White - White/Caucasian/European Heritage	Ukraine	Female	1.6
HZA106837.0000622	FF/VI 100/25 OD	50	African American/African Heritage	United States	Male	2.7
HZA106837.0005811	FF 100 OD	51	White - White/Caucasian/European Heritage	Russian Federation	Female	7. 7

Patient ID	Assigned Treatment	Age*	Race	Country	Gender	Asthma Duration*
HZA106837.0005522	FF 100 OD	52	White - White/Caucasian/European Heritage	Russian Federation	Male	10.0
HZA106837.0000343	FF/VI 100/25 OD	54	White - White/Caucasian/European Heritage	United States	Female	7.0
HZA106837.0005805	FF/VI 100/25 OD	56	White - White/Caucasian/European Heritage	Russian Federation	Female	9.3
HZA106837.0005836	FF/VI 100/25 OD	56	White - White/Caucasian/European Heritage	Russian Federation	Female	1.4
HZA106837.0005491	FF 100 OD	70	White - White/Caucasian/European Heritage	Russian Federation	Female	6.2
HZA106839.0003220	FP 500 BD	12	White - White/Caucasian/European Heritage	Ukraine	Male	4.9
HZA106839.0003123	FP 500 BD	40	White - White/Caucasian/European Heritage	Ukraine	Female	4.0
HZA106839.0004211	FF/VI 100/25 OD	51	Asian - South East Asian Heritage	Thailand	Female	0.6
HZA113091.0016041	FF/VI 100/25 OD	27	Asian - South East Asian Heritage	Philippines	Female	15.0
HZA113091.0017344	FP/Salm 250/50 BD	37	Asian - East Asian Heritage	Korea	Male	3.0
HZA113091.0015688	FP/Salm 250/50 BD	59	White - White/Caucasian/European Heritage	Netherlands	Female	19.5
HZA113714.0045367	FF/VI 200/25 OD	41	Asian - East Asian Heritage	China	Female	19.8
HZA113714.0045083	FP 500 BD	68	Asian - East Asian Heritage	China	Female	24.8

FF=fluticasone furoate, FP= fluticasone propionate, Salm=Salmeterol, VI=vilanterol, OD=once-daily, BD=twice daily
*Presented in years.
Shaded region shows patients with events in exacerbation trial, HZA106837.
Source: Created by the statistical reviewer

APPENDIX II Baseline Characterisitics in Analysis Sets

Baseline Characteristics	Primary Meta-Analysis Set[1]		Trial HZA106837[2]	
	FFVI, N=2099	FF, N=1756	FFVI, N=1009	FF=1010
Sex, n (%)				
Male	777 (37.0)	629 (35.8)	348 (34.5)	321 (31.8)
Female	1322 (63.0)	1127 (64.2)	661 (65.5)	689 (68.2)
Race, n (%)				
White	1684 (80.2)	1384 (78.8)	740 (73.3)	743 (73.6)
Non-white	415 (19.8)	372 (21.2)	269 (26.7)	267 (26.4)
Age, in years				
Mean (SD)	43.3 (16.4)	42.8 (16.5)	41.1 (17.1)	42.3 (16.8)
Range	12 – 82	12 – 84	12 – 82	12 – 79
Age Group, n (%)				
<18 years	219 (10.4)	191 (10.9)	151 (15.0)	130 (12.9)
18-65 years	1704 (81.2)	1431 (81.5)	788 (78.1)	809 (80.1)
≥65 years	176 (8.4)	134 (7.6)	70 (6.9)	71 (7.0)
BMI, in kg/m^2				
Mean (SD)	27.9 (6.4)	27.7 (6.2)	27.4 (6.4)	27.5 (6.3)
Range	13.8 – 67.5	14.5 – 55.8	13.9 – 67.5	14.5 – 55.8
Asthma Duration, n (%)				
<1 year	28 (1.3)	26 (1.5)	--*	--*
1-10 years	829 (39.5)	671 (38.2)	428 (42.4)	403 (39.9)
≥10 years	1242 (59.2)	1059 (60.3)	581 (57.6)	607 (60.1)
Region, n (%)				
US	459 (21.9)	390 (22.2)	187 (18.5)	186 (18.4)
Non-US	1640 (78.1)	1366 (77.8)	822 (81.5)	824 (81.6)

[1]The primary meta-analysis set was composed of randomized patients in HZA106827, HZA116863, HZA106829, and HZA106837.
[2] Composed of patients in trial HZA106837.
N=number of patients in analysis population, n=number of patients in subgroup level, SD=standard deviation
*Patients with asthma duration less than 1 year excluded in accordance with trial criteria.
Source: Created by the statistical reviewer

MEMORANDUM

Subject: BREO ELLIPTA

From: Ann W. McMahon, MD, MS

Deputy Director of Science

M. Dianne Murphy, MD

Director

Office of Pediatric Therapeutics

To: Sally Seymour, MD

Deputy Director for Safety

Division of Pulmonary Allergy and Rheumatology Products

Date: March 19, 2015

BREO ELLIPTA (FFVI) is a combination of fluticasone furoate (FF), an inhaled corticosteroid (ICS), and vilanterol (VI), a long-acting beta$_2$-adrenergic agonist (LABA). The Applicant, GlaxoSmithKline (GSK) is proposing that BREO ELLIPTA be indicated for once-daily treatment of asthma in patients 12 years and older. See Statistical Review (1).

Please see the DIVISION MEMORANDUM from Director and Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC) and Drug Safety and Risk Management Advisory Committee (DSARM) (2) for a discussion of the history of LABA safety, including the risk of asthma-related hospitalizations in children. Class labeling for the pediatric asthma risk was added to the Boxed Warning ("**Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients.").**

The asthma clinical development program included 23 Phase 2 and 3 trials composed of 12051 randomized patients, of which 3478 were randomized to FFVI and 4727 were randomized to FF. The trials had varying designs (e.g. with respect to blinding, randomization ratios, etc.) and treatment durations which ranged from 4 weeks up to 76 weeks. There were 8 Phase 2 trials with durations of 4-8 weeks and 15 Phase 3 trials of durations 6-76 weeks. On analysis of the efficacy

of BREO ELLIPTA in the subset 12-17 years of age (2), there appeared not to be statistically or clinically significant findings in the adolescent age group (see Table 1).

Table 1. Bronchodilator studies 106827, 106829, and 116863; Patients 12 to 17 years of age; Mean change from baseline in weighted mean FEV_1 0-24 hour and trough FEV_1

Treatment *	FEV_1 0-24 hour			Trough FEV_1		
	N	Change (mL)	Difference from FF (95% CI) †	N	Change (mL)	Difference from FF (95% CI) †
Study 106827, on day 84						
FF/VI 100/25	14	675	27 (-347, 400)	21	526	6 (-286, 300)
FF 100	19	648		28	520	
Placebo	24	442		33	365	
Study 106829, on day 168						
FF/VI 200/25	5	644	-51 (-993, 891)	6	1043	207 (-773, 1186)
FF 200	4	695		5	836	
FP 500	5	1084		8	648	
Study 116863, on day 84						
FF/VI 200/25	13	985		14	854	
FF/VI 100/25	21	770	-190 (-496, 115)	21	758	-196 (-498, 105)
FF 100	21	967		23	954	

* FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF = fluticasone furoate in Ellipta device; FP = fluticasone propionate

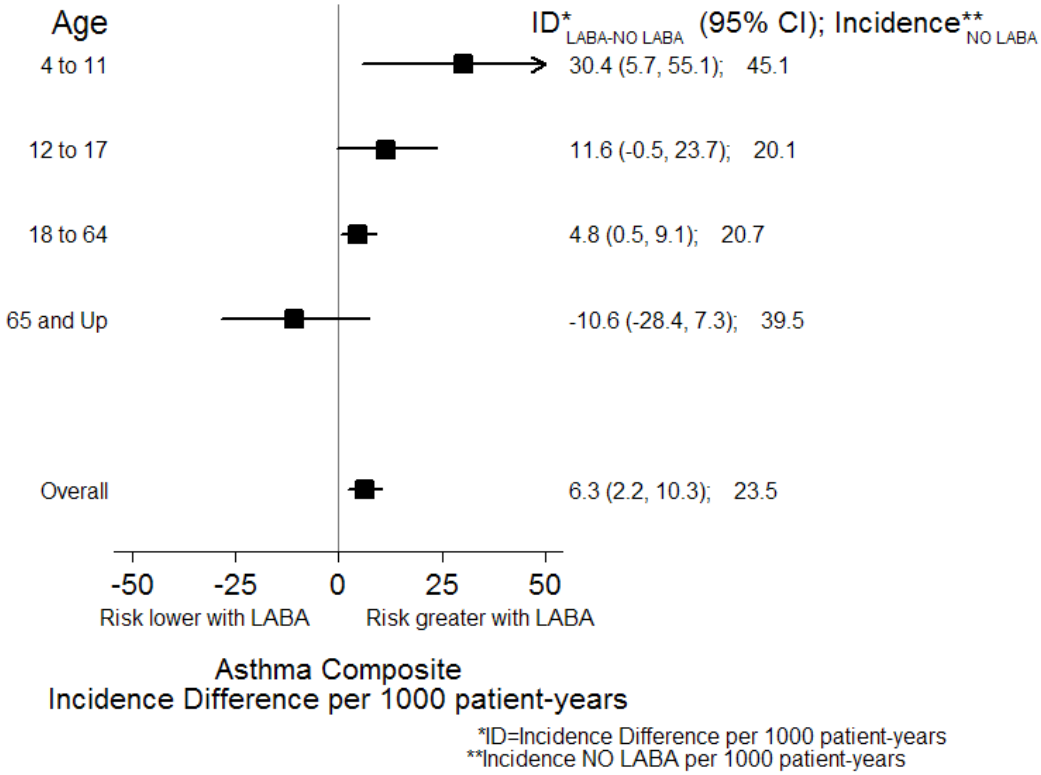
† Descriptive, not for formal inferential comparison.

Source: Table 10 of DPARP Memo to PADAC and DSaRM for 3/19/15 Breo Ellipta meeting

As part of the safety evaluation for the BREO ELLIPTA sNDA, FDA conducted a retrospective meta-analysis of Phase 2 and 3 trials to investigate the risk of asthma-related serious adverse events (SAEs) in FFVI patients compared to FF patients. All safety outcomes included in the FDA meta-analysis were positively adjudicated by an independent, blinded committee established by GSK to determine events that were considered asthma related.

This current BREO ELLIPTA meta-analysis should be viewed in the context of an earlier meta-analysis (N~60,000 patients) performed by the FDA on data for patients treated with any of the LABAs approved for asthma results of which were published in 2011 in Pediatrics (3). The published FDA meta-analysis focused on patient age and the incidence of a composite of asthma-related hospitalizations, intubations and deaths for asthma patients treated with LABAs vs. those not exposed to LABAs. The results suggest a higher risk in the younger age groups – with the following incidence rate differences (IRD) per 1,000 patient years of exposure (to LABA vs. no LABA): 30.4 in 4-11 year olds, 11.6 in 12-17 year olds, 4.8 in 18-64 year olds, and -10.6 in 65+ year olds. These IRDs had overlapping confidence intervals (See Figure 1). Therefore, the extent of the age trend in IRDs is still unclear.

Figure 1. Incidence Rate Differences for Age Groups in Meta-Analysis of LABA studies



The current BREO ELLIPTA meta-analysis had a smaller sample size (N~12,000) compared to the published FDA meta-analysis and did not include any patients under 12 years old. There was one trial (HZA106837) included in the current BREO ELLIPTA meta-analysis that gives the appearance of an age effect (See Table 2.). That trial had a longer duration (76 weeks) than the other BREO ELLIPTA trials (4 to 52 weeks) and for that trial the enrolled patients had to have a history of one or more asthma exacerbations within the 12 months prior to visit 1. The sample size of this individual (but exacerbations-enriched) trial was only 1,009 in the FFVI-treated group and 1,010 in the FF-treated group.

Table 2. Age Subgroup IRD Results* from BREO ELLIPTA Trial HZA106837

Subgroup	FFVI, n/PY (IR)	FF, n/PY (IR)	IRD**(95% CI)
Age Group			
< 18 years[1]	4/146 (2.7)	0/129 (0.0)	2.7 (0.01, 5.4)
18-65 years	6/825 (0.7)	5/826 (0.6)	0.1 (-0.6, 0.9)
≥ 65 years	0/68 (0.0)	1/71 (1.4)	-1.4 (-4.2, 1.3)

*: events are asthma-related hospitalizations

Notice that the Incidence Rate Difference (IRD) for asthma-related hospitalizations is highest (2.7) in the <18 year old group, lower in the 18-65 year age group (0.1) and lowest in the individuals ≥65 years old age group (-1.4). The confidence intervals are fairly wide because the event numbers (IRD numerators) are small. Nevertheless, these confidence intervals overlap, and the apparent age trend is inconclusive.

In the context of the age-specific composite of asthma-related serious adverse events (hospitalization + intubations + deaths) in the ~60,000 patient FDA meta-analysis presented above, the pattern of IRD seen in the single long-term BREO ELLIPTA trial is concerning.

