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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 1, 2013
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 204-275/SN00
Applicant	GlaxoSmithKline (GSK)
Date of Submission	July 12, 2012
PDUFA Goal Date	May 12, 2013
Proprietary Name / Established (USAN) names	Breo Ellipta/fluticasone furoate and vilanterol inhalation powder
Dosage forms / Strength	Fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder
Proposed Indication(s)	1. Long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) 2. Reduction of COPD exacerbations
Recommended:	Approval

1. Introduction

GlaxoSmithKline (GSK) submitted a 505(b)(1) New Drug Application (NDA) 204-275 on July 12, 2012, for fluticasone furoate and vilanterol inhalation powder at a dose of 100/25 mcg once daily, proposed for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Fluticasone furoate/vilanterol (FF/VI) is a new combination inhalation product comprised of an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA). Neither component is currently marketed as a single-ingredient inhalation product. FF, the ICS component, is available as an intranasal formulation for the treatment of allergic rhinitis (Veramyst Nasal Spray). VI, the LABA component, is a new molecular entity. FF/VI is supplied as a dry powder inhalation formulation administered by the novel Ellipta inhaler device.

To support the 100/25 mcg once daily dose for the proposed indications, GSK conducted a clinical program that included dose-ranging trials for the individual ICS and LABA components in asthma and COPD patients, two Phase 3 efficacy and safety trials to support the bronchodilation claim, and two additional Phase 3 trials to support the COPD exacerbation claim. 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 corticosteroids. While there are distinct clinical differences between asthma and COPD, the similarities between these two obstructive lung conditions have been the basis for

extrapolation of dose selection of other ICS/LABA products from asthma to COPD in the past. Also, the LABA monotherapies, namely salmeterol and formoterol, were developed and marketed for use in COPD, prior to the development of the related ICS/LABA combination products in COPD. As a result, there was extensive clinical experience with the pharmacologic entities individually and in combination before the approval of earlier ICS/LABA products for COPD. Patients who required treatment in addition to a LABA were a natural patient population for the corresponding ICS/LABA product.

In contrast, the program for FF/VI has been conducted concurrently with the development of the individual monocomponents in both COPD and asthma, and GSK has informed the Agency that there are no plans to market VI monotherapy. In many respects, the development program for FF/VI is an umbrella program that encompasses the individual development programs for FF and VI and spans two disease indications. GSK was asked to provide data to support the following: 1) the nominal dose and dosing frequency for each of the components, including evidence of efficacy and safety for FF alone in asthma and VI alone in COPD; 2) data demonstrating the efficacy contribution of VI to the FF/VI combination; and 3) data demonstrating that FF/VI confers a treatment benefit over VI alone in COPD (the contribution of FF). Demonstration of an added benefit is a key requirement for the FF/VI application, particularly given the safety concerns associated with corticosteroids in as a drug class. These concerns include increased risks of pneumonia and bone disorders.

This memo provides an overview of the application, with emphases on the strength of the data to support the benefit of the FF/VI 100/25 combination over the VI component alone and the risk-benefit balance associated with the addition of an ICS. The memo also addresses the recommendations from each of the individual review disciplines. Of note, this memo was finalized prior to the Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting on the application, so this memo does not cover the entire review period. The recommendations made in the memo are conditional, pending feedback from the PADAC meeting.

2. Background

Several drug classes are available for the treatment of COPD. These include beta-adrenergic agonists, combination products containing long-acting beta-adrenergic agonists and corticosteroids, anticholinergic agents, combination products containing anticholinergic and beta-adrenergic agonists, methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. With the exception of methylxanthines and PDE4 inhibitors, these are all inhalation products.

LABAs currently marketed in the United States for the treatment of COPD include salmeterol, formoterol, arformoterol, and indacaterol. Arfomoterol and indacaterol are marketed as single-ingredient products, while salmeterol and formoterol are marketed individual and in combination with inhaled corticosteroids (fluticasone propionate and mometasone furoate, respectively). Salmeterol, formoterol, and arformoterol are dosed twice-daily and indacaterol is dosed once-daily. There are no ICS single-ingredient products approved for use in COPD,

as clinical studies to date have failed to demonstrate efficacy for ICS when used alone in COPD.

Currently, there are two other ICS/LABA combination products approved for the relief of airflow obstruction in patients with COPD: fluticasone propionate/salmeterol 250/50 mcg one inhalation twice daily (Advair Diskus) and budesonide/formoterol fumarate dihydrate 160/4.5 mcg two inhalations twice daily (Symbicort). Advair Diskus is also approved for the reduction of COPD exacerbations. Of note, the Advair development program evaluated a higher dose level, 500/50 mcg, in addition to the 250/50 mcg dose level. Both doses were efficacious in the treatment of lung obstruction and exacerbations, but an increased risk of pneumonia was observed with the 500/50 mcg dose.[1] As there was no clear efficacy advantage for the 500/50 mcg dose level over the 250/50 mcg dose level to offset an increased risk of pulmonary infections, only the 250/50 mcg dose level was approved. Presumably, the increased risk of pulmonary infection is attributable to the ICS component of the combination, and pneumonias are an adverse event of interest for other ICS-containing drug products.

As mentioned in the Introduction, 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 is impacted by safety concerns specific to each drug class. For LABAs, dose exploration is conducted in the context of safety concerns regarding severe asthma exacerbations and asthma-related deaths which have been associated with both short-acting and long-acting beta-2 adrenergic agonists.[2, 3, 4, 5, 6] The issue has been discussed at previous FDA Advisory Committee meetings[7] and in the literature,[8, 9, 10] and is the subject of a safe use strategy outlined by the Agency.[11] Controlled postmarketing trials for all LABAs approved for asthma in the US are ongoing to further assess the safety of LABAs when used in conjunction with ICS.[12] While the underlying pathophysiology for these asthma-related severe adverse events remains uncertain, studies suggest that these events may be dose-related[13]. As a result, a higher dose of inhaled formoterol was not approved in the US due to the occurrence of severe asthma-related adverse events[14]. Although the same risk in COPD has not been identified, the selection of an

[1] Advair Diskus prescribing information, GSK. Retrieved from http://us.gsk.com/products/assets/us_advair.pdf on February 7, 2013
[2] Benson RL, Perlman F. J Allergy 1948; 19:129-140.
[3] Lowell FC, Curry JJ, Schiller IW. N Eng J Med 1949; 240:45-51.
[4] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Thorax 1991; 46:105-111.
[5] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al. N Eng J Med 1992; 326:501-506.
[6] US Product Labels of salmeterol and formoterol containing products
[7] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[8] Martinez FD. New Eng J Med 2005; 353:2637-2639.
[9] Kramer JM. New Eng J Med 2009; 360:1952-1955.
[10] Drazen JM, O'Byrne PM. New Eng J Med 2009; 360:1671-1672.
[11] Chowdhury BA, DalPan G. New Eng J Med 2010; 362:1169-1171.
[12] Chowdhury BA, Seymour SM, Levenson MS. New Eng J Med 2011;364:2473-5
[13] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Chest 2003; 124:70-74.
[14] Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. N Eng J Med 2011; 365:2247-2249.

appropriate dose is a priority for all LABAs, including VI. For this reason, FDA requested that GSK fully characterize the dose-response curve and optimal dosing frequency for VI in bronchodilator-sensitive patients, i.e., asthmatic patients, prior to conducting confirmatory trials in COPD.