Therefore, if the safety concerns were not accompanied by efficacy concerns in 12-17 year olds, one might recommend a post-marketing requirement in this age group. However, in view of the safety concerns, the lack of definitive efficacy findings in the 12-17 year old age group would suggest that the committee consider very carefully whether BREO ELLIPTA has a positive benefit/risk profile in this age group. **However, if the Committee determines that there is a positive benefit/risk ratio for the asthma indication in age 12 years+ and a PMR for safety for all ages is required, an adequately designed trial to assess the risk in the subgroup of patients ages 12-17 years should be considered.**

REFERENCES

1. Statistical Briefing Material for the Joint Meeting of the Pulmonary Allergy Drugs Advisory Committee and Drug Safety and Risk Management Advisory Committee on March 19, 2015. Meta-Analysis of Asthma-Related Serious Adverse Events. Janelle K. Charles, Mat Soukup, Mark Levenson. 2015

2. DIVISION MEMORANDUM from Director and Deputy Director for Safety, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) To: Members, Pulmonary-Allergy Drugs Advisory Committee (PADAC) and Drug Safety and Risk Management Advisory Committee (DSARM), Badrul A. Chowdhury, MD, PhD, Sally Seymour, MD Date: March 19, 2015

3. McMahon AW, Levenson MS, McEvoy BW, Mosholder AD, Murphy D. Age and risks of FDA-approved long-acting β_2-adrenergic receptor agonists. Pediatrics. 2011 Nov;128(5):e1147-54.

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Epidemiology & Drug Utilization Review

Date:	2-19-15 DRAFT
Reviewers:	Tracy Pham, Pharm.D. Drug Use Data Analyst, Division of Epidemiology II (DEPI-II) Esther Zhou, MD, Ph.D. Data Management & Analysis Team Leader, DEPI-II Margie Goulding, Ph.D. Epidemiology Team Leader, DEPI-II
Team Leaders:	Justin Mathew, Pharm.D. Drug Utilization Data Analysis, Acting Team Leader, DEPI-II
Director:	Judy Staffa, Ph.D., R.Ph. DEPI-II
Subject:	Review of Utilization Patterns of Breo Ellipta and Other Selected Long-Acting $Beta_2$-Adrenergic Agonists (LABAs) as Background for 3/19/15 AC meeting on the application for an asthma indication for the corticosteroid-LABA combination Breo Ellipta
Drug Name(s):	Breo® Ellipta® (Fluticasone-Vilanterol) Selected Long-Acting $Beta_2$-Adrenergic Agonists (LABAs)
Application Type/Number:	NDA 204275
Applicant/sponsor:	GlaxoSmithKline
OSE RCM #:	2014-2017

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

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EXECUTIVE SUMMARY

The purpose of this review is to provide the Office of New Drug's Division of Pulmonary Allergy and Rheumatology Products (DPARP) with data on the use of Breo® Ellipta® and other selected Long Acting Beta2–Adrenergic Agonist (LABA) drug products as background for consideration and discussion at an upcoming combined DSaRM (Drug Safety and Risk Management) and PADAC (Pulmonary Allergy Drugs Advisory Committee) meeting. The topic for discussion at the meeting is an application for adding an asthma indication for patients age 12 years+ for the combination fluticasone furoate-vilanterol trifenatate inhalation powder product, Breo® Ellipta®. Breo® Ellipta® is currently approved for long-term treatment in patients with chronic obstructive pulmonary disease (COPD), but carries the warning that LABAs, such as vilanterol, increase the risk of asthma-related death. The Office of Pharmacovigilance and Epidemiology (OPE) requested the inclusion of its DSARM committee in the meeting because of the known safety issues associated with LABAs. Members of the Pediatric Advisory Committee (PAC) are also included because of previous evidence of excess risk of severe asthma exacerbations in children treated with LABAs. In this review, DEPI-II is providing several different data streams from recent internal (OPE/DEPI) analyses of longitudinal LABA use over time as well as annual (cross sectional) data on outpatient retail use of Breo® Ellipta® and other LABAs for the years 2009-2014. These materials are being provided for the background briefing package for, and oral presentation at, the Breo® Ellipta® DSaRM-PADAC meeting planned for March 19, 2015.

The multiple data streams summarized and integrated in this document include:

National level data on prescribing of Breo® Ellipta® and other LABAs to include:

1. Annual (cross sectional) estimates of **prescriptions** dispensed from US retail pharmacies for Breo® Ellipta® or other selected single-ingredient or combination LABA-containing products for 2009-2014;

2. Annual (cross sectional) estimates of **patients** receiving Breo® Ellipta®, or other selected single-ingredient or combination LABA-containing products from US outpatient retail pharmacies for 2009-2014, overall and stratified by both product and patient age;

3. Estimates of **patients receiving Breo® Ellipta®** from US outpatient retail pharmacies, stratified by patient age, for the cumulative time period of May 2013 through December 2014;

Longitudinal data analyses of trends in LABA prescribing patterns, per FDA labeling recommendations, using IMS Health Plan Claims data:

1. Semi-annual estimates of the proportion of **single-ingredient (SI) LABA initiators** among all LABA initiators, stratified by age groups, 2003-2012;

2. Estimates, for two age groups, of **the proportions of asthma patients dispensed a non-LABA asthma controller medication (ACM) 6 months before starting a LABA**, during three time periods (2003-4, 2005-9, 2010-12);

3. **Estimates of LABA initiation in patients with poorly controlled asthma**, during three time periods (2003-4, 2005-9, 2010-12);

4. **Estimates of the length of the first continuous LABA use**, over the 2003-12 study period; and

5. Annual estimates (and trend tests) for **the proportion of incident LABA patients who had longer than 2 or 4 months of continuous supply of LABAs** over the 2003-12 study period, for two age groups.

The methods and results of these data analyses are briefly described in this review. Our interpretation of these data focuses on characterizing how LABA products are being used in the US and separately, specifically how Breo® Ellipta® is being used. The results suggest:

- While LABA product use is still high in the US, in recent years, most of its use has been in combination products, not single ingredient products;

- The proportion of SI-LABA initiators among all LABA initiators has declined significantly over 2003-12 in both the pediatric (<18 years old) and adult (18-64 years old) age groups;

- Use of ACMs before LABA initiation was not found to be highly prevalent, and while it increased in children it did not increase in adults. Thus, adherence to the recommendation of prior ACM use before LABA initiation still seems only partial in scope;

- Little, if any, possible off-label use of Breo® Ellipta® has been occurring.

The data in this review were not intended to provide any direct evidence on the efficacy or safety of Breo® Ellipta® for asthma treatment in age 12 years+ asthma patients. However, these drug utilization data provide some background information on current use of LABA products in the US. The results suggest some favorable and some unfavorable degrees of adherence to most of FDA's recommendations on the safe use of LABA products. What is still largely unknown is the extent of adherence to FDA's recommendation to discontinue LABA use ("step down") once asthma control has been achieved and maintained. For evidence on that aspect of current LABA prescribing practice, more granular clinical data are needed. Therefore, the entrance of another combination LABA product to the asthma drug market would be into a context of largely unknown adherence to the LABA step down recommendation. Also, it would be expanding FDC-LABA product options for use in the age 12 years+ pediatric asthma population. If Breo® Ellipta® is approved for asthma treatment, continued periodic post-marketing surveillance for evidence of off-label (in age groups outside those labeled)) and other inappropriate uses of Breo® Ellipta® should be conducted.

1 INTRODUCTION

1.1 BACKGROUND

DPARP reached out to OSE on planning for the envisaged 3/19/15 Advisory Committee (AC) meeting on the asthma indication application for the combination fluticasone furoate-vilanterol trifenatate inhalation powder product Breo® Ellipta® because of known safety issues (asthma exacerbations & deaths) associated with Long Acting Beta Agonists (LABA). (Vilanterol is a LABA.) OSE/OPE provided input on the advisory committee membership for what will be a combined meeting of the PADAC (Pulmonary Allergy Drugs Advisory Committee) and the DSaRM (Drug Safety and Risk Management) committee. Members of the Pediatric Advisory Committee (PAC) are also invited. The presentations and discussion will include review of the combination drug's efficacy and safety data. The main focus of the joint AC meeting will be on overall safety, as well as efficacy and safety in the pediatric age group, 12-17 years. Discussions will include the adequacy of the safety data to support

approval and whether a large safety trial to evaluate serious asthma outcomes is recommended for Breo® Ellipta®. (Four LABA products – Foradil (formoterol), Symbicort (formoterol-budesonide), Dulera (formoterol-mometasone), and Advair Diskus (fluticasone propionate-salmeterol) -- have ongoing PMR safety trials for patients age 12 years and older. There is also an ongoing pediatric study in patients aged 4-11 years old with the Advair Diskus, but for all of these trials the results are not due until 2017.) OSE/DEPI offered to provide LABA and specifically Breo® Ellipta® use data as background. This review provides that data for inclusion in the AC meeting background document and for oral presentations on March 19.

1.1 REGULATORY HISTORY

The Sponsor submitted a supplement for fluticasone–vilanterol (Breo® Ellipta®) on 6/30/2014 for the treatment of asthma in patients age 12 years and older. Breo Ellipta is a combination of the corticosteroid fluticasone furoate (used for once daily maintenance treatment of asthma in patients age12 years+) and the LABA vilanterol. Fluticasone-vilanterol is already approved (5/10/13) for long-term, once-daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD), but not for acute symptoms. This is the first application that Breo Ellipta's sponsor submitted for the asthma indication.

There is a long history of FDA regulatory actions/communications surrounding LABAs. The highlights include:

-- Reports of serious asthma exacerbations and deaths following approval of the first single-ingredient LABA, salmeterol (Serevent Diskus, approved in 1997)

-- The start of a large safety randomized controlled trial in 1996, the Salmeterol Multicenter Asthma Research Trial (SMART),

-- Approval of a fixed dose combination of ICS and LABA (fluticasone-salmeterol (Advair diskus)) for asthma in 2000,

-- The early termination of SMART in 2003, after interim analysis suggested increased risk of severe asthma exacerbations, including asthma-related death,

-- Approval in 2001, of formoterol (Foradil Aerolizer), another single ingredient LABA for asthma,

-- The addition of a boxed warning for severe-asthma exacerbations (from preliminary results of SMART) to salmeterol and salmeterol-fluticasone product labels in August 2003,

-- Evidence from a Phase IV randomized controlled trial in 2002-4 of an increase in serious asthma exacerbations with high-dose formoterol,

-- The recommendation from a Pulmonary and Allergy Drugs Advisory Committee (AC) meeting in July 2005 that formoterol labeling include the same warning as salmeterol products,

-- In November 2005, FDA issued press releases with information for health care professionals on the formoterol and salmeterol LABA products (Foradil, Advair Diskus and Serevent), and requested Medication Guides accompany their dispensing,

-- In May 2006, public health advisory with update on new labeling,

-- Two more AC meetings on LABAs were held: PAC in November 2007, and PAC/PADAC/DSaRM in December 2008,

-- February 18, 2010: FDA Drug Safety Communication announced new safety requirements for LABAs, followed by

-- A March 2010 joint PADAC-DSaRM AC meeting where there was discussion of the postmarketing required clinical trial.

Therefore, for approval of the new (asthma) indication for fluticasone-vilanterol (Breo® Ellipta®), evidence of its efficacy and safety in treating asthma is under Agency review. Also, as background, evidence of the extent of appropriate use of LABAs (as recommended by FDA in February 2010) is germane to consideration of whether the fluticasone-vilanterol combination product is likely to be used appropriately in asthmatic patients. In addition, there is particular concern about the use of LABA-containing products in patients age 12 years and younger because of prior findings from an FDA meta-analysis of clinical trials that found the highest excess risk of serious asthma-related events (deaths, intubations and hospitalizations combined), for LABA users compared to non-users, in the patients ages 4-11 years old.[1]

2 METHODS AND MATERIALS

2.1 NATIONAL CROSS-SECTIONAL DRUG UTILIZATION ANALYSES

2.1.1 Drugs of Interest

Single-ingredient LABAs (SI-LABAs) examined for the cross-sectional part of the review include: salmeterol, formoterol, arformoterol, and indacaterol products. Fixed-dose combination inhaled corticosteroids and LABA products (FDC-ICS/LABAs) include: fluticasone-salmeterol, budesonide-formoterol, mometasone-formoterol, and fluticasone-vilanterol (Breo® Ellipta®) products.

2.1.2 Determining Settings of Care

Based on IMS Health, IMS National Sales Perspectives™, approximately 76%, 12%, and 12% of Breo® Ellipta® packages were distributed to outpatient retail pharmacies, mail-order/specialty settings, and non-retail settings, respectively, in 2014.* As a result, only outpatient retail pharmacy utilization patterns of Breo® Ellipta® were examined. Breo® Ellipta® utilization patterns in mail-order/specialty and non-retail pharmacy settings were not included in this review.

2.1.3 Data Sources Used

Proprietary drug utilization databases were used to conduct the national annual (cross sectional) data analyses in this review (see Appendix A for full database descriptions).

Analyses for Selected LABA-Containing Products

Manufacturers' Sales Data

* Source: IMS Health, IMS National Sales Perspectives™. Year 2014. Data extracted February 2015. File: NSP 2014-2017 Breo Ellipta AC channel 2-4-2015.xlsx

The IMS Health, IMS National Sales Perspective™ database was used to analyze national estimates of packages (units) of Breo® Ellipta® and other selected SI-LABA and FDC-ICS/LABA products sold from manufacturers to retail and non-retail channels of distribution from 2009 through 2014. These sales distribution data do not provide a direct estimate of patient use, but do provide a national estimate of units sold from manufacturers to various channels of distribution. The amount of product purchased by these retail and non-retail channels of distribution may be a possible surrogate for use, if we assume that facilities purchase drugs in quantities reflective of actual patient use.

Dispensed Prescriptions Data

The IMS Health, National Prescription Audit™ database was used to obtain national estimates of prescriptions dispensed for Breo® Ellipta®, or other selected SI-LABA and FDC-ICS/LABA products from U.S. outpatient retail pharmacies from 2009 through 2014.

Data on Patients Receiving Dispensed Prescriptions

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide national estimates of patients receiving prescriptions dispensed for Breo® Ellipta®, or other selected SI-LABA and FDC-ICS/LABA products, stratified by patient age (0-3, 4-11, 12-17, 18-44, 45-64, and 65+ years), from U.S. outpatient retail pharmacies from 2009 through 2014. These patient analyses are inclusive of any indication and not limited to asthma. Furthermore, these patient analyses focus on only outpatient retail pharmacies; therefore, these estimates may not apply to other settings of care such as mail-order/specialty pharmacies and non-retail settings in which these products are used.

Analyses for Breo® Ellipta® Only

Data on Patients Receiving Dispensed Prescriptions

The IMS Health, Vector One®: Total Patient Tracker (TPT) database was used to provide national estimates of patients receiving prescriptions dispensed for Breo® Ellipta®, stratified by patient age (0-3, 4-11, 12-17, 18-44, 45-64, and 65+ years), from U.S. outpatient retail pharmacies from May 2013 through December 2014, cumulative.

Dispensed Prescriptions Data

The top 10 prescriber specialties for Breo® Ellipta® from May 2013 through December 2014, cumulative, were obtained from the IMS Health, National Prescription Audit™ database.

Office-Based Physician Survey Data

The Encuity Research, LLC., TreatmentAnswers™ with Pain Panel database was used to obtain diagnoses associated with the use of Breo® Ellipta®, stratified by patient age (0-3, 4-11, 12-17, 18-44, 45-64, and 65+ years), as reported from U.S. office-based physician practices from May 2013 through December 2014, cumulative.

2.2 LONGITUDINAL DRUG UTILIZATION ANALYSES

In addition to the cross-sectional LABA use analyses, we also present in this review analyses undertaken with longitudinal data on LABA use. The longitudinal data were used to analyze use of LABA and asthma control medications (ACM), looking for concurrent, prior & continuing use in the same patients over time, particularly to examine: a) the proportion of single ingredient LABA (SI-

LABA) initiation among all LABA initiators; b) whether non-LABAs were used, as recommended before LABAs were started; and c) the duration of use of LABAs.

2.2.1 Drugs of Interest

This part of the review examines all LABA-containing products: single ingredient LABA (SI-LABA) and fixed-dose combination inhaled corticosteroids (ICS) and LABA (FDC-ICS/LABA). The SI-LABA group includes salmeterol, formoterol, and arformoterol products. The FDC-ICS/LABA products group includes budesonide-formoterol, fluticasone-salmeterol, and mometasone-salmeterol products.

In this current report, we focused on incident dispensing patterns of LABA and long-term ACM products in relation to the LABA. Long-term ACMs include oral corticosteroids, inhaled corticosteroids (ICS), cromones, immunomodulators, leukotriene modifiers (LM), and methylxanthines.

2.2.2 Data Source

For the longitudinal analyses of use of LABA-containing products, we used patient-level IMS LifeLink™ Health Plan Claims data (IMS health plan claims data) with a focus on examining changes in the dispensing patterns of LABAs in asthma patients after FDA's multiple regulatory activities over the 2003-2010 period.[2, 3] The IMS health plan claims data captures adjudicated claims across the US. This database covers approximately 65.8 million de-identified patients; approximately 9% of the commercially-insured US population based on year 2007 U.S. Census data. The medical claims are captured from doctor's offices, pharmacies, specialists, hospitalizations, ER visits, tests, procedures, and injections.

The analysis with IMS health plan claims data used a longitudinal new user cohort design to assess the SI-LABA and FDC-ICS/LABA dispensing patterns in asthma patients between 2003 and 2012, to look for possible effects of FDA regulatory activities (described briefly in Section 1.1). Since these regulatory activities and asthma treatment guideline changes were undertaken intermittently at several different time points, the study time was also divided into three periods based on the important regulatory actions. The three time periods are 2003–2004 (Period 1=after the 1st labeling change), 2005–2009 (Period 2=after regulatory actions in 2005, but before the 2010 labeling change and DSC), and 2010–2012 (Period 3=after the 2010 labeling change and DSC).

2.2.3 Key Design Elements of the Longitudinal LABA Study

Study C**ohort**:

With the IMS health plan claims data, we identified patients who had a claim with at least one asthma diagnosis (including asthma-related ED visit or hospitalization) during the study period from 2002 to 2012, using ICD-9 CM codes.[†] SI-LABA and FDC-ICS/LABA new user cohorts were defined as asthma patients younger than 64 years old with a new LABA prescription (index date) sometime during 2003–2012. Patients were included in the study if they were continuously enrolled for 12 months prior to the new LABA prescription (index) date with at least one asthma diagnosis during the preceding year. "Incident LABA dispensing" is defined as having no LABA prescription in the 6 months before the index date. We also excluded patients with any claims for diagnoses of chronic

[†]asthma diagnosis (ICD- 9CM code 493.xx)

obstructive pulmonary disease (COPD), cystic fibrosis, bronchiectasis, pulmonary hypertension or embolism, bronchopulmonary dysplasia, or congestive heart failure during the 12 months prior to or on the index date.

Outcome Measures:

We examined the LABA dispensing pattern changes over the 10-year study period, with a focus on the four safety recommendations (Appendix C: Table 1) for LABA use in asthma treatment, issued in the 2010 Drug Safety Communication:[4,5]

On recommendation I— Contraindicated Use of SI-LABA: we estimated the proportion of incident SI-LABA dispensing among all incident LABA dispensing.

On recommendation II—Add-on Therapy: we estimated who had been dispensed ICS or other ACMs within 180 days before their first dispensing of a LABA.

We also attempted to assess the consistency of LABA use with asthma management guidelines in initiators of LABA. Patients were defined as having had poorly controlled asthma if they met at least one criterion in the pre-index period: (a) >=1 dispensing of an ICS or a Leukotriene Receptor Antagonist dispensed 1-90 days prior to index date; (b) >=1 asthma-related emergency department visit or hospitalization[‡] 1-90 days prior to index date; (c) >=2 oral corticosteroid (OCS) of <=21 days supply during 1-90 days prior to index date; (d) >=3 canisters of a short-acting beta agonist (SABA) 1-180 days prior to index date.

On recommendation III—"Step-down Strategy": we calculated the length of the first "continuous treatment", defined as starting from the date of the index LABA until a gap of >25% of the prior prescription days' supply. We calculated mean and median duration of "continuous treatment" and then estimated the proportion of patients who had longer than two or four months of first "continuous treatment" on a LABA.

On recommendation IV—Pediatric and adolescent patients should only use FDC-ICS/LABA; that was examined with the data evaluating recommendation I (estimates of incident SI-LABA as a proportion of all new LABA use), for only the children's cohort.

Statistical Analyses:

We evaluated the patient characteristics and dispensing patterns in SI-LABA and FDC-ICS/LABA initiators for the three periods: 2003-04, 2005-09, and 2010-12. First, a time series plot was used to portray and examine the proportion of patients who initiated SI-LABA quarterly among all LABA initiators over the study period. For a closer examination by age, the proportion of SI-LABA initiators was stratified into two age groups for both children and adults: 0-11 and 12-17 years old; and 18-45 and 46-64 years old. Second, we estimated the proportion of patients who were dispensed ICS or ACM before initiating a LABA and tested the trends (consistent increases or decreases) over the three study periods using a 2-sided Cochran–Armitage test for linear trend.[6] Third, mean & median of the duration (continuous dispensing) of the patient's first continuous episode of LABA treatment were calculated and the trend in the proportion of patients with longer than two or four months of continuous LABA treatment in the 10-year study period was also tested.

[‡] We use these procedure codes: 99281, 99282, 99283, 99284, 99285, 99288; 450, 452, 459 or hospitalization; in addition to the asthma diagnosis (ICD-9CM code 493.xx) to define emergency department visit or hospitalization due to asthma.

3 RESULTS

3.1 NATIONAL CROSS-SECTIONAL DRUG UTILIZATION

3.1.1 Manufacturers' Sales Distribution of LABA-Containing Products

Table 3.1.1 in Appendix B provides the national estimates of packages[§] of selected LABA-containing products sold from manufacturers to retail and non-retail channels of distribution in the U.S. Throughout the time period from 2009 through 2014, the majority of packages of all LABA-containing products except for SI-formoterol and SI-arformoterol products were distributed to outpatient retail pharmacies. In 2014, the proportion of sales to outpatient retail pharmacies was approximately:

- 67% for combination fluticasone-salmeterol packages,
- 70% for combination budesonide-formoterol packages,
- 71% for combination mometasone-formoterol packages,
- 76% for combination fluticasone-vilanterol (Breo® Ellipta®) packages,
- 60% for SI-salmeterol packages, and
- 70% for SI-indacaterol packages.

However, about half of SI-arformoterol packages were distributed to the mail-order/specialty setting with 51% of packages sold in 2014. Since 2012, much of SI-formoterol sales distribution switched from mail-order/specialty setting to retail setting. In 2014, approximately 47% of SI-formoterol packages were sold to outpatient retail pharmacies.

3.1.2 Dispensed Prescriptions for LABA-Containing Products

Table 3.1.2 in Appendix B provides annual national estimates of dispensed prescriptions for selected LABA-containing products, from U.S. outpatient retail pharmacies. From 2009 through 2014, the estimated annual number of prescriptions dispensed for all selected LABA-containing products remained relatively steady. In 2014, approximately 22.9 million total prescriptions were dispensed for all selected LABA-containing products. Of these dispensed prescriptions, the FDC-ICS/LABA products accounted for approximately 97%, while only 3% were for SI-LABA products.

From 2009 through 2014, the most frequently dispensed FDC-ICS/LABA product and SI-LABA product were combination fluticasone-salmeterol and SI-formoterol, respectively. In 2014, the proportions of FDC-ICS/LABA prescriptions were 59% for fluticasone-salmeterol, 32% for budesonide-formoterol, 9% for mometasone-formoterol, and 1% for fluticasone-vilanterol. In the same year, the proportions of SI-LABA prescriptions were 38% for SI-formoterol, 35% for SI-salmeterol, 24% for SI-arformoterol, and 3% for SI-indacaterol.

The annual numbers of dispensed prescriptions for combination fluticasone-salmeterol, SI-formoterol, and SI-salmeterol decreased from year 2009 to 2014. In contrast, the annual numbers of dispensed prescriptions for combination budesonide-formoterol, combination mometasone-formoterol, SI-arformoterol, and SI-indacaterol increased during the same time period.

3.1.3 Patients Receiving Dispensed Prescriptions for LABA-Containing Products

Analyses of Patient Data, by Age

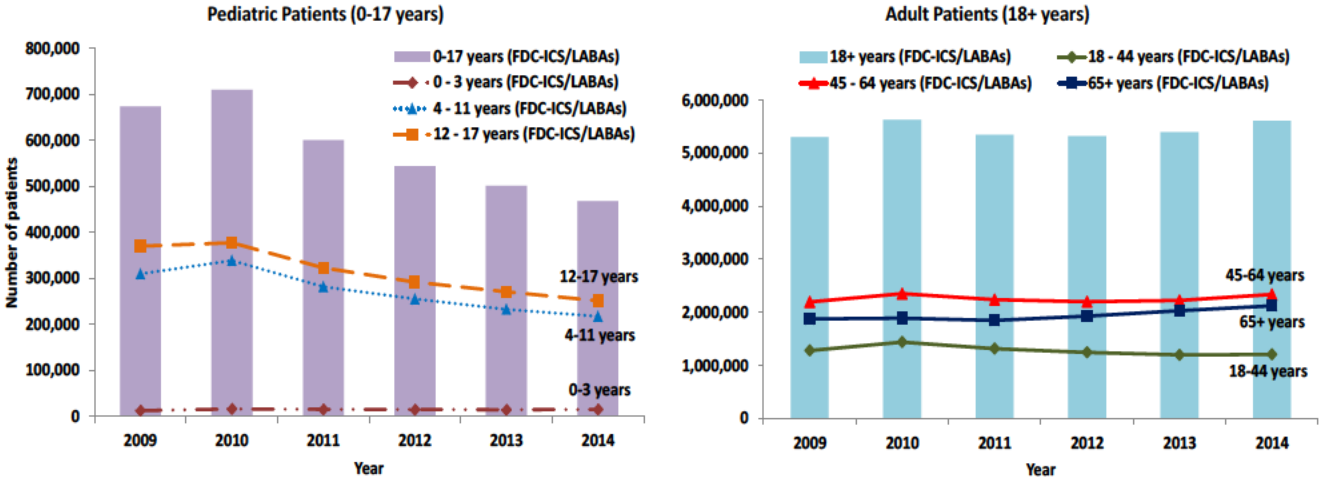
[§] An example is a package of salmeterol containing a teal green plastic inhaler with 60 blister doses or a package of arformoterol containing 30 unit-dose vials of medicine which is administered via a nebulizer.