For the ICS component, dose selection in COPD is challenging given the lack of efficacy for ICS monotherapy that has been observed to date. Therefore, FDA has requested that sponsors conduct dose-ranging for ICS products in asthmatic patients, since asthmatic patients are thought to be more steroid-responsive than COPD patients. This approach has limitations, however, as there may be fundamental differences in the underlying pathophysiology that factor in the effect of ICS in COPD. There are also concerns for dose-related, corticosteroid toxicities, such as an increased risk of pneumonia which has been associated specifically with ICS use in COPD. In addition, while spirometric endpoints like trough FEV1 have been used traditionally to assess the effect of ICS in both asthma and COPD, trough FEV1 remains a surrogate endpoint. Other efficacy variables, such as exacerbations, may be a more meaningful assessment of the added benefit of an ICS in an ICS/LABA combination, but the design and conduct of an exacerbation trial for the purposes of dose selection are challenging. For this reason, FDA has recommended that sponsors consider carrying forward more than one dose of ICS into confirmatory trials for COPD.

The issues surrounding the concurrent development of FF, VI, and FF/VI have been the subject of extensive discussion with GSK, as described in the next section. 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 FF alone in asthma and VI alone in COPD. These data were viewed as necessary for evaluating the FF/VI combination, in addition to data to support the efficacy of VI in the FF/VI combination and the benefit of FF/VI over VI alone (the relative contribution of FF).

Relevant Regulatory History for FF/VI

GSK studied several different doses and formulations for FF/VI in its COPD development program. As mentioned in the Introduction, the program for FF/VI was conducted concurrently with the development of the individual monocomponents in both COPD and asthma, so many of the regulatory interactions encompassed one or more components and the combination as well as both disease indications. The following timeline highlights the major discussions that occurred during clinical development:

- **January 31, 2007, Pre-IND meeting for VI:** The Division recommended that GSK characterize the VI monocomponent fully prior to developing the FF/VI combination.
- **April 29, 2008, Pre-IND meeting for FF/VI:** GSK questioned what data were needed to confirm a once-daily dosing interval for FF/VI. The Division recommended a comparison to a twice-daily dosing interval. The Division also noted that the program will need to demonstrate added benefit to justify multiple dose levels of the combination.
- **March 31, 2009, End-of-Phase-2 meeting for FF/VI (asthma program):** The Division reiterated the need for confirmation of the dosing interval prior to initiating Phase 3 trials.

- **June 17, 2009, End-of-Phase-2 meeting for FF/VI (COPD program):** The Division confirmed that the proposed doses of 50, 100, and 200 mcg FF QD appeared reasonable based on the Phase 2 results in asthma. The Division noted that it was difficult to confirm the selection of the 25 mcg nominal dose or QD dosing interval for VI based on the available information. The Division agreed that dosing interval studies in asthma could be extrapolated to COPD. The Division also stated that replicate clinical trials were expected to support a bronchodilator claim and an exacerbation claim.
- **March 24, 2010, Type C teleconference meeting (asthma and COPD program):** The Division confirmed that the proposed VI 25 mg QD dose appeared reasonable for further evaluation in Phase 3 trials.
- **June 30, 2010, Type C meeting (second End-of-Phase 2 meeting for asthma program):** The Division requested that relevant information from the asthma program, such as dose selection data for the FF and VI monocomponents, be included in the COPD NDA.
- **July 13, 2011, Pre-NDA meeting (COPD program):** GSK and the Division discussed the challenges of evaluating FF/VI for COPD prior to evaluation in asthma and the established use of either the FF and VI monocomponents, which differs from prior precedent. GSK stated that they do not plan to market VI as a monotherapy. The Division also expressed concerns about the strength of the efficacy data based on preliminary review. In particular, the Division noted the lack of a consistent benefit for FF/VI over VI alone in terms of spirometry. How supportive data from the ongoing exacerbation programs would be remained uncertain at the time of the meeting.
- **October 12, 2011, Pre-NDA meeting (asthma program):** The Division requested that an application for asthma be submitted concurrently with the COPD application, given the novelty of both the FF and VI components. GSK stated that the recommendation would be taken under advisement. GSK reported mixed efficacy results from the asthma program[15].
- **July 12, 2012, NDA submission**

3. CMC/Device

The recommended action from a CMC perspective is pending at the time of this memorandum. Outstanding issues include the following:

  - Drug product manufacturing site inspection pending
  - Agreement (b) (4) for aerodynamic particle size distribution (APSD) testing
  - Agreement regarding post-approval dose content uniformity (DCU) testing sample sizes for stability studies
  - Validation of the analytical method

- General product quality considerations

[15] GSK, January 9, 2012 [press release]. Retrieved from http://us.gsk.com/html/media-news/pressreleases/2012/2012-pressrelease-840722.htm on February 7, 2013.

FF/VI is administered by a novel dry powder inhaler device, the Ellipta inhaler, which 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. One strip contains micronized FF and lactose. The second strip contains micronized VI, magnesium stearate, and lactose. The device is designed to deliver the contents from a single blister from each of the two blister strips simultaneously. Each inhalation contains 100 mcg of FF and 25 mcg of VI.

The inhaler is sealed inside a hermetically sealed (b) (4) foil tray with a dessicant packet and packaged in a cardboard carton. Stability data support a shelf-life of 24 months with a 6-weeks' in-use expiry once the protective foil packaging is opened. The recommended storage conditions are at room temperature from 20º to 25º C (68 to 77ºF); excursions permitted from 15º to 30ºC (59º - 86ºF)." The review has found the drug substances specifications, excipients, and container-closure systems to be acceptable. The Product Quality Microbiology review recommends approval of the product, which is a non-sterile dry powder.

In addition to routine bench testing for device ruggedness, the Applicant sampled partially used devices from the clinical trials and all complaint/malfunctioning devices. The rate of malfunctioning devices was low and did not indicate any systematic problems with device design. Patient use did not appear to influence the functionality of the device.

- Facilities review/inspection

The drug substances are manufactured by Glaxo Wellcome Manufacturing PTE Ltd. (Jurong, Singapore) and micronized by Glaxo Operations UK Ltd. (Ware, UK). The drug product is manufactured by Glaxo Operations UK Ltd. (Ware, UK). The drug substances and device DMFs were deemed adequate. A recommendation from the Office of Compliance regarding manufacturing and testing facilities is pending at this time.

- Other notable issues (resolved or outstanding)

In order to meet the requirements of a combination product as outlined in 21 CFR 300.50, the Applicant provided data to demonstrate comparability in aerosolization performance for FF and VI as monoproducts and in combination. The CMC review concluded that the degree of variability observed was typical for inhalation products and did not indicate a discernible performance difference between the combination product and the related monoproducts. The submitted data supported the use of the monoproducts in the confirmatory clinical trials.