Figure 3.1.1 and Figure 3.1.2 below and Table 3.1.3 in Appendix B provide annual national estimates of patients receiving dispensed prescriptions for FDC-ICS/LABA or SI-LABA products, stratified by patient age, from U.S. outpatient retail pharmacies. From 2009 through 2014, the majority of use of all LABA-containing products was among the combination products. In 2014, approximately 6.1 million patients (98% of all LABA patients) and 178,000 patients (3% of all LABA patients) received dispensed prescriptions for FDC-ICS/LABA and SI-LABA products, respectively. The annual number of patients receiving dispensed prescriptions for FDC-ICS/LABA products remained relatively steady – at about 6 million patients per year, over 2009-14. In contrast, the annual number of patients receiving dispensed prescriptions for SI-LABA products decreased by approximately 35% from 2009 to 2014. (Table 3.1.3)

In terms of patient age, the adult population aged 18 years and older accounted for the majority of use of all LABA-containing products. In 2014, adult patients and children aged 0-17 years accounted for 92% (5.6 million patients) and 8% (468,000 patients) of patients receiving dispensed prescriptions for FDC-ICS/LABA products, respectively. The highest proportion of all adult patients who received dispensed prescriptions for FDC-ICS/LABA products was among those aged 45-64 years at 42% in 2014. The highest proportion of all pediatric patients who received dispensed prescriptions for FDC-ICS/LABA products was among those aged 12-17 years at 54% in 2014. (Figure 3.1.1)

From 2009 through 2014, the use of FDC-ICS/LABA products among patients aged 0-3 years and 45-64 years remained relatively steady. The use of FDC-ICS/LABA products among patients aged 65 years and older increased by 13% from year 2009 to 2014, while the use of FDC-ICS/LABA products among patients aged 18-44 years peaked in 2010, before decreasing by 16% from year 2010 to 2014. The use of FDC-ICS/LABA products in patients aged 4-11 years and 12-17 years decreased by 30% and 32%, respectively, from 2009 to 2014. (Figure 3.1.1)

Figure 3.1.1. National estimates of patients receiving dispensed prescriptions for FDC-ICS/LABAs, stratified by patient age, from U.S. outpatient retail pharmacies, years 2009-2014



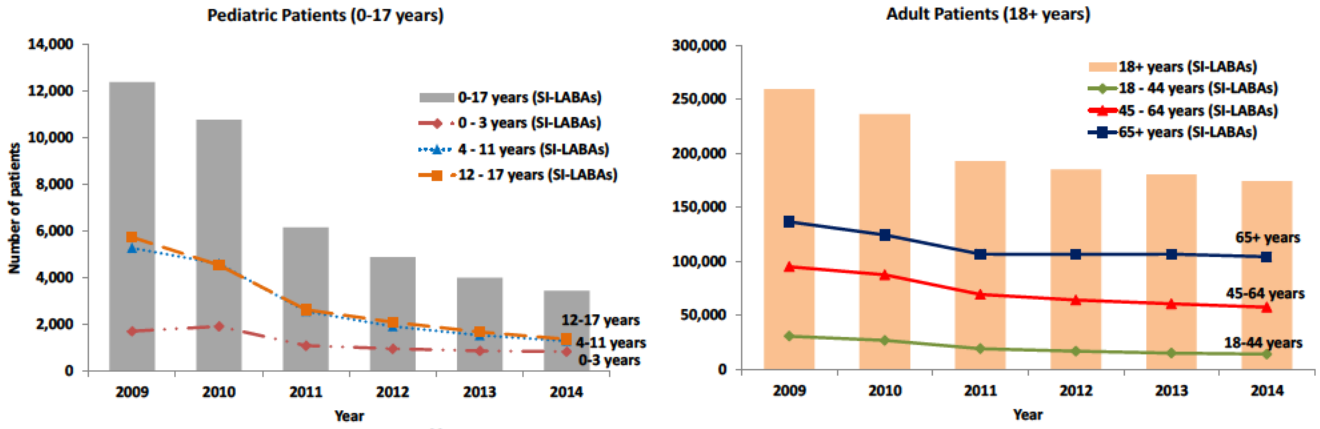
Source: IMS Health, Vector One®: Total Patient Tracker. Years 2009 through 2014. Data extracted January 2015.

In 2014, adult patients (18+ years) and children (0-17 years) accounted for 98% (174,000 patients) and 2% (3,500 patients) of patients receiving dispensed prescriptions for SI-LABA products, respectively

(Figure 3.1.2). The highest proportion of adult patients who received a prescription for SI-LABA products was among those aged 65 years and older, at 60% in 2014. The highest proportion of pediatric patients who received a prescription for SI-LABA products was among those aged 12-17 years, at 40% in 2014.

From 2009 through 2014, the use of SI-LABA products decreased across all adult and pediatric age groups. The use of SI-LABA products among patients aged 0-3 years, 4-11 years, 12-17 years, 18-44, years, 45-64 years, and 65 years and older decreased by 51%, 75%, 76%, 54%, 40%, and 24%, respectively, from 2009 to 2014.

Figure 3.1.2. National estimates of patients receiving dispensed prescriptions for SI-LABAs, stratified by patient age, from U.S. outpatient retail pharmacies, years 2009-2014



Source: IMS Health, Vector One®: Total Patient Tracker. Years 2009 through 2014. Data extracted January 2015.

Analyses of Patient Data, by Product and Age

Table 3.1.4 in Appendix B provides annual national estimates of patients receiving dispensed prescriptions for FDC-ICS/LABA or SI-LABA products, stratified by product and patient age, from U.S. outpatient retail pharmacies. Among all FDC-ICS/LABA products, the most used product was fluticasone-salmeterol from 2009 through 2014. In 2014, fluticasone-salmeterol accounted for approximately 58% of the total 6.1 million patients receiving dispensed prescriptions for FDC-ICS/LABA products. Budesonide-formoterol, mometasone-formoterol, and fluticasone-vilanterol followed at 34%, 12%, and 2%, respectively, of the total 6.1 million patients receiving dispensed prescriptions for FDC-ICS/LABA products.

Among all SI-LABA products, SI-salmeterol and SI-formoterol were the most commonly used products from 2009 through 2014. In 2014, SI-salmeterol and SI-formoterol each accounted for approximately 36% of the total 178,000 patients receiving dispensed prescriptions for SI-LABA products, followed by SI-arformoterol and SI-indacaterol at 28% and 3%, respectively.

The annual number of patients receiving dispensed prescriptions for combination fluticasone-salmeterol, SI-formoterol, or SI-salmeterol decreased from year 2009 through 2014. However, the annual number of patients receiving dispensed prescriptions for combination budesonide-formoterol, combination mometasone-formoterol, or SI-arformoterol increased from 2009 through 2014.

Utilization trending for combination fluticasone-vilanterol and SI-indacaterol are not provided because these products were approved more recently (in mid-2013 and mid-2011, respectively).

3.1.4 Patients Receiving Dispensed Prescriptions for Breo® Ellipta®

Table 3.1.5 in Appendix B provides national estimates of patients receiving dispensed prescriptions for Breo® Ellipta®, by patient age, from U.S. outpatient retail pharmacies. Over the cumulative time period from May 2013 through December 2014, a total of approximately 101,000 patients received dispensed prescriptions for Breo® Ellipta®. Adult patients aged 18 years and older, and pediatric patients aged 0-17 years accounted for 99% and 0.2% of total patients receiving dispensed prescriptions for Breo® Ellipta®, respectively. Patients aged 65 years and older accounted for approximately 56% of those 100,000 adult patients, followed by patients aged 45-64 years at 37% and patients aged 18-44 years at 7%.

3.1.5 Top 10 Prescriber Specialties for Breo® Ellipta®

Table 3.1.6 in Appendix B provides the top 10 prescriber specialties for Breo® Ellipta®, as measured from U.S. outpatient retail pharmacies. Cumulative from May 2013 through December 2014, a total of approximately 221,000 prescriptions were dispensed for Breo® Ellipta®. Pulmonary disease specialists accounted for approximately 41% of the total Breo® Ellipta® prescriptions, followed by General Practice/Family Practice/Doctor of Osteopathy specialists with almost 25% and Internal Medicine specialists with almost 18%. Fourth were nurse practitioners with 7%. Pediatricians accounted for less than 1% of the total Breo® Ellipta® prescriptions (data not shown).

3.1.6 Indications for Breo® Ellipta® Use

Table 3.1.7 in Appendix B provides diagnoses associated with the use of Breo® Ellipta®, stratified by patient age, as reported from U.S. office-based physician practices from May 2013 through December 2014, cumulative. The diagnoses for drug use mentions** of Breo® Ellipta® were coded according to the International Classification of Diseases (ICD-9-CM). Diagnoses associated with Breo® Ellipta® users under age 18 years were <u>not</u> captured in the database. For the 18-44 and 45-64 age groups, the Breo® Ellipta® drug use mentions were too small (<100,000 mentions) for reliable national estimates of use by diagnoses. However, "Obstructive chronic bronchitis" (ICD-9 491.2) accounted for 48% of Breo® Ellipta® use mentions in patients aged 18-44 years, and "Chronic airway obstruction" (ICD-9 496.0) accounted for 71% of Breo® Ellipta® use mentions in patients aged 45-64 years. For the age 65+ group, an estimated 80% of the Breo® Ellipta® use mentions were coded as "Chronic airway obstruction".

3.2 LONGITUDINAL DRUG UTILIZATION

3.2.1 Asthma Patient LABA Initiators by Age

There were approximately 6 million patients with at least one claim for an asthma diagnosis between 2002 and 2012 in the IMS health plan claims database. Among these patients with an asthma claim,

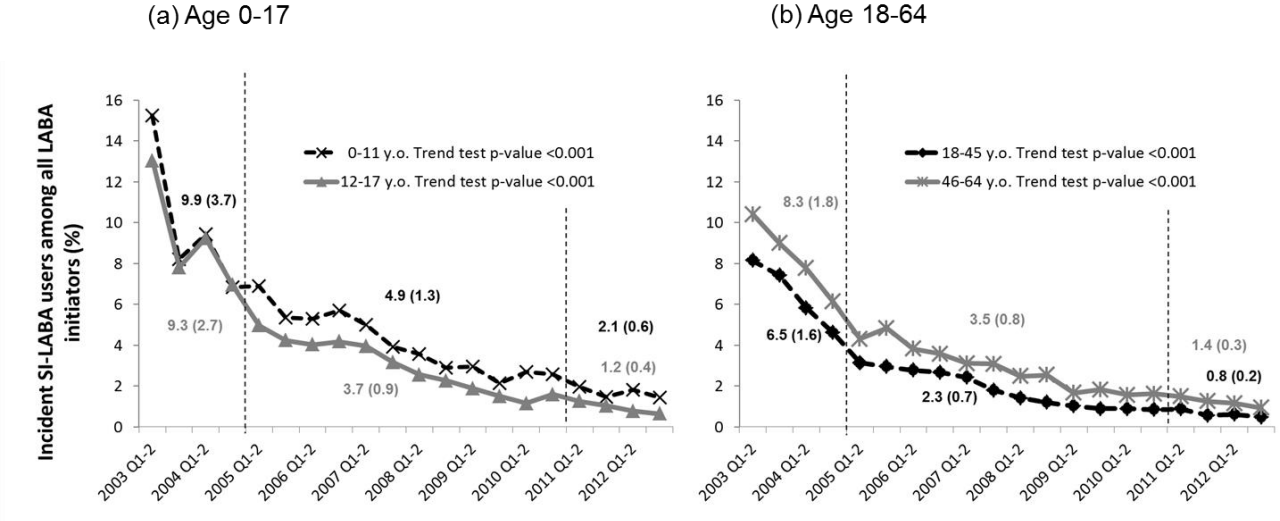
** The term "drug use mentions" refers to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnoses for which the drug is mentioned. Note: A "drug use" does not necessarily result in a prescription being generated. The term only indicates that a given drug was mentioned during an office visit.

639,466 were dispensed a new LABA prescription during 2003-2012. Among these 639,466 LABA initiators, there were 161,544 patients 0-17 years old and 477,922 adult patients 18-64 years old. Half of the LABA initiators under the age of 18 years were aged 12-17 years old. Half of the adult LABA initiators were 18-45 years old.

3.2.2 Single Ingredient-LABA Use Among any LABA Initiators

In children 0-17 years old, among all LABA initiators, 9% initiated SI-LABA in the period 2003–2004. But this proportion decreased to 4% and then 2% in the 2005–2009 and 2010–2012 periods, respectively (*p*-value <.001 for linear trend). Figure 3a illustrates SI-LABA initiation in children stratified by two ago groups (0-11 and 12-17 years old). Similar declines in SI-LABA use over these time periods were also seen for the adult LABA initiators ages 18-64 years old. In these 18-64 year old LABA initiators with asthma claims , the proportion of SI-LABA initiators decreased from 7% in 2003–2005, to 2% in 2006–2009, then to 1% in 2010–2012 (*p*-value <.001 for linear trend). Figure 3b illustrates SI-LABA initiation in the adults stratified by two age groups (18-45 and 46-64 years old). *(Note: In the adult population, those who initiated a SI-LABA and had same day dispensing of an ACM were counted as using combination therapy. However, since the recommendation for pediatric & adolescent patients who need a LABA added to an ICS is stricter, i.e. only to use a fixed dose combination ICS-LABA drug (Recommendation IV), if a young patient had an SI-LABA and ICS dispensed on the same date, he/she was still counted as an SI-LABA initiator.)*

Figure 3. Proportion of single-ingredient (SI) LABA* initiators among all LABA initiators, stratified by age groups, 2003-2012 (by half-year): (a) 0–17 years old and (b) 18–64 years old, IMS LifeLink™ Health Plan Claims Database, **years 2003-2012**



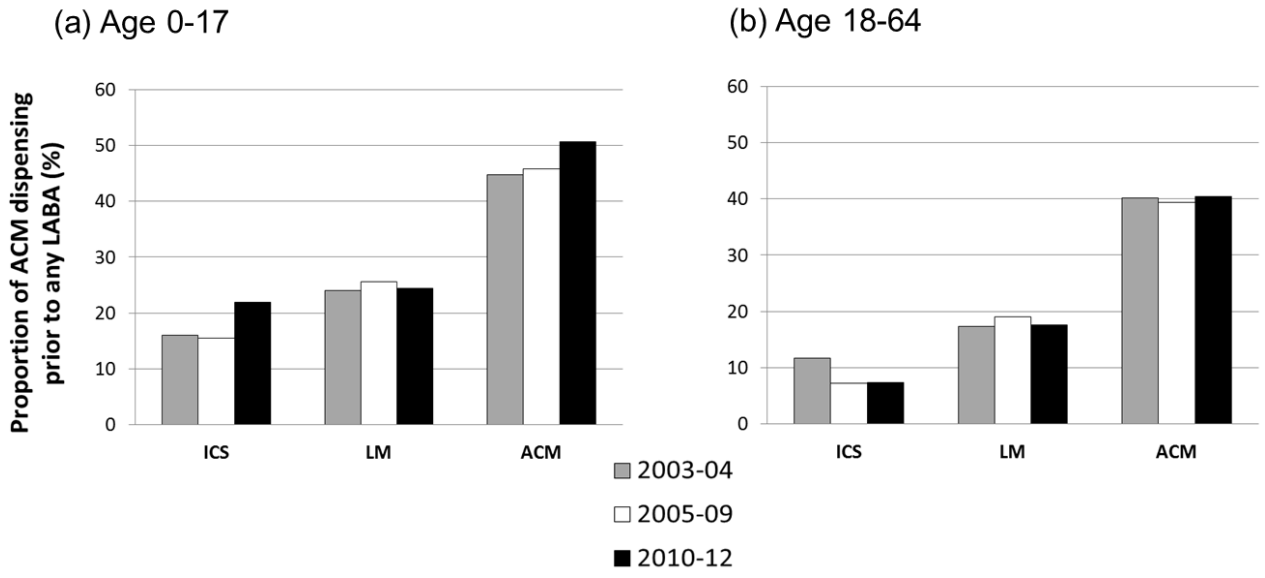
* In the child population, the numerator is those who initiated a SI-LABA with or without concurrent dispensing of an ICS; whereas in the adult population, those who initiated SI-LABA and had a same day dispensing of an ACM were considered as using combination therapy, and therefore, were excluded from the numerator. The denominators were defined the same across the age groups, as anyone who initiated a LABA during the same half year period.

3.2.3 Prior ACM Dispensing

The proportion of patients with an asthma claim who were dispensed a non-LABA ACM in the 6 months before initiating a LABA was calculated for the three time periods of interest, in both children/adolescents (0-17 years old) and adults (18-64 years old). Figures 4a & 4b illustrate the proportion of asthma patients who were dispensed an ICS, LM, or any non-LABA ACM within 6 months before initiating a LABA in the three periods: 2003-04, 2005-09, and 2010-12. For children, there were only 15%, 15%, and 21% of patients dispensed an ICS during 1-180 days prior to the initiation of a LABA, for the three time periods, respectively (*p*-value <.001 for linear trend). Also, for the pediatric asthma patients, the proportions of any ACM dispensing in the six months before initiating a LABA increased from 45%, to 46%, to 50% (*p*-value <.001 for linear trend) (Figure 4a).

The results were different for the adults aged 18-64 years with a claim for asthma. The proportion of that subgroup that were dispensed an ICS in the six months before initiating a LABA decreased from 12% in 2003–2005, to 7% in the last two periods. In addition, there were no significant changes in the proportion of these adults getting an ACM dispensing prior to a LABA in the three time periods (40%, 39%, and 40%, respectively) (Figure 4b).

Figure 4. Proportion of asthma patients who were dispensed non-LABA asthma controller medications (ACM) 6 months before initiating a LABA during the three periods, 2003-04 in grey, 2005-09 in white, and 2010-12 in black; for (a) 0–17 years old and (b) 18–64 years old.



Abbreviations: LABA—long-acting beta2-adrenergic agonist(s); ICS—inhaled corticosteroid(s); LM—leukotriene modifier(s); ACM—long-term non-LABA asthma controller medication(s)

3.2.4 Incident LABA Dispensing in Patients with Poorly Controlled Asthma

Recommendation-II advised that LABAs only be used as additional therapy for asthma patients, who are taking, but are not adequately controlled on, a long-term ACM, such as an ICS. Only 36% of the LABA initiators younger than 18 years old were identified as having poorly controlled asthma prior to

starting a LABA in the 2003-4 and 2005-09 periods, but that increased to 40% in the 2010-12 period. In addition, only 34% of the LABA initiators ages 18-64 years old were identified as having poorly controlled asthma prior to starting a LABA in the 2003-4 period, but this proportion was closer to 31% in the 2005-9 and 2010-12 periods.

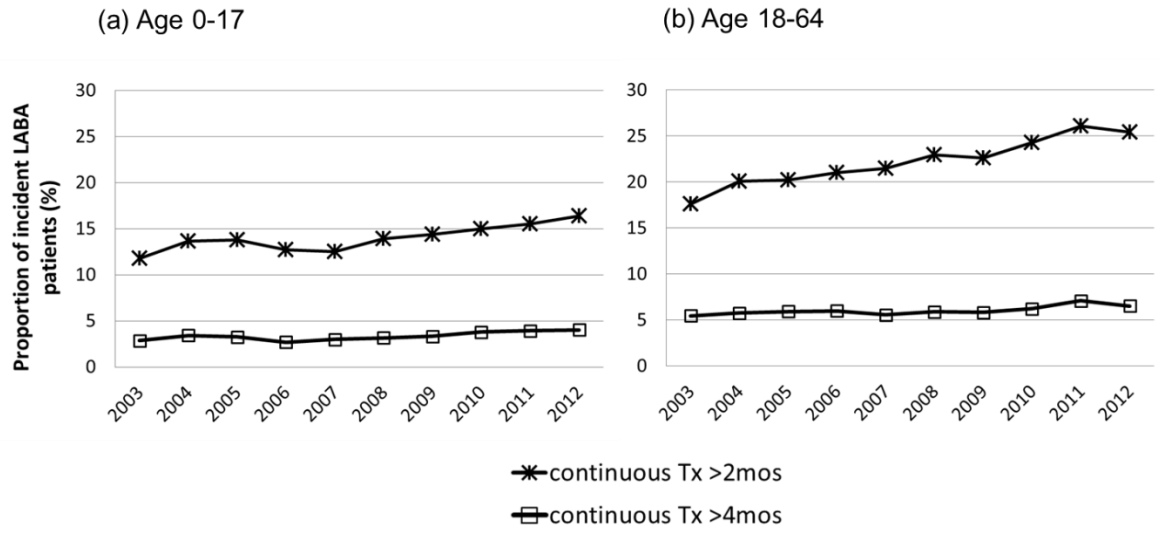
3.2.5 Duration of LABA Dispensing

On recommendation III—Step-down Strategy. Basic descriptive measures were also produced for the duration of continuous LABA treatment (after the index dispensing). On average, there were 2.6 (±3.2) LABA treatment episodes per patient; and the median was 1 episode (inter-quartiles: 1, 3 episodes), throughout the 10-year period. For the first treatment episode, the median for continuous days' supplies of LABA dispensing was 30 days consistently over the 2003-2012 time period for both the child and adult populations. Appendix C Table 2 shows the mean (standard deviation), and first and third quartiles of continuous days' supply of LABA dispensing over the 10-year period. The mean appears to have increased for both populations over the 2003-12 period.

Figure 5 illustrates, over the 2003-2012 period, the trends in the proportion of incident LABA patients in each year who had longer than 2 months or longer than 4 months of continuous days' supply of LABA dispensing. In children, the proportion of incident LABA users who had longer than 2 months continuous days' supply of a LABA increased from 11.8% in 2003 to 16.4% in 2012 (p-value <.001 for linear trend); whereas the proportions with longer than 4 months continuous days' supply of LABA dispensing were not as high over the 10-year study period, but still increased from 2.9% in 2003 to 4.0% in 2012, with some minor variations in between these years (See Figure 5a).

In adults aged 18-64 years, the proportion of incident LABA users who had longer than 2 months continuous days' supply of a LABA increased from 17.6% in 2003 to 25.4% in 2012 (p-value <.001 for linear trend); and the proportion increased from 5.4% in 2003 to 6.5% in 2012 for those with longer than a 4 month continuous supply of a LABA (Figure 5b).

Figure 5. Proportion of incident LABA patients who had longer than 2 months or longer than 4 months of continuous days' supply of LABA dispensing (continuous Tx, for 1st dispensing episode) over the study period, 2003-2012: (a) 0–17 years old and (b) 18–64 years old



4 DISCUSSION

The evidence from multiple data sources and analyses presented in section 3 above help form a picture of current use of LABA-containing products as well as some aspects of use of Breo® Ellipta®.

4.1 HOW LABA-CONTAINING PRODUCTS ARE BEING USED

There continues to be substantial use of LABAs in the US. In 2014, approximately 22.9 million prescriptions were dispensed through US outpatient retail pharmacies for selected SI and FDC-ICS/LABA-containing products combined, with the combination products representing approximately 97% of total prescriptions, and the SI-LABAs only 3%. In terms of patients, FDC-ICS/LABA products were dispensed to about 6 million patients annually, from 2009 through 2014. That figure remained relatively steady, while there was about a 35% decline over the same period in the comparatively small number of patients receiving a dispensed prescription for SI-LABA products. For the SI-LABAs, the declines were across all age groups. *Note: While these cross sectional estimates are national estimates, no statistical tests were performed to determine statistically significant changes over time or between products. Therefore, all changes over time or between products should be considered approximate, and some changes may be due to random error. Furthermore, these cross sectional analyses focus on only the outpatient retail pharmacies; therefore, these estimates may not apply to other settings of care such as mail-order/specialty setting in which LABA-containing products are used.* In addition, these patient estimates were based on cross-sectional data that cannot connect SI-LABA prescription recipients with other prior, concurrent or subsequent dispensings, so the data cannot be used to identify patients who received only a single ingredient LABA as opposed to a SI-LABA dispensed at around the same time as an ICS, LM, or any ACM product. The longitudinal data analyses, although not nationally representative (only captures 9% of the commercially-insured US population), can incorporate preceding or concomitant drug dispensing as well as diagnoses preceding an index drug dispensing, and thus complement the national data, which is why the longitudinal data analyses were included in this review.

In the cross-sectional data in 2014, adults represented about 92% of the patients receiving dispensed prescriptions for FDC-ICS/LABAs (for any indication) and 98% of those receiving SI-LABA dispensed prescriptions (for any indication). In the longitudinal data, looking over the 2003-12 period at patients with a claim for an asthma diagnosis who started on a LABA and were under 65 years old, approximately three-quarters were adults 18-64 years old, and one quarter was children and adolescents.

Among all the FDC-ICS/LABA products, the most used in 2014 (by 58% of FDC-ICS/LABA patients) was fluticasone-salmeterol. Among the SI-LABA products, SI-salmeterol and SI-formoterol were the most commonly used in 2014 (each by 36% of patients dispensed SI-LABAs).

Multiple times since 2003, FDA has communicated to healthcare professionals and the public information on risks associated with the use of LABA products and recommendations for their safe use. It is important for future FDA decisions on LABAs to try to ascertain if those recommendations are being followed or to what extent they are/not being followed. To review, the four recommendations are:[4, 5]

I. LABA products should not be used alone for the treatment of asthma;

II. A LABA product should be used as additional therapy only in patients who are not adequately controlled on an ACM, such as ICS;

III. Patients should commence step down therapy of a LABA once asthma control is achieved and maintained; and

IV. Specifically for pediatric and adolescent asthma patients who require the addition of a LABA to an ICS, they should use a FDC-ICS/LABA to ensure adherence with both medications.

On Recommendation I

The most encouraging news from this review is that the longitudinal IMS health care claims data showed that the proportion of patients starting single ingredient LABAs, as a share of all LABA initiators, declined significantly over the 2003-12 study period in both the <18 and 18-64 years old age groups. In addition, the estimates showing that after 2010 only a small share (<3%) of LABA initiators were SI-LABA initiators, may still be slightly overestimated. A new SI-LABA user was defined as having no SI-LABA prescription during the 6 months prior to the new LABA's dispensing (index) date, but some of these patients may have had SI-LABA treatment longer ago than 6 months. If the look back period were extended, the estimates might decline slightly.

On Recommendation II

The evidence on adherence to recommendation II (LABA only as add-on therapy) is not quite as encouraging. Even though prior ICS or other ACM dispensing before initiating the LABA increased in children, the overall proportions were not high (<51%) in children and lower (only 40%), and didn't increase, in adults age 18-64 years over the 2003-12 period. In particular, the data show a decrease in prior ICS dispensing before LABA initiation in these adult patients with a diagnostic claim for asthma.