4. Nonclinical Pharmacology/Toxicology

The recommended regulatory action from a Nonclinical Pharmacology/Toxicology perspective is Approval. There are no outstanding nonclinical issues at this time.

The preclinical program included studies in which animals were dosed with the individual monocomponents and in combination via inhalation to assess the general toxicity, genetic

toxicity, carcinogenicity, and reproductive toxicity of FF and VI individually. In general, these studies showed that FF and VI each possessed toxicity profiles typical of their respective pharmacological classes, and studies of the combination did not suggest any major interactions or synergistic effects between the two components.

The toxicity profile of fluticasone furoate alone had been characterized previously in the Veramyst Nasal Spray application (NDA 22-051, approved on April 27, 2007). Briefly, fluticasone furoate was non-genotoxic, non-carcinogenic, non-teratogenic, and had no effect on fertility in animals. The fluticasone furoate label carries a Pregnancy Category C designation because of the known effects of corticosteroids on embryofetal development.

The general toxicity of VI was evaluated after the inhalation route of administration of the drug for up to 13-, 26- and 39- weeks in mice, rats and dogs, respectively. These studies identified the upper airways, lung, heart, liver and testes as target organs of toxicity, and findings were typical of beta agonists. In terms of genetic testing, VI tested negative in the Ames assay, UDS assay in vitro, and SHE cell assay in vitro, and rat bone marrow micronucleus assay in vivo; and equivocal in the mouse lymphoma assay. Two-year carcinogenicity studies in rodents showed a dose-related shortening of latency for pituitary neoplasms in both sexes of the rat and increases in the incidence of leiomyomas in female rats. Female mice showed increases in the incidence of tubulostromal carcinomas in the ovaries. Non-significant increases in the leiomyomas and leiomyosarcomas were observed in the uterus in mice. These findings were typical of beta agonists in rodents.

A battery of reproductive and developmental studies evaluated the effects of vilanterol on male and female fertility in rats, the teratogenicity of vilanterol in rats and rabbits, and peri- and post-natal development of vilanterol in rats. Results showed that vilanterol caused dose-dependent, statistically non-significant increases in the incidence of cleft palate and opened/partially opened eyelids, and statistically significant increases in the incidence of skeletal variations at high doses in rabbit fetuses. The drug caused dose-dependent, statistically significant decreases in fetal weights at high doses in rats. It had no effects on fertility in rats.

5. Clinical Pharmacology/Biopharmaceutics

The recommended regulatory action from a Clinical Pharmacology perspective is Approval. There are no outstanding clinical pharmacology issues at this time.

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism and the pharmacokinetics after single and multiple inhaled doses of FF, VI, and FF/VI. The majority of studies were conducted in healthy volunteers, but several studies were done specifically to assess pharmacokinetics in COPD patients and the effect of renal and hepatic impairment.

Inhaled FF and VI when administered by 4 inhalations of FF/VI 200/25 mcg FF/VI have an approximate absolute bioavailability of 15% and 27%, respectively. Given low oral bioavailability, systemic exposure for both components is primarily due to absorption of the

inhaled portion. The estimated half-life for FF and VI is 24 hours and 2.5 hours, respectively. FF C_{max} and $AUC_{(0-24)}$ were 47% and 46% lower in COPD patients compared to healthy subjects. In patients with asthma, FF C_{max} and $AUC_{(0-24)}$ were 18% and 7% lower compared to healthy subjects. For VI, FF C_{max} and $AUC_{(0-24)}$ were 67% lower and 24% higher in COPD patients compared to healthy subjects. In asthma, VI C_{max} and $AUC_{(0-24)}$ were 62% and 21% lower than in healthy subjects. No significant effects due to age, renal, or hepatic impairment, on pharmacokinetic parameters were observed, so no dose adjustment for age, hepatic function, or renal function is recommended.

In terms of drug-drug-interactions, FF and VI are metabolized principally via CYP3A4. Co-administration with ketoconazole, a strong CYP3A4 and potent P-gp inhibitor, resulted in 36 and 33% increase in mean FF $AUC_{(0-24)}$ and C_{max}, respectively, and in 65% and 22% increase in mean VI $AUC_{(0-t)}$ and C_{max}, respectively. These changes are relatively modest in comparison to drug-drug interactions observed for fluticasone propionate and salmeterol[1], and no dose adjustment is recommended for FF/VI when co-administered with ketoconazole.

A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval. A more detailed discussion of the pharmacokinetic information can be found in the Clinical Pharmacology Summary included in these background materials.

6. Clinical Microbiology

Clinical microbiology is not applicable for this NDA.

7. Clinical/Statistical- Efficacy

Overview of the clinical program

As noted in the background, previous ICS/LABA combination products were developed after the successful development of the individual components. In contrast, GSK conducted a development program for the FF/VI combination product that was largely concurrent with development of the individual monocomponents. Furthermore, the clinical program included trials to support both a bronchodilation claim and an exacerbation claim. As a result, the clinical program for FF/VI is quite extensive. Table 1 and Table 2 summarize the main studies conducted in both COPD and asthma to support dose selection and dosing frequency for the FF and VI monocomponents with the to-be-marketed device, and the confirmatory trials conducted specifically for the combination. This memorandum summarizes the main results from these trials; additional information regarding these trials can be found in the other supporting documents included in the backgrounder. For brevity, the trials are identified here by the last four digits of the study number for the remainder of this memorandum (e.g., Trial HZC112206 is Trial 2206).

Table 1 FF, VI, and FF/VI dose selection

Trial *Trial period*	Design[a]	N[b]	Treatment[c]	Endpoint	Sites *% US sites*
FF component – asthma					
FFA109684 *Dec 2007-Sep 2008*	8-wk, R, DB DD, PC, PG	99 101 107 102 110 103	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	Trough FEV1	94 sites (US, Canada, Mexico, E. and W. Europe, Australia, S. Africa, Thailand) *18%*
FFA109685 *Dec 2007-Nov 2008*	8-wk, R, DB, DD, PC, PG	105 101 103 99 100 107	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo	Trough FEV1	98 sites (US, Canada, Mexico, E. and W. Europe, Korea, Philippines) *32%*
FFA109687 *Dec 2007 – Oct 2008*	8-wk, R, DB, PC , PG	97 100 110 95 110 94	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo	Trough FEV1	107 sites (US, Canada, Mexico, Korea, E. and W. Europe, Peru, Philippines) *36%*
FFA112202 *Oct 2008 – Mar 2009*	28-day, R, DB, XO, PC trial to assess dosing frequency	190	FF 200 QPM FF 100 BID FP 200 QPM FP 100 BID Placebo	Trough FEV1	16 sites (US) *100%*
FFA112059 *Jun 2010 – Apr 2012*	24-wk, R, DB, DD, PG	114 114 115	FF 100 QPM FP 250 BID Placebo	Trough FEV1	56 sites (US, E. And W. Europe) *57%*
VI component – asthma					
B2C109575 *Dec 2007-Sep 2008*	28-day, R, DB, PC, PG	101 101 100 101 102 102	VI 3 QPM VI 6.25 QPM VI 12.5 QPM VI 25 QPM VI 50 QPM Placebo	Trough FEV1 Weighted mean FEV1	88 sites (E. and W. Europe, Canada, S. America, Korea, Philippines, Thailand, S. Africa, US) *36%*
HZA113310 *Sep 2009 – Jan 2010*	7-day, R, DB, XO PC trial to assess dosing frequency	75	VI 6.25 BID VI 6.25 QPM VI 12.5 QPM VI 25 QPM Placebo	Trough FEV1 Serial FEV1	9 sites (US) *100%*
B2C112060 *Sep 2010 – Aug 2011*	R, DB, DD, PG, PC	115 116 116	VI 25 QD Salmeterol 50 BID Placebo	Serial FEV1	34 sites (US, E. and W. Europe, Peru) *20%*
VI component – COPD					
B2C111045 *Feb 2008 – Oct 2008*	4-wk, R, DB, PC, PG	99 101 101 101 99 101	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD Placebo	Trough FEV1	49 sites (US, Canada, Mexico, E. and W. Europe, S. America, Korea, Philippines) *50%*

Table 1 FF, VI, and FF/VI dose selection					
Trial ***Trial period***	**Design**[a]	**N**[b]	**Treatment**[c]	**Endpoint**	**Sites** *% US sites*
FF/VI					
HZA114624 *Oct 2010 – Sep 2011*	14-day, R, DB, XO, PC trial to assess AM v. PM dosing in asthma	26	FF/VI 100/25 QAM FF/VI 100/25 QPM Placebo	Weighted mean $FEV1_{0-24h}$	1 site (New Zealand) *0%*
HZC110946 *Jan 2010 – Jul 2010*	28-day R, DB, PC, XO in COPD	54	FF/VI 50/25 QD FF/VI 100/25 QD FF/VI 200/25 QD Placebo	Serial $FEV1_{0-24h}$	8 sites (US) *100%*

[a] R=randomized, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, SD=single dose, XO=crossover
[b] Intent-to-treat
[c] FF=fluticasone furoate, FP=fluticasone propionate, VI=vilanterol,

Table 2 FF/VI clinical development program

Trial *Trial period*	Design[a]	N[b]	Treatment	Endpoint	Sites *% US sites*
Bronchodilation efficacy and safety trials					
HZC112206 *Oct 2009 – Feb 2011*	24-wk, R, DB, PC, PG	206 206 206 205 207	FF/VI 50/25 QD FF/VI 100/25 QD FF 100 QD VI 25 QD Placebo	Weighted mean $FEV1_{0-4h}$ Trough FEV1	221 sites (US, Germany, E. Europe, Chile, Japan, Korea, Philippines) *39%*
HZC112207 *Oct 2009 – Mar 2011*	24-wk, R, DB, PC, PG	204 205 204 203 203 205	FF/VI 100/25 QD FF/VI 200/25 QD FF 100 QD FF 200 QD VI 25 QD Placebo	Weighted mean $FEV1_{0-4h}$ Trough FEV1	138 sites (US, Germany, E. Europe, Japan) *25%*
COPD exacerbation efficacy and safety trials					
HZC102871 *Sep 2009 – Oct 2011*	52-wk, R, DB, AC, PG	408 403 402 409	FF/VI 50/25 QD FF/VI 100/25 QD FF/VI 200/25 QD VI 25 QD	Annual rate of moderate-severe COPD exacerbations	167 sites (Latin America, Australia, Canada, W. and E. Europe, Philippines, S. Africa, US) *33%*
HZC102970 *Sep 2009 – Oct 2011*	52-wk, R, DB, AC, PG	412 403 409 409	FF/VI 50/25 QD FF/VI 100/25 QD FF/VI 200/25 QD VI 25 QD	Annual rate of moderate-severe COPD exacerbations	183 sites (Latin America, Australia, Canada, W. Europe, S. Africa, US) *36%*
Active comparator trials					
HCZ113107 *Feb 2011 – Oct 2011*	12-wk, R, DB, DD, PG	266 262	FF/VI 100/25 QD Advair 500/50 BID	Weighted mean serial $FEV1_{0-24h}$	61 sites (W. and E. Europe, Philippines) *0%*
HCZ113109 *Mar 2011 – Dec 2011*	12-wk, R, DB, DD, PG	260 259	FF/VI 100/25 QD Advair 250/50 BID	Weighted mean serial $FEV1_0$	51 sites (Germany, E. Europe, US) *28%*
HCZ112352 *Mar 2011 – Jan 2012*	12-wk, R, DB, DD, PG	259 252	FF/VI 100/25 QD Advair 250/50 BID	Weighted mean serial $FEV1_0$	48 sites (Ukraine, S. Africa, Spain, Italy, US) *29%*
HZA113091 *Jun 2010 – Jul 2011*	24-wk, R, DB, DD, PG in asthma	403 403	FF/VI 100/25 Advair 250/50 BID	Weighted mean serial $FEV1_0$	65 sites (US, S. America, Netherlands, Philippines, S. Korea) *30%*

[a] AC= active-controlled, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, R=randomized, SD=single dose, XO=crossover

[b] Intent-to-treat

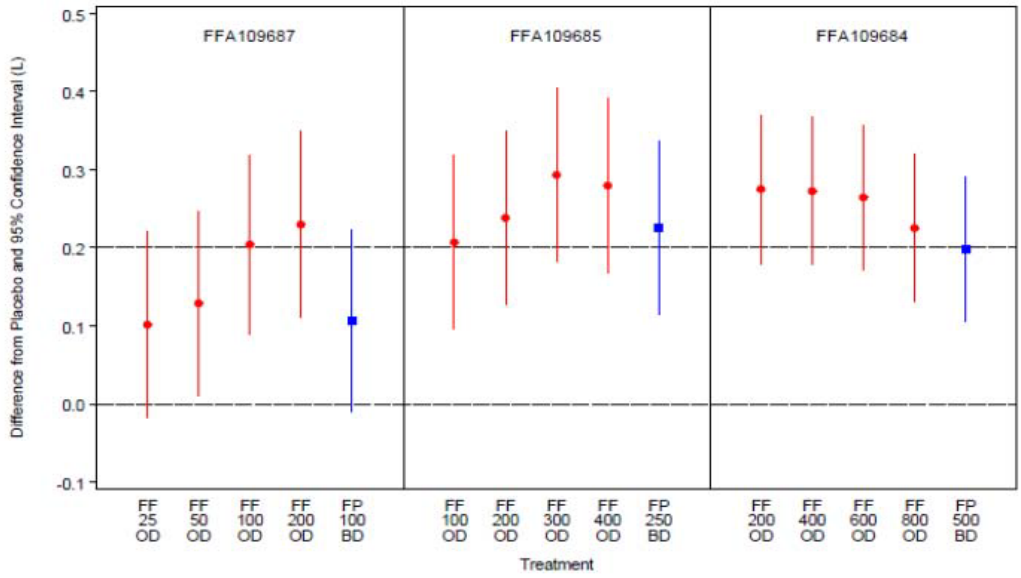
Dose selection

FF component: Dose exploration in asthma

- **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. 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.