Low prevalence of dispensing of ICS/ACM prior to LABA initiation may suggest patients were put on LABA without a trial of ICS/ACM. The reasons for the low prevalence of ACM use prior to the initiation of a LABA are not fully understood, but one reason may be the aggressive marketing of FDC-ICS/LABA products.[7] Detailing by pharmaceutical representatives and the broad availability of samples may have contributed to these results. Samples provided to patients would also not be included in any of the data analyzed in our review. Studies have shown that physicians are more likely to prescribe medications for which they have samples in their offices.[8, 9]

On Recommendation III

The claims data are not detailed enough to capture well the extent of adherence to the LABA therapy step down recommendation. For both children and adults, the proportion with longer than 2 months of first treatment episode continuous LABA dispensing increased over the 2003-12 period, but we cannot say why or if these reflect appropriate continuation of LABA therapy. Measuring the duration of LABA dispensing over time is a surrogate measure. For confirmation of appropriate step down therapy, one would need more granular clinical data to indicate that the LABA therapy had achieved control of the asthma symptoms and step down from LABA was intentionally undertaken, as opposed to any other reason (formulary change, patient experiencing side effects) for ending LABA dispensing.

On Recommendation IV

For children, the LABA add-on therapy guideline is stricter than for adults, so the estimates were calculated differently (see Note in Section 3.2.2.). Nevertheless, the results for children showed low proportions (<3%) of SI-initiators/all LABA initiators in the year 2011-12 period. The cross sectional data are consistent with the longitudinal data. The majority of LABA products in children were FDC-ICS/LABA compared to SI-LABA (Section 3.1). Nearly 468,000 pediatric patients received a prescription for an FDC-ICS/LABA product compared to only 3,500 pediatric patients who received a prescription for a SI-LABA in 2014.

These findings, both more and less favorable, from the longitudinal IMS health plan claims data analysis were largely supported by the results of a similar study in the Mini-Sentinel (MS) Distributed Database. The MS study involved 1.4 million child and adult patients with a diagnostic claims for asthma who started a LABA during Jan. 2005 through June 2011.[10] In the MS data, like in the IMS health plan claims data analysis, the results relevant to recommendation I, were favorable: SI-LABA initiation declined significantly from 14% in Jan. 2005 to 4% in June 2011, in asthma patients younger than 65 years old. For recommendation IV, a similar significant decrease in SI-LABA initiation was observed in children. Regarding recommendation II, the MS results, like in IMS, were not favorable: <50% of asthma patients had any evidence of receipt of an ACM within 90 days of the LABA index date, and no increase in trend was observed from 2005 to 2011. For recommendation III, in the MS data, also over 55% of patients discontinued a LABA at 30 days, and this first treatment episode of continuous LABA dispensing also increased after 2010. However, again those measures are too broad to discern appropriate step down therapy.

4.2 HOW BREO® ELLIPTA® IS BEING USED

Use of Breo® Ellipta®, with the approved indication for adults of long term control in COPD, represents only a small part of the combination LABA market – only 1% of dispensed FDC-ICS/LABA prescriptions in 2014. And only approximately 101,000 patients received dispensed Breo® Ellipta® prescriptions from May 2013 through Dec. 2014, cumulative, with adult and pediatric patients accounting for 99% and 0.2% of total Breo® Ellipta® patients, respectively.

The National Prescription Audit data showed about 41% of the Breo® Ellipta® prescriptions were written by pulmonary disease specialists. From a limited sample of physician surveys (Encuity Research), the largest number of uses, and therefore most reliable estimates for the indication for use (diagnosis), were for the age 65 years+ group. For that group, an estimated 80% of the Breo® Ellipta® use mentions were coded as "Chronic airway obstruction". However, for drug use mentions in patients in the under age 65 groups, the diagnosis information dipped below the threshold (<100,000 mentions) for reliability, but still were reported as "Chronic airway obstruction" for 71% of the Breo® Ellipta® use mentions in patients ages 45-64 years, and as "Obstructive chronic bronchitis" for 48% of Breo® Ellipta® use mentions in patients ages 18-44 years. No indications were captured for the pediatric age group of 0-17 years. Though limited, the available estimates, along with the very small share of Breo® Ellipta® use in pediatric age groups point favorably to little possible off-label use (in children or for non-COPD) of Breo® Ellipta®.

5 CONCLUSIONS

The data in this review were not intended to provide any direct evidence on the efficacy or safety of Breo® Ellipta® for asthma treatment in age 12 years+ asthma patients. However, these drug utilization

data provide some background information on current use of LABA products in the US. The results suggest both favorable and unfavorable adherence to some of FDA's recommendations on the safe use of LABA products. The favorable news is the evidence that SI-LABA use as a proportion of any LABA use has declined in both adults and children. The unfavorable news is prior use of ACMs before LABA initiation was not found to be highly prevalent, and while it increased in children it did not increase in adults. What is still largely unknown is the extent of adherence to the LABA therapy step down recommendation. For evidence on that aspect of current LABA prescribing practice, more granular clinical data are needed.

Therefore, the entrance of another combination LABA product to the asthma drug market would be into a context of largely unknown adherence to the LABA step down recommendation. Also it would be expanding the FDC-ICS/LABA product options for use in the age 12 years+ pediatric asthma population. If Breo® Ellipta® is approved for asthma treatment, continued periodic post-marketing surveillance for evidence of off-label (in age groups outside those labeled) and other inappropriate uses of Breo® Ellipta® should be conducted.

6 APPENDIX A: DATABASE DESCRIPTIONS AND LIMITATIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, National Prescription Audit

The National Prescription Audit (NPA™) measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures both what is prescribed by the physician and what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies.

NPA™ receives over 2.7 billion prescription claims per year, captured from a sample of the universe of approximately 57,000 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 86% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

IMS Health, Vector One®: Total Patient Tracker (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

Encuity Research, LLC., TreatmentAnswers™ with Pain Panel

Encuity Research, LLC., TreatmentAnswers™ and TreatmentAnswers™ with Pain Panel is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from over 3,200 office-based physicians representing 30 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends

of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The Pain Panel supplement surveys over 115 pain specialists physicians each month. With the inclusion of visits to pain specialists, this will allow additional insight into the pain market. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Indications for use were obtained using a monthly survey of 3,200 office-based physicians. Although these data are helpful to understand how drug products are prescribed by physicians, the small sample size and the relatively low usage of these products limits the ability to identify trends in the data. In general, physician survey data are best used to identify the typical uses for the products in clinical practice. Results should not be overstated when nationally projected estimates of annual uses or mentions fall below 100,000 as the sample size is very small with correspondingly large confidence intervals.

IMS Health, LifeLink Health Plan Claims Database

The IMS Health Plan Claims Database is a health plan claims database representing approximately 101 managed care plans and covering approximately 65.8 million de-identified patients. The medical claims are captured from doctor's offices, retail and mail order pharmacies, patient visits to specialists and hospitalizations including diagnoses, ER visits, office visits, home care, diagnostic tests, procedures and injections. The data are not nationally projected; however, it represents approximately 9% of the United States commercially insured population based on year 2007 United States Census.

7 APPENDIX B: TABLES FOR CROSS-SECTIONAL DRUG UTILIZATION

Table 3.1.1. Nationally estimates of packages of selected products containing a long-acting beta$_2$-adrenoceptor agonist sold from manufacturers to U.S. retail* and non-retail channels of distribution, years 2009 through 2014**

	Year 2009		Year 2010		Year 2011		Year 2012		Year 2013		Year 2014	
	Units***	%	Units	%	Units	%	Units	%	Units	%	Units	%
Total LABA Sales Market	**35,135,770**	***100.0%***	**36,955,457**	***100.0%***	**36,220,397**	***100.0%***	**34,253,452**	***100.0%***	**35,143,706**	***100.0%***	**35,027,571**	***100.0%***
LABAs Administered via an Inhaler	**32,599,968**	***92.8%***	**34,215,711**	***92.6%***	**33,981,449**	***93.8%***	**32,931,742**	***96.1%***	**33,817,366**	***96.2%***	**33,706,479**	***96.2%***
Fluticasone-Salmeterol	27,824,971	*85.4%*	27,871,553	*81.5%*	26,268,088	*77.3%*	24,654,077	*74.9%*	23,812,716	*70.4%*	20,374,672	*60.4%*
Retail	18,064,620	*64.9%*	17,613,244	*63.2%*	16,338,332	*62.2%*	15,612,879	*63.3%*	15,312,572	*64.3%*	13,592,795	*66.7%*
Non-Retail	4,855,175	*17.5%*	4,851,951	*17.4%*	4,882,709	*18.6%*	4,721,179	*19.2%*	4,620,583	*19.4%*	4,198,666	*20.6%*
Mail-Order/Specialty	4,905,176	*17.6%*	5,406,358	*19.4%*	5,047,047	*19.2%*	4,320,019	*17.5%*	3,879,561	*16.3%*	2,583,211	*12.7%*
Budesonide-Formoterol	3,739,142	*11.5%*	5,448,088	*15.9%*	6,385,673	*18.8%*	6,654,558	*20.2%*	7,828,574	*23.1%*	9,998,054	*29.7%*
Retail	2,649,606	*70.9%*	3,722,133	*68.3%*	4,061,231	*63.6%*	4,546,061	*68.3%*	5,467,103	*69.8%*	6,997,078	*70.0%*
Non-Retail	564,799	*15.1%*	850,287	*15.6%*	1,072,393	*16.8%*	1,121,524	*16.9%*	1,315,869	*16.8%*	1,604,863	*16.1%*
Mail-Order/Specialty	524,737	*14.0%*	875,668	*16.1%*	1,252,049	*19.6%*	986,973	*14.8%*	1,045,602	*13.4%*	1,396,113	*14.0%*
Formoterol-Mometasone	--	--	46,102	*0.1%*	550,248	*1.6%*	1,063,213	*3.2%*	1,644,226	*4.9%*	2,626,911	*7.8%*
Retail	--	--	38,558	*83.6%*	332,107	*60.4%*	796,876	*75.0%*	1,208,658	*73.5%*	1,858,324	*70.7%*
Mail-Order/Specialty	--	--	5,882	*12.8%*	132,465	*24.1%*	159,074	*15.0%*	229,723	*14.0%*	440,210	*16.8%*
Non-Retail	--	--	1,662	*3.6%*	85,676	*15.6%*	107,263	*10.1%*	205,845	*12.5%*	328,377	*12.5%*
Salmeterol	1,035,855	*3.2%*	849,968	*2.5%*	777,440	*2.3%*	547,044	*1.7%*	481,029	*1.4%*	411,900	*1.2%*
Retail	519,166	*50.1%*	428,162	*50.4%*	361,040	*46.4%*	313,860	*57.4%*	282,886	*58.8%*	244,885	*59.5%*
Mail-Order/Specialty	326,031	*31.5%*	272,712	*32.1%*	254,346	*32.7%*	141,932	*26.0%*	116,720	*24.3%*	93,436	*22.7%*
Non-Retail	190,658	*18.4%*	149,094	*17.5%*	162,054	*20.8%*	91,252	*16.7%*	81,423	*16.9%*	73,579	*17.9%*
Fluticasone-Vilanterol (Breo® Ellipta®)	--	--	--	--	--	--	--	--	16,536	*<0.1%*	262,544	*0.8%*
Retail	--	--	--	--	--	--	--	--	15,487	*93.7%*	200,485	*76.4%*
Non-Retail	--	--	--	--	--	--	--	--	472	*2.9%*	31,672	*12.1%*
Mail-Order/Specialty	--	--	--	--	--	--	--	--	577	*3.5%*	30,387	*11.6%*
Indacaterol	--	--	--	--	--	--	12,850	*<0.1%*	34,285	*0.1%*	32,398	*0.1%*
Retail	--	--	--	--	--	--	9,637	*75.0%*	25,320	*73.9%*	22,669	*70.0%*
Mail-Order/Specialty	--	--	--	--	--	--	2,770	*21.6%*	7,462	*21.8%*	7,842	*24.2%*
Non-Retail	--	--	--	--	--	--	443	*3.5%*	1,503	*4.4%*	1,887	*5.8%*
LABAs Administered via a Nebulizer	2,535,802	*7.2%*	2,739,746	*7.4%*	2,238,948	*6.2%*	1,321,710	*3.9%*	1,326,340	*3.8%*	1,321,092	*3.8%*
Arformoterol	333,873	*13.2%*	454,661	*16.6%*	551,131	*24.6%*	653,932	*49.5%*	700,547	*52.8%*	739,755	*56.0%*
Mail-Order/Specialty	141,192	*42.3%*	222,287	*48.9%*	286,229	*51.9%*	354,515	*54.2%*	364,628	*52.1%*	376,678	*50.9%*
Retail	134,974	*40.4%*	156,426	*34.4%*	178,095	*32.3%*	199,485	*30.5%*	221,608	*31.6%*	225,873	*30.5%*
Non-Retail	57,707	*17.3%*	75,948	*16.7%*	86,807	*15.8%*	99,932	*15.3%*	114,311	*16.3%*	137,204	*18.6%*
Formoterol	2,201,929	*86.8%*	2,285,085	*83.4%*	1,687,817	*75.4%*	667,778	*50.5%*	625,793	*47.2%*	581,337	*44.0%*
Retail	523,037	*23.8%*	450,146	*19.7%*	310,039	*18.4%*	306,378	*45.9%*	293,017	*46.8%*	273,258	*47.0%*
Mail-Order/Specialty	1,286,569	*58.4%*	1,425,538	*62.4%*	1,093,043	*64.8%*	246,097	*36.9%*	226,783	*36.2%*	201,996	*34.8%*
Non-Retail	392,323	*17.8%*	409,401	*17.9%*	284,735	*16.9%*	115,303	*17.3%*	105,993	*16.9%*	106,083	*18.3%*

Source: IMS Health, National Sales Perspectives™. Years 2009 through 2014. Data extracted February 2015. File: NSP 2014-2017 LABA AC channel 2-4-2015.xlsx

*Retail channels include chain, independent, foodstore, mail order, and mass merchandise pharmacies in the entire United States.