Figure 1 Trials 9684, 9685, and 9687: Adjusted treatment differences from placebo of change from baseline in trough FEV1 (L) at Week 8



Source: Module 5.3.5.3, Integrated Summary of Efficacy, Figure 19
FF= fluticasone furoate, FP= fluticasone propionate

Similar support for the FF 100 mcg dose was generated in Trial 2059, a randomized, double-blind, double-dummy, placebo-controlled that compared FF 110 mcg QPM to FP 250 mcg BID. At Week 24, both FF and FP demonstrated statistically significant changes from baseline compared to placebo with similar effect sizes (146 and 145 ml, respectively).

- **Dosing frequency**

As the use of ICS in COPD is directed at treatment of chronic inflammatory aspects of the disease, the effect of dosing frequency in terms of efficacy would be expected to be subtle, if present. Dosing frequency with FF was explored in patients with asthma. GSK conducted Trial 2202, 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 mcg100 BID appeared similar, whereas FP 100 mcg BID dosing resulted in a numerically higher trough

FEV1 compared to FP 200 mcg QD (Table 3). These results supported the selection of the QD regimen for further evaluation.

Table 3 Trials 2202: Mean change from baseline in trough FEV1 at Day 28

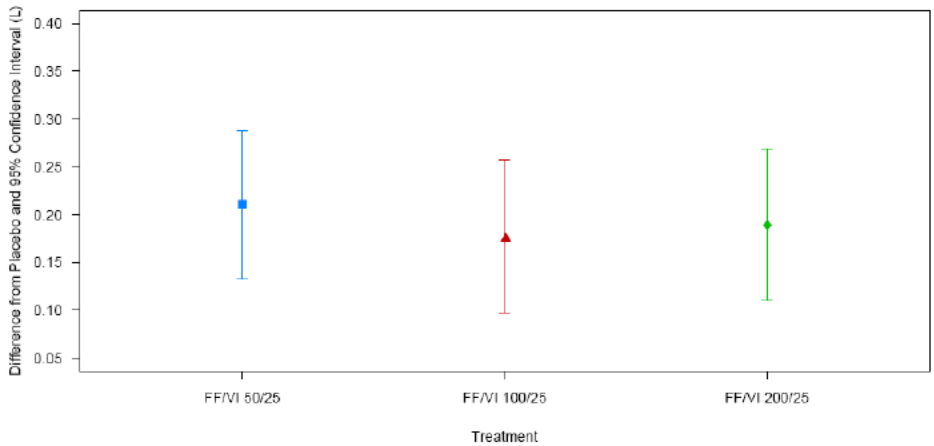
Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
FF 200 QPM	140	2.714	0.221	0.108 (0.064, 0.153)	<0.001
FF 100 BID	142	2.703	0.210	0.098 (0.054, 0.142)	<0.001
FP 200 QD	42	2.693	0.199	0.087 (0.014, 0.161)	0.020
FP 100 BID	43	2.737	0.244	0.132 (0.059, 0.205)	<0.001
Placebo	187	2.605	0.112	-	-

Source: Module 5.3.5.4, CSR FFA112202, Table 12

FF component: Dose exploration in COPD

Given the lack of efficacy observed for ICS monotherapy in COPD in previous trials, formal dose exploration of the FF monocomponent in patients with COPD was not included in the FF/VI program. However, GSK did conduct Trial 0946, a 28-day, three-way, incomplete block crossover trial in 54 patients with moderate to severe COPD that evaluated three dose levels of FF/VI: 50/25, 100/25, and 200/25 mcg administered once daily. As the VI dose of 25 mcg was held constant, Trial 0946 provided some insight into the relative benefit of varying doses of FF in COPD. While all FF/VI doses demonstrated a statistically significant increase in various FEV1 parameters compared to placebo (weighted mean FEV1 (0-24h), trough FEV1, and serial FEV1 (0-24h)), there was no apparent dose response (Figure 2). These results could be interpreted to mean that this range of FF doses is already at the plateau of the dose-response curve. Alternatively, it may be an indication that the benefit of ICS therapy in COPD is better captured by non-spirometric variables. No VI monotherapy arm was included for comparison.

Figure 2 Trial 0946: Differences from placebo in change from period baseline trough FEV1 (L) at Day 29



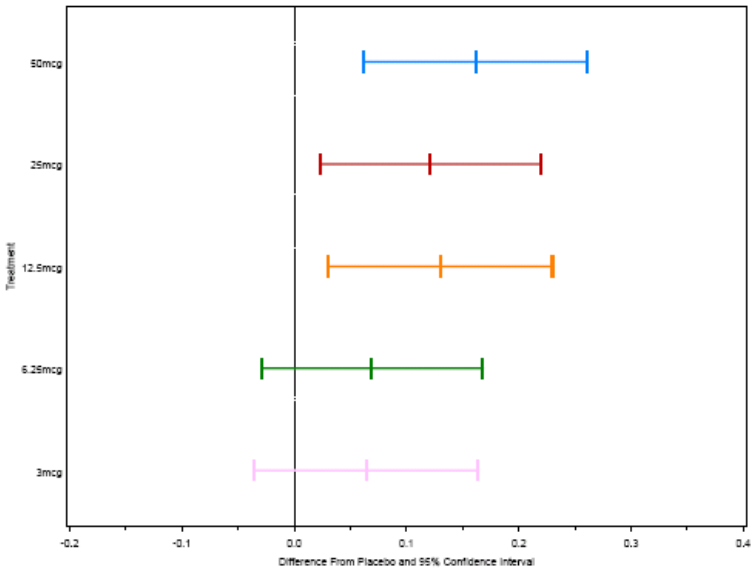
Source: Module 5.3.5.1, CSR, Figure 6.07

VI component: Dose exploration in asthma

- **Nominal dose selection**

GSK explored a range of nominal doses for the VI component in both asthma and COPD. Trial 9575 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 3 Trial B2C109575: Adjusted treatment differences of change from baseline in trough FEV1 (LOCF) at Day 28