**Non-Retail channels include hospitals, long-term care facilities, clinics, home healthcare providers, and HMOs in the entire United States.

***Units refer to the number of packages of a product shipped in a unit. An example of a Unit is a package of salmeterol containing a teal green plastic inhaler with 60 blister doses or a package of arformoterol containing 30 unit-dose vials of medicine which is administered via a nebulizer.

Table 3.1.2. Nationally estimates of prescriptions dispensed for selected products containing a long-acting beta$_2$-adrenoceptor agonist (for any indication) from U.S. outpatient retail pharmacies, years 2009 through 2014

	Year 2009		Year 2010		Year 2011		Year 2012		Year 2013		Year 2014	
	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%	TRxs	%
Total LABA Prescriptions	**21,556,925**	***100.0%***	**22,255,907**	***100.0%***	**21,582,695**	***100.0%***	**21,505,994**	***100.0%***	**22,039,878**	***100.0%***	**22,859,459**	***100.0%***
Combination	20,510,789	*95.1%*	21,366,272	*96.0%*	20,820,576	*96.5%*	20,782,327	*96.6%*	21,337,694	*96.8%*	22,169,832	*97.0%*
Fluticasone-Salmeterol	17,914,862	*87.3%*	17,603,066	*82.4%*	16,357,360	*78.6%*	15,350,278	*73.9%*	14,657,576	*68.7%*	13,037,395	*58.8%*
Budesonide-Formoterol	2,595,927	*12.7%*	3,732,237	*17.5%*	4,109,350	*19.7%*	4,574,691	*22.0%*	5,368,616	*25.2%*	6,979,657	*31.5%*
Mometasone-Formoterol	--	--	30,969	*0.1%*	353,866	*1.7%*	857,358	*4.1%*	1,307,014	*6.1%*	1,936,489	*8.7%*
Fluticasone-Vilanterol (Breo® Ellipta®)	--	--	--	--	--	--	--	--	4,488	*<0.1%*	216,291	*1.0%*
Single-Ingredient	1,046,136	*4.9%*	889,635	*4.0%*	762,119	*3.5%*	723,667	*3.4%*	702,184	*3.2%*	689,627	*3.0%*
Formoterol	483,779	*46.2%*	403,240	*45.3%*	313,165	*41.1%*	289,056	*39.9%*	269,029	*38.3%*	259,873	*37.7%*
Salmeterol	472,362	*45.2%*	381,221	*42.9%*	323,889	*42.5%*	285,614	*39.5%*	256,638	*36.5%*	241,107	*35.0%*
Arformoterol	89,995	*8.6%*	105,174	*11.8%*	125,061	*16.4%*	140,974	*19.5%*	154,140	*22.0%*	167,011	*24.2%*
Indacaterol	--	--	--	--	4	*<0.1%*	8,023	*1.1%*	22,377	*3.2%*	21,636	*3.1%*

Source: IMS Health, National Prescription Audit™. Years 2009 through 2014. Data extracted February 2015. File: NPA 2014-2017 LABA AC combo SI 2-4-2015 xlsx

*LABA prescriptions were dispensed for any indication, and not limited to asthma or COPD.

Table 3.1.3. Nationally estimated number of patients receiving dispensed prescriptions for selected products containing a long-acting beta$_2$-adrenergic agonist (for any indication), stratified by patient age*, from U.S. outpatient retail pharmacies, years 2009 through 2014

	Year											
	2009		2010		2011		2012		2013		2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Total LABA Patients	**6,182,242**	***100.0%***	**6,536,278**	***100.0%***	**6,104,292**	***100.0%***	**6,014,285**	***100.0%***	**6,040,827**	***100.0%***	**6,228,293**	***100.0%***
Combination	5,965,555	*96.5%*	6,335,025	*96.9%*	5,944,933	*97.4%*	5,860,671	*97.4%*	5,891,863	*97.5%*	6,084,464	*97.7%*
0-17 years	673,897	*11.3%*	710,418	*11.2%*	600,483	*10.1%*	544,153	*9.3%*	501,479	*8.5%*	468,155	*7.7%*
0 - 3 years	12,325	*1.8%*	15,986	*2.3%*	14,921	*2.5%*	14,458	*2.7%*	14,123	*2.8%*	14,716	*3.1%*
4 - 11 years	309,636	*45.9%*	338,537	*47.7%*	281,757	*46.9%*	255,153	*46.9%*	232,471	*46.4%*	217,265	*46.4%*
12 - 17 years	370,196	*54.9%*	377,374	*53.1%*	323,006	*53.8%*	292,078	*53.7%*	270,769	*54.0%*	251,222	*53.7%*
18+ years	5,302,929	*88.9%*	5,626,384	*88.8%*	5,346,728	*89.9%*	5,318,835	*90.8%*	5,394,764	*91.6%*	5,608,802	*92.2%*
18 - 44 years	1,279,713	*24.1%*	1,437,552	*25.6%*	1,315,729	*24.6%*	1,244,371	*23.4%*	1,196,752	*22.2%*	1,205,999	*21.5%*
45 - 64 years	2,194,585	*41.4%*	2,350,266	*41.8%*	2,237,501	*41.8%*	2,199,281	*41.3%*	2,223,542	*41.2%*	2,335,692	*41.6%*
65+ years	1,874,493	*35.3%*	1,889,759	*33.6%*	1,847,377	*34.6%*	1,928,695	*36.3%*	2,029,441	*37.6%*	2,121,929	*37.8%*
Unknown Age	700	*<0.1%*	3,582	*0.1%*	1,127	*<0.1%*	73	*<0.1%*	1,594	*<0.1%*	44,660	*0.7%*
Single-Ingredient	272,196	*4.4%*	247,202	*3.8%*	199,302	*3.3%*	190,150	*3.2%*	184,371	*3.1%*	178,076	*2.9%*
0-17 years	12,397	*4.6%*	10,785	*4.4%*	6,166	*3.1%*	4,891	*2.6%*	4,011	*2.2%*	3,460	*1.9%*
0 - 3 years	1,723	*13.9%*	1,929	*17.9%*	1,105	*17.9%*	973	*19.9%*	882	*22.0%*	850	*24.6%*
4 - 11 years	5,288	*42.7%*	4,616	*42.8%*	2,577	*41.8%*	1,926	*39.4%*	1,547	*38.6%*	1,304	*37.7%*
12 - 17 years	5,747	*46.4%*	4,557	*42.3%*	2,643	*42.9%*	2,108	*43.1%*	1,688	*42.1%*	1,383	*40.0%*
18+ years	259,684	*95.4%*	236,278	*95.6%*	192,993	*96.8%*	185,240	*97.4%*	180,342	*97.8%*	174,191	*97.8%*
18 - 44 years	30,543	*11.8%*	26,708	*11.3%*	19,018	*9.9%*	16,664	*9.0%*	14,915	*8.3%*	13,941	*8.0%*
45 - 64 years	94,997	*36.6%*	87,428	*37.0%*	69,321	*35.9%*	64,060	*34.6%*	60,569	*33.6%*	57,455	*33.0%*
65+ years	136,631	*52.6%*	124,377	*52.6%*	106,667	*55.3%*	106,341	*57.4%*	106,565	*59.1%*	104,172	*59.8%*
Unknown Age	51	*<0.1%*	167	*0.1%*	30	*<0.1%*	6	*<0.1%*	74	*<0.1%*	1,616	*0.9%*

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2009 through 2014. Data extracted January 2015. Files: TPT 2014-2017 total breo ellipta and LABAs age 1-20-2015.xls; TPT 2014-2017 LABAs combo age 1-20-2015.xls; TPT 2014-2017 LABAs SI age 1-20-2015.xls; TPT 2014-2017 LABAs SI age 0-17 1-28-2015.xls; TPT 2014-2017 LABAs combo age 0-17 1-20-2015.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands or time periods will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

***Patients received a dispensed prescription for a LABA for any indication, and not limited to asthma or COPD.

Table 3.1.4. Nationally estimated number of patients receiving dispensed prescriptions for selected products containing a long-acting beta$_2$-adrenergic agonist (for any indication), stratified by product and patient age*, from U.S. outpatient retail pharmacies, years 2009 through 2014