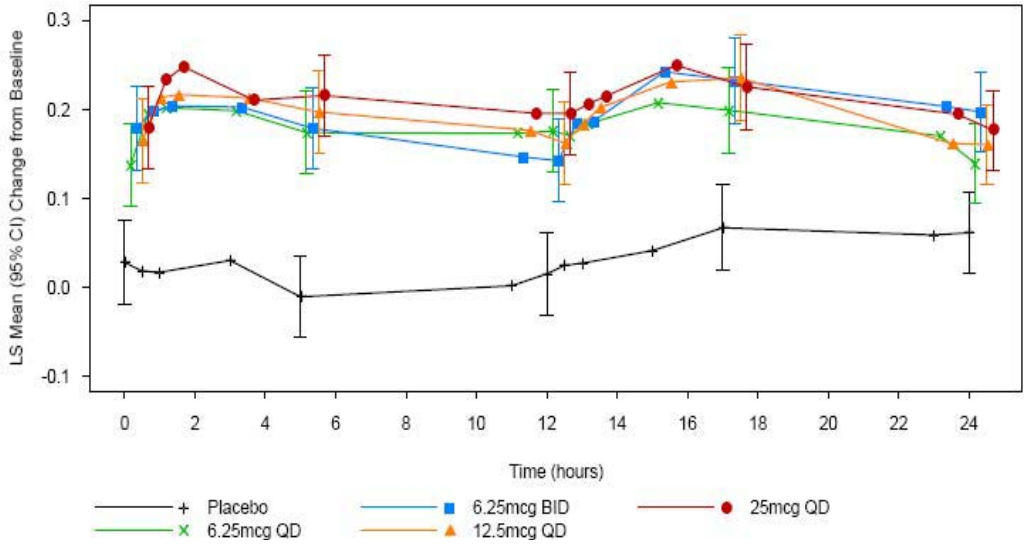


Source: Module 5.3.5.4, CSR, Figure 7.1

- **Dosing frequency**

The once-daily versus twice-daily dosing regimen was evaluated in Trial 3310, 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 the contention that BID dosing is not superior to QPM dosing (Figure 4). 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, 4624, indicated that once-daily dosing with FF/VI 100/25 in the PM was similar to AM dosing (results not shown).

Figure 4 Trial 3310: Repeated measures adjusted mean change from period baseline in FEV1 (L) over time at Day 7



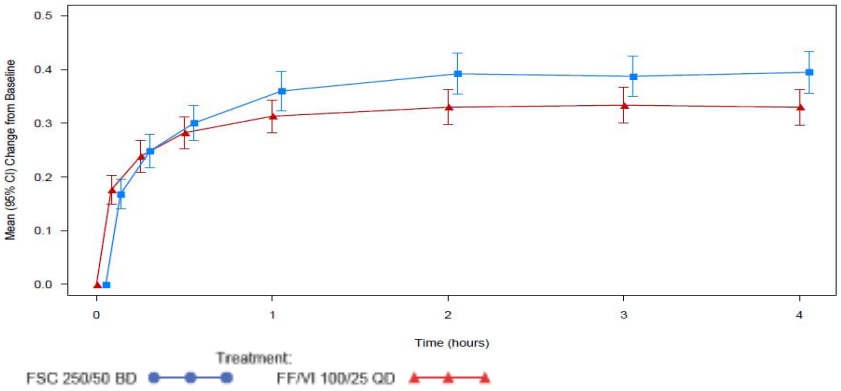
Source: Module 5.3.5.4, Complete Study Report, Figure 6.12

- **Comparison to salmeterol**

Another trial in asthma, 2060, provided a benchmark comparison for VI 25 mcg QD to another LABA approved for COPD, salmeterol 50 mcg BID. Trial 2060 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.

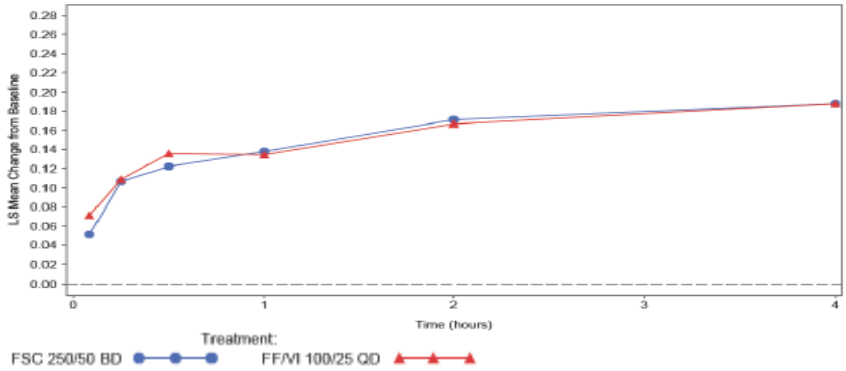
The FF/VI program included other trials with an active comparator to help benchmark the bronchodilatory effects of VI. GSK conducted one trial in asthma (Trial 3091) and two trials in COPD (3109 and 2352) comparing FF/VI 100/25 to Advair 250/50 (fluticasone propionate/salmeterol). Although these trials 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. Figure 5 and Figure 6 are shown as representative figures from asthma and COPD patients, respectively. As can be seen in the figures, 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, i.e., VI 25. 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 the section on efficacy findings.

Figure 5 Trial 3091 (asthma): Raw change from baseline in FEV1 (0-4h) at Day 1



Source: Module 5.3.5, Complete Study Report Figure 3

Figure 6 Trial 2352 (COPD): LS mean change from baseline in FEV1 (0-4h) at Day 1



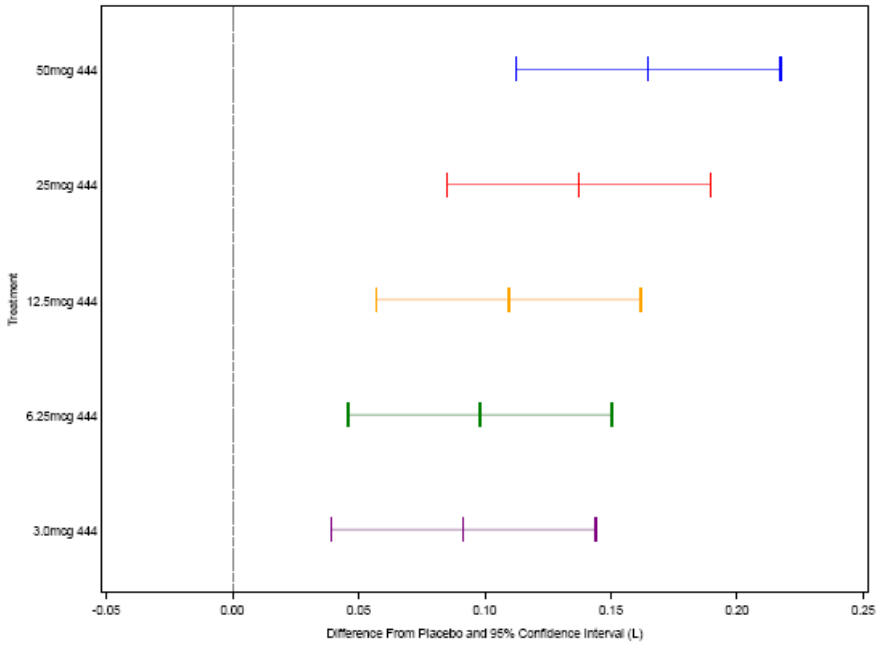
Source: Module 5.3.5, Complete Study Reports, Figure 2