	Year											
	2009		2010		2011		2012		2013		2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Total LABA Patients	**6,182,242**	***100.0%***	**6,536,278**	***100.0%***	**6,104,292**	***100.0%***	**6,014,285**	***100.0%***	**6,040,827**	***100.0%***	**6,228,293**	***100.0%***
Combination LABAs	5,965,555	*96.5%*	6,335,025	*96.9%*	5,944,933	*97.4%*	5,860,671	*97.4%*	5,891,863	*97.5%*	6,084,464	*97.7%*
Fluticasone-Salmeterol	5,099,946	*85.5%*	5,151,090	*81.3%*	4,588,217	*77.2%*	4,241,713	*72.4%*	3,968,242	*67.4%*	3,553,813	*58.4%*
0 - 3 years	9,055	*0.2%*	11,578	*0.2%*	11,042	*0.2%*	10,047	*0.2%*	7,464	*0.2%*	6,722	*0.2%*
4 - 11 years	269,950	*5.3%*	286,925	*5.6%*	231,294	*5.0%*	198,374	*4.7%*	158,931	*4.0%*	125,669	*3.5%*
12 - 17 years	323,220	*6.3%*	320,998	*6.2%*	262,706	*5.7%*	222,008	*5.2%*	186,401	*4.7%*	147,668	*4.2%*
18 - 44 years	1,087,108	*21.3%*	1,161,919	*22.6%*	1,007,810	*22.0%*	889,010	*21.0%*	793,096	*20.0%*	687,578	*19.3%*
45 - 64 years	1,869,889	*36.7%*	1,894,275	*36.8%*	1,705,188	*37.2%*	1,569,136	*37.0%*	1,478,694	*37.3%*	1,334,365	*37.5%*
65+ years	1,606,868	*31.5%*	1,535,647	*29.8%*	1,428,442	*31.1%*	1,406,276	*33.2%*	1,394,004	*35.1%*	1,286,574	*36.2%*
Unknown Age	621	*<0.1%*	2,808	*0.1%*	886	*<0.1%*	51	*<0.1%*	1,061	*<0.1%*	25,441	*0.7%*
Budesonide-Formoterol	997,888	*16.7%*	1,300,187	*20.5%*	1,319,293	*22.2%*	1,408,653	*24.0%*	1,636,360	*27.8%*	2,060,648	*33.9%*
0 - 3 years	3,433	*0.3%*	4,567	*0.4%*	3,518	*0.3%*	3,430	*0.2%*	5,136	*0.3%*	6,032	*0.3%*
4 - 11 years	44,008	*4.4%*	55,863	*4.3%*	47,369	*3.6%*	44,986	*3.2%*	56,910	*3.5%*	64,960	*3.2%*
12 - 17 years	52,795	*5.3%*	60,422	*4.6%*	53,864	*4.1%*	51,985	*3.7%*	61,206	*3.7%*	70,859	*3.4%*
18 - 44 years	215,549	*21.6%*	294,626	*22.7%*	282,927	*21.4%*	280,939	*19.9%*	312,088	*19.1%*	390,084	*18.9%*
45 - 64 years	376,511	*37.7%*	500,921	*38.5%*	515,187	*39.1%*	545,731	*38.7%*	632,189	*38.6%*	821,258	*39.9%*
65+ years	313,631	*31.4%*	396,429	*30.5%*	430,588	*32.6%*	495,834	*35.2%*	584,651	*35.7%*	722,300	*35.1%*
Unknown Age	89	*<0.1%*	833	*0.1%*	227	*<0.1%*	17	*<0.1%*	466	*<0.1%*	15,166	*0.7%*
Mometasone-Formoterol	--	--	22,756	*0.4%*	191,684	*3.2%*	388,622	*6.6%*	515,887	*8.8%*	702,296	*11.5%*
0 - 3 years	--	--	81	*0.4%*	729	*0.4%*	1,517	*0.4%*	2,100	*0.4%*	2,754	*0.4%*
4 - 11 years	--	--	1,170	*5.1%*	9,763	*5.1%*	20,061	*5.2%*	27,630	*5.4%*	37,620	*5.4%*
12 - 17 years	--	--	1,663	*7.3%*	12,992	*6.8%*	25,511	*6.6%*	33,061	*6.4%*	43,193	*6.2%*
18 - 44 years	--	--	6,471	*28.4%*	53,176	*27.7%*	105,582	*27.2%*	131,279	*25.4%*	176,518	*25.1%*
45 - 64 years	--	--	9,344	*41.1%*	78,741	*41.1%*	153,178	*39.4%*	201,527	*39.1%*	279,482	*39.8%*
65+ years	--	--	4,054	*17.8%*	37,553	*19.6%*	86,679	*22.3%*	125,991	*24.4%*	170,051	*24.2%*
Unknown Age	--	--	7	*<0.1%*	16	*<0.1%*	7	*<0.1%*	81	*<0.1%*	4,209	*0.6%*
Fluticasone-Vilanterol (Breo® Ellipta®)	--	--	--	--	--	--	--	--	4,330	*0.1%*	98,229	*1.6%*
0 - 3 years	--	--	--	--	--	--	--	--	--	--	7	*<0.1%*
4 - 11 years	--	--	--	--	--	--	--	--	4	*0.1%*	14	*<0.1%*
12 - 17 years	--	--	--	--	--	--	--	--	13	*0.3%*	185	*0.2%*
18 - 44 years	--	--	--	--	--	--	--	--	386	*8.9%*	6,697	*6.8%*
45 - 64 years	--	--	--	--	--	--	--	--	1,713	*39.6%*	36,291	*36.9%*
65+ years	--	--	--	--	--	--	--	--	2,220	*51.3%*	55,041	*56.0%*
Unknown Age	--	--	--	--	--	--	--	--	--	--	715	*0.7%*
Single-Ingredient LABAs	272,196	*4.4%*	247,202	*3.8%*	199,302	*3.3%*	190,150	*3.2%*	184,371	*3.1%*	178,076	*2.9%*
Salmeterol	118,746	*43.6%*	101,148	*40.9%*	84,731	*42.5%*	71,544	*37.6%*	65,269	*35.4%*	63,263	*35.5%*
0 - 3 years	42	*<0.1%*	28	*<0.1%*	29	*<0.1%*	14	*<0.1%*	25	*<0.1%*	7	*<0.1%*
4 - 11 years	1,018	*0.9%*	950	*0.9%*	623	*0.7%*	481	*0.7%*	417	*0.6%*	338	*0.5%*
12 - 17 years	2,045	*1.7%*	1,768	*1.7%*	1,191	*1.4%*	957	*1.3%*	717	*1.1%*	621	*1.0%*
18 - 44 years	17,385	*14.6%*	15,369	*15.2%*	11,669	*13.8%*	9,578	*13.4%*	8,379	*12.8%*	8,139	*12.9%*
45 - 64 years	48,064	*40.5%*	42,650	*42.2%*	35,611	*42.0%*	30,136	*42.1%*	27,559	*42.2%*	26,735	*42.3%*
65+ years	51,595	*43.5%*	41,542	*41.1%*	36,706	*43.3%*	31,260	*43.7%*	29,041	*44.5%*	28,029	*44.3%*
Unknown Age	14	*<0.1%*	71	*0.1%*	9	*<0.1%*	--	--	26	*<0.1%*	514	*0.8%*
Formoterol	128,584	*47.2%*	113,722	*46.0%*	80,478	*40.4%*	72,875	*38.3%*	67,157	*36.4%*	63,148	*35.5%*
0 - 3 years	1,655	*1.3%*	1,861	*1.6%*	1,032	*1.3%*	909	*1.2%*	808	*1.2%*	783	*1.2%*
4 - 11 years	4,161	*3.2%*	3,493	*3.1%*	1,834	*2.3%*	1,360	*1.9%*	1,056	*1.6%*	915	*1.4%*
12 - 17 years	3,637	*2.8%*	2,736	*2.4%*	1,416	*1.8%*	1,087	*1.5%*	908	*1.4%*	699	*1.1%*
18 - 44 years	12,046	*9.4%*	9,911	*8.7%*	6,148	*7.6%*	5,519	*7.6%*	4,767	*7.1%*	4,142	*6.6%*
45 - 64 years	40,559	*31.5%*	36,732	*32.3%*	25,713	*32.0%*	23,132	*31.7%*	20,815	*31.0%*	19,017	*30.1%*
65+ years	67,650	*52.6%*	60,156	*52.9%*	45,170	*56.1%*	41,751	*57.3%*	39,518	*58.8%*	38,044	*60.2%*
Unknown Age	37	*<0.1%*	83	*0.1%*	7	*<0.1%*	2	*<0.1%*	27	*<0.1%*	569	*0.9%*
Arformoterol	28,452	*10.5%*	36,191	*14.6%*	40,042	*20.1%*	45,759	*24.1%*	48,585	*26.4%*	49,524	*27.8%*
0 - 3 years	31	*0.1%*	46	*0.1%*	61	*0.2%*	63	*0.1%*	57	*0.1%*	66	*0.1%*
4 - 11 years	134	*0.5%*	179	*0.5%*	125	*0.3%*	89	*0.2%*	71	*0.1%*	47	*0.1%*
12 - 17 years	88	*0.3%*	77	*0.2%*	60	*0.1%*	78	*0.2%*	70	*0.1%*	67	*0.1%*
18 - 44 years	1,387	*4.9%*	1,651	*4.6%*	1,440	*3.6%*	1,637	*3.6%*	1,701	*3.5%*	1,656	*3.3%*
45 - 64 years	7,552	*26.5%*	9,205	*25.4%*	9,862	*24.6%*	10,866	*23.7%*	11,111	*22.9%*	11,232	*22.7%*
65+ years	19,404	*68.2%*	25,114	*69.4%*	28,608	*71.4%*	33,228	*72.6%*	35,802	*73.7%*	36,435	*73.6%*
Unknown Age	3	*<0.1%*	13	*<0.1%*	10	*<0.1%*	5	*<0.1%*	22	*<0.1%*	511	*1.0%*
Indacaterol	--	--	--	--	--	--	3,244	*1.7%*	6,610	*3.6%*	4,919	*2.8%*
4 - 11 years	--	--	--	--	--	--	3	*0.1%*	--	--	8	*0.2%*
12 - 17 years	--	--	--	--	--	--	2	*0.1%*	12	*0.2%*	8	*0.2%*
18 - 44 years	--	--	--	--	--	--	105	*3.2%*	222	*3.4%*	118	*2.4%*
45 - 64 years	--	--	--	--	--	--	1,052	*32.4%*	2,099	*31.8%*	1,438	*29.2%*
65+ years	--	--	--	--	--	--	2,089	*64.4%*	4,344	*65.7%*	3,406	*69.2%*
Unknown Age	--	--	--	--	--	--	--	--	2	*<0.1%*	31	*0.6%*

Source: IMS Health, Vector One®: Total Patient Tracker. Years 2009 through 2014. Data extracted January 2015. Files: TPT 2014-2017 total breo ellipta and LABAs age 1-20-2015.xls; TPT 2014-2017 LABAs combo age 1-20-2015.xls; TPT 2014-2017 LABAs SI age 1-20-2015.xls; TPT 2014-2017 arformoterol age 1-20-2015.xls; TPT 2014-2017 budesonide-formoterol age 1-20-2015 xls; TPT 2014-2017 fluticasone-vilanterol age 1-20-2015 xls; TPT 2014-2017 formoterol age 1-20-2015.xls; TPT 2014-2017 indacaterol age 1-20-2015.xls; TPT 2014-2017 mometasone-formoterol age 1-20-2015.xls; TPT 2014-2017 salmeterol age 1-20-2015.xls; TPT 2014-2017 salmeterol-fluticasone age 1-20-2015.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands, products, or time periods will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

***Patients received a dispensed prescription for a LABA for any indication, and not limited to asthma or COPD.

Table 3.1.5. Nationally estimated number of patients receiving dispensed prescriptions for Breo® Ellipta® (for any indication), stratified by patient age*, from U.S. outpatient retail pharmacies, cumulative May 2013 through December 2014

	Cumulative 5/2013-12/2014	
	N	%
Total Breo® Ellipta®	**100,965**	***100.0%***
0-17 years	222	*0.2%*
0 - 3 years	7	*3.4%*
4 - 11 years	18	*8.1%*
12 - 17 years	198	*89.5%*
18+ years	100,324	*99.4%*
18 - 44 years	6,989	*7.0%*
45 - 64 years	37,398	*37.3%*
65+ years	56,382	*56.2%*
Unknown Age	715	*0.7%*

Source: IMS Health, Vector One®: Total Patient Tracker. May 2013 through December 2014. Data extracted January and February 2015. File: TPT 2014-2017 fluticasone-vilanterol age aggregate 1-20-2015.xls; TPT 2014-2017 fluticasone-vilanterol 0-17 age aggregate 2-10-2015.xls

*Patient age groups are inclusive of all patients up to the day before their next birthday. For example, patients aged 0 - 16 years includes patients aged 16 years and 11 months.

**Summing patients across patient age bands will result in double counting and overestimates of patient counts. Moreover, the sum of the percentages will be greater than 100% because patients are double counted across age bands.

***Patients received a Breo® Ellipta® prescription for any indication, and not limited to asthma or COPD.

Table 3.1.6. Nationally estimated number of prescriptions dispensed for Breo® Ellipta®, stratified by top 10 prescriber specialties, from U.S. outpatient retail pharmacies, cumulative May 2013 through December 2014

	Cumulative 5/2013-12/2014	
	TRxs	%
Total Breo® Ellipta® Prescriptions	**220,779**	***100.0%***
Pulmonary Diseases	90,162	*40.8%*
Family Practice/General Practice/Doctor of Osteopathy	55,187	*25.0%*
Internal Medicine	38,860	*17.6%*
Nurse Practitioner	14,502	*6.6%*
Physician Assistant	7,680	*3.5%*
Unspecified	3,141	*1.4%*
Allergy/Immunology	2,604	*1.2%*
Critical Care Medicine	1,787	*0.8%*
Cardiology	1,671	*0.8%*
Geriatrics	1,071	*0.5%*
Others	4,114	*1.9%*

Source: IMS Health, National Prescription Audit™. May 2013 through December 2014. Data extracted February 2015. Files: NPA 2014-2017 Breo Ellipta AC top 10 MD 2-4-2015.xlsx; NPA 2014-2017 Breo Ellipta AC total MD 2-4-2015.xlsx

Table 3.1.7. Diagnoses associated with the use of Breo® Ellipta®, stratified by patient age, as reported from U.S. office-based physician practices, cumulative May 2013 through December 2014

	Cumulative 5/2013-12/2014		
	Uses	95% CI	%
Total Breo® Ellipta® Uses	**362,000**	**(267,000 - 457,000)**	***100.0%***
18-44 years	32,000	(4,000 - 61,000)	*8.9%*
4912 OBSTRUCT CHR BRONCHITIS	15,000	(<500 - 35,000)	*47.8%*
7860 DYSPNEA/RESPIRATORY ABN	10,000	(<500 - 25,000)	*29.6%*
4960 CHR AIRWAY OBSTRUCT NEC	7,000	(<500 - 21,000)	*22.6%*
45-64 years	87,000	(40,000 - 133,000)	*24.0%*
4960 CHR AIRWAY OBSTRUCT NEC	61,000	(22,000 - 100,000)	*70.5%*
4939 ASTHMA NOS	19,000	(<500 - 41,000)	*21.8%*
4912 OBSTRUCT CHR BRONCHITIS	7,000	(<500 - 20,000)	*7.7%*
65+ years	212,000	(139,000 - 285,000)	*58.7%*
4960 CHR AIRWAY OBSTRUCT NEC	171,000	(105,000 - 236,000)	*80.3%*
4912 OBSTRUCT CHR BRONCHITIS	27,000	(1,000 - 54,000)	*12.9%*
4928 EMPHYSEMA NEC	8,000	(<500 - 22,000)	*3.7%*
4939 ASTHMA NOS	7,000	(<500 - 19,000)	*3.1%*
Unknown Age	30,000	(3,000 - 58,000)	*8.4%*
4928 EMPHYSEMA NEC	30,000	(3,000 - 58,000)	*100.0%*

Source: Encuity Research, LLC., TreatmentAnswers™. May 2013 through December 2014. Data extracted February 2015. File: PDDA_2014-2017_breo_ellipta_AC_age_dx4_2-4-2015.xls

*Diagnoses associated with Breo® Ellipta® use in pediatric population aged 0-17 years were not reported in the database.

8 APPENDIX C: TABLES AND FIGURES FOR LONGITUDINAL DRUG UTILIZATION

Table 1. The FDA Drug Safety Communication (DSC), 06/02/2010.[4] These new recommendations only apply to the use of LABAs in the treatment of asthma. To ensure the safe use of LABA products:

- (Item 1) Use of a LABA alone without use of a ACM, such as an ICS, is contraindicated (absolutely advised against).
- (Item 2) LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose ICS. LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a ACM.
- (Item 3) Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA).
- (Item 4) Pediatric and adolescent patients who require the addition of a LABA to an ICS should use a combination product containing both an ICS and a LABA.

Table 2. The mean (SD) and quartiles (Q1, Q3) of continuous days' supply of LABA dispensing (duration of the 1st dispensing episode) for child and adult populations, over 2003-2012

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
0-17 Years Old, Days Supply										
Mean (SD)	39 (29)	41 (31)	41 (31)	40 (29)	40 (30)	41 (31)	42 (32)	43 (33)	43 (34)	44 (34)
Q1, Q3	30, 30	30, 30	30, 30	30, 30	30, 30	30, 30	30, 30	30, 30	30, 30	30, 30
18-64 Years Old, Days Supply										
Mean (SD)	45 (38)	47 (40)	48 (41)	49 (41)	48 (40)	50 (42)	50 (41)	51 (42)	53 (44)	52 (43)
Q1, Q3	30, 30	30, 30	30, 34	30, 49	30, 51	30, 58	30, 58	30, 60	30, 64	30, 62

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