VI component: Dose exploration in COPD

- **Nominal dose selection**

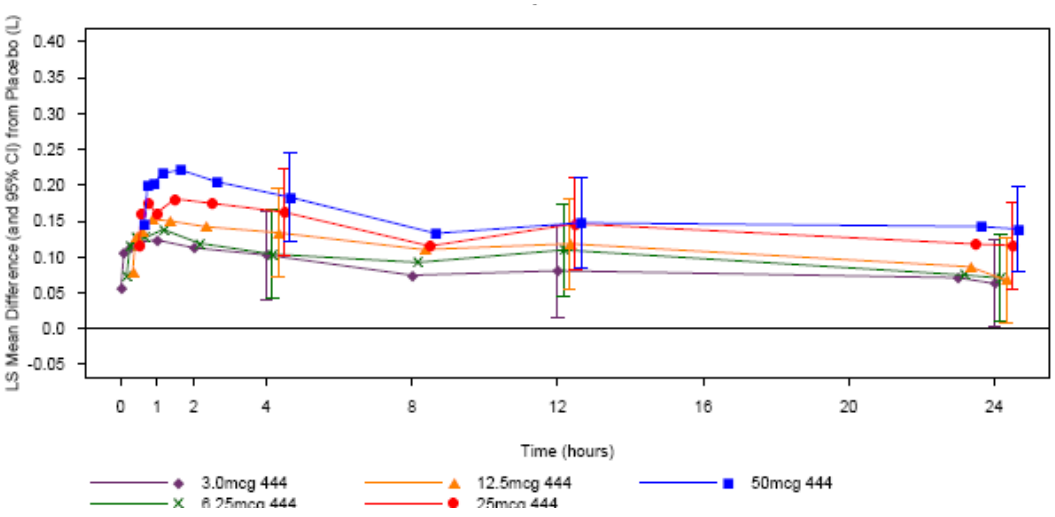
A similar range of nominal doses was evaluated in patients with COPD. Trial 1045 was a 28-day, randomized, double-blind, placebo-controlled, parallel group trial in 602 patients with moderate COPD. Patients were randomized by bronchodilator reversibility at baseline. Patients were randomized to once-daily treatment with 3, 6.25, 12.5, 25, or 50 mcg VI administered in the morning or placebo. Separation of doses was observed by Day 29 in terms of trough FEV1 (Figure 7). A comparison of serial FEV1 measurements demonstrated a fairly consistent dose response over the range of doses evaluated (Figure 8).

Figure 7 Trial 1045: Adjusted treatment differences from placebo in change from baseline trough FEV1 (L) at Day 29



Source: Module 5.3.5.4, Complete Study Report B2C111045,

Figure 8 Trial 1045: Repeated measures adjusted treatment differences from placebo in change from baseline FEV1 (L) over time on Day 28



Source: Module 5.3.5.4, Complete Study Report B2C111045, Figure 7.20

Dose selection summary for FF/VI

In summary, dose-ranging data for the FF component in asthma supported efficacy for the range of doses (50, 100, and 200 mcg) carried forward for confirmation in the Phase 3 COPD program. In terms of VI, data for the nominal dose and dosing frequency in asthma appeared reasonable in support of VI 25 mcg QD. While assessment of VI's effect on trough FEV1 in

asthma suggested that a lower dose of VI 12.5 mcg QD or 6.25 mcg BID might also be efficacious, a comparison of the serial FEV1 time curves showed a numerically greater effect for the 25 mcg QD dose. These findings were further supported by VI dose exploration in COPD, which indicated that a dose as high as 50 mcg QD dose could also be considered. Therefore, the selection of VI 25 mcg QD for further study in the confirmatory trials in COPD appeared reasonable.

Confirmatory trial design

Confirmatory lung function trials: 2206 and 2007

Two trials were conducted in support of lung function claims, Trials 2206 and 2207. The trials were similar in design with the exception of the nominal dose levels that were evaluated. Trial 2206 assessed FF/VI 50/25, FF/VI 100/25, FF 100, VI 25, and placebo administered once daily in the AM. Trial 2207 assessed FF/VI 100/25, FF/VI 200/25, FF 200, FF 100, VI 25, and placebo administered once daily in the AM. They were both 24-week, multinational, randomized, double-blind, placebo-controlled, parallel group trials in patients with moderate to severe COPD. The full factorial design was intended to help evaluate the relative contributions of the individual components to the combination product. Patients 40 years or older were required to have a clinical history of COPD as defined by ATS/ERS criteria,[16] a post-bronchodilator FEV1/FVC ratio ≤0.70, a post-bronchodilator FEV1 ≤70% predicted, and a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC).

Ipratropium bromide at a constant dose, mucolytics, oxygen therapy ≤12 hours/day, and albuterol/salbutamol for rescue were permitted as concomitant treatments. Prohibited medications included systemic or inhaled corticosteroids, LABAs, other ICS/LABA products, long-acting anticholinergics, ipratropium/albuterol (salbutamol), and theophylline preparations. The use of a placebo control for up to 6 months was considered ethically acceptable given the availability of rescue SABA in conjunction with close clinical monitoring for exacerbation symptoms, and withdrawal criteria.

After an initial screening and 2-week run-in period on placebo, patients were randomized 1:1:1:1:1 or 1:1:1:1:1:1, respectively, and stratified by smoking status. The primary efficacy endpoints were the weighted mean FEV1 0-4 hours post-dose on Treatment Day 168 (intended to assess the effect of VI) and the change from baseline in trough FEV1 on Treatment Day 169 (intended mainly to assess the effect of FF in the combination). Secondary endpoints included peak FEV1 and time to onset on Day 1. COPD exacerbations were not assessed as a formal efficacy endpoint but were evaluated as a safety outcome. A COPD exacerbation was defined as an acute worsening of COPD symptoms requiring the use of any treatment besides study medication or rescue bronchodilator. Patients who experienced an exacerbation during the Treatment Period were withdrawn. Other safety assessments included adverse events (AEs), physical exams, clinical laboratory parameters, vital signs, ECGs, and in a subset of patients, Holter monitoring. AEs of special interest included COPD exacerbations and pneumonias. Urinary cortisol excretion was assessed in a subset of patients. Treatment compliance was assessed via dose counter checks at interval clinical visits.

[16] Celli BR, MacNee W. Standards of the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J. 2004;23: 932-46.

Exacerbation trials: Trials 2871 and 2970

Trials 2871 and 2970 had a similar design and were intended to evaluate the effect of FF/VI 50/25, FF/VI 100/25, FF/VI 200/25, and VI 25 on the annual rate of moderate and severe COPD exacerbations over a 52-week treatment period. Both trials were multi-center, randomized, double-blind, parallel-group trials. Inclusion/exclusion criteria were similar to those criteria outlined for Trial 2206 and 2207, with the exception of an additional requirement for a documented history of at least one COPD exacerbation that required antibiotics and/or systemic steroids or hospitalization in the past year. Permitted concomitant treatments included those listed for Trials 2206 and 2207, as well as the use of oral corticosteroids and antibiotics for 14 days or less for the short term treatment of COPD exacerbations.

Following an initial screening and a 4-week run-in period on fluticasone propionate/salmeterol 250/50 mcg twice daily, patients were randomized 1:1:1:1 and stratified by smoking status. The primary efficacy endpoint was the annual rate of moderate and severe COPD exacerbations. COPD exacerbations were identified based on a diary review (via phone contact or clinic visit) and investigator's judgment using the following criteria: worsening of 2 or more major symptoms (dyspnea, sputum volume, sputum color) for at least two consecutive days OR worsening of any 1 major symptom with any one of minor symptoms (sore throat, colds, fever without other cause, increased cough, increased wheeze). COPD exacerbations were categorized as mild, moderate, or severe by the investigator, depending on whether symptoms were self-managed by the patient, required treatment with oral corticosteroids/antibiotics, or required hospitalization, respectively. Secondary endpoints included the time to first moderate or severe exacerbation, annual rate of exacerbations requiring systemic/oral corticosteroids, and change from baseline in trough FEV1 at Visit 11.

Safety variables assessed included AEs, vital signs, ECGs measurements, physical exams, and laboratory parameters. The safety assessment included specified analyses for composite adverse events of interest, which included the following: cardiovascular effects, local and systemic steroid effects, hypersensitivity, lower respiratory tract infections excluding pneumonia, pneumonia, bone disorders, effects on glucose and potassium, tremor, and ocular effects. For pneumonias, the protocol specified that patients diagnosed with a moderate to severe exacerbation were to undergo a chest x-ray within 48 hours, which was then evaluated by a central reader for signs of pneumonia. Cases of pneumonia required confirmation by the presence of a new infiltrate on x-ray, as well as at least 2 of the following signs and symptoms: increased cough, increased sputum purulence or production, consistent auscultatory findings, dyspnea or tachypnea, fever, leukocytosis, or hypoxemia. On-treatment AEs were AEs with an onset date the same or after the treatment start date but prior to or the same as the treatment stop date +1 day. Post-treatment AEs were defined as AEs with an onset date after the treatment stop date +1 day.

Efficacy findings

Lung function

The two lung function trials, 2206 and 2007, included a total of 2,254 patients in the ITT population, of which 410 patients received the proposed FF/VI 100/25 dose. The mean age was 62 years and 70% were male. Twenty-four percent reported ≥1 exacerbation in the past year that required systemic corticosteroids and/or antibiotics (no hospitalization) and 9% reported ≥1 hospitalization in the past year due to an exacerbation.

In each of the two lung function trials, 2206 and 2007, study withdrawal rates ranged from 21 to 33%, with the highest rate of early discontinuations occurring in the placebo arms. Lack of efficacy was cited as a reason for discontinuation more commonly in the placebo arms. While these rates of discontinuation are not insubstantial, the results of various imputation analyses for missing data are consistent with the results for the primary analysis and the reasons for discontinuations were well-balanced across the active treatment arms. Further discussion of the issue of missing data can be found in the Agency's statistical briefing document.

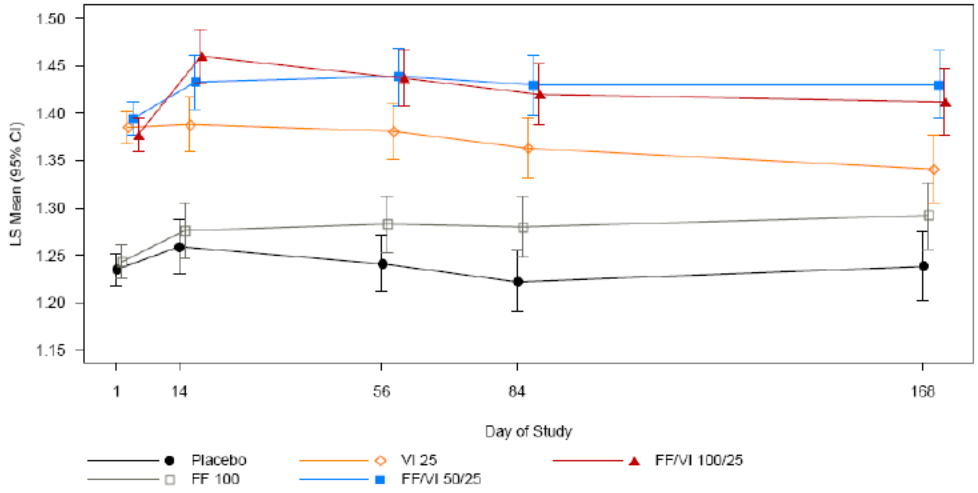
- **Weighted mean FEV1**

The change from baseline in weighted mean FEV1 0-4 hours (post-dose) at Day 167 was assessed as a primary endpoint in Trials 2206 and 2207 (Table 4). In Trial 2206, a statistically significant result for VI 25 versus placebo was observed ($p<0.001$), as well as for FF/VI 100/25 over FF 100 ($p<0.006$) (Figure 9). The latter comparison reflects the relative contribution of VI 25 to the FF/VI combination. There was no difference between FF/VI 100/25 and FF/VI 50/25 in terms of the weighted mean FEV1 0-4 hours. In Trial 2207, similar results were observed for comparisons between VI 25 and placebo ($p<0.001$), FF/VI 100/25 vs. FF 100 ($p<0.001$), and FF/VI 200/25 vs FF 200 ($p<0.001$) (Figure 10). Likewise, there was no apparent difference between FF/VI 100/25 and FF/200/25.

Table 4 Trials 2206 and 2207: Summary of 0-4h weighted mean FEV1(L) at Day 168 (ITT population)							
Treatment	**N**	**LS mean (L)**	**LS mean change**	**Difference from placebo (95% CI)**	**P**	**Difference from FF [95% CI]**	**P**
2206							
FF/VI 100/25	206	1.412	0.200	0.173 (0.123, 0.224)	<0.001	0.120 (0.070, 0.170)	<0.001
FF/VI 50/25	206	1.430	0.218	0.192 (0.141, 0.243)	<0.001	-	-
VI 25	205	1.341	0.129	0.103 (0.052, 0.153)	<0.001	-	-
FF 100	206	1.292	0.080	0.053 (0.003, 0.104)	0.04	-	-
Placebo	207	1.238	0.026	-	-	-	-
2207							
FF/VI 200/25	205	1.540	0.197	0.209 (0.157, 0.261)	<0.001	0.168 (0.117, 0.219)	<0.001
FF/VI 100/25	204	1.545	0.202	0.214 (0.161, 0.266)	<0.001	0.168 (0.116, 0.220)	<0.001
VI 25	203	1.516	0.173	0.185 (0.133, 0.237)	<0.001	-	-
FF 100	204	1.372	0.029	0.041 (-0.011, 0.093)	0.123	-	-
FF 200	203	1.377	0.034	0.046 (-0.006, 0.098)	0.085	-	-
Placebo	205	1.331	-0.012	-	-	-	-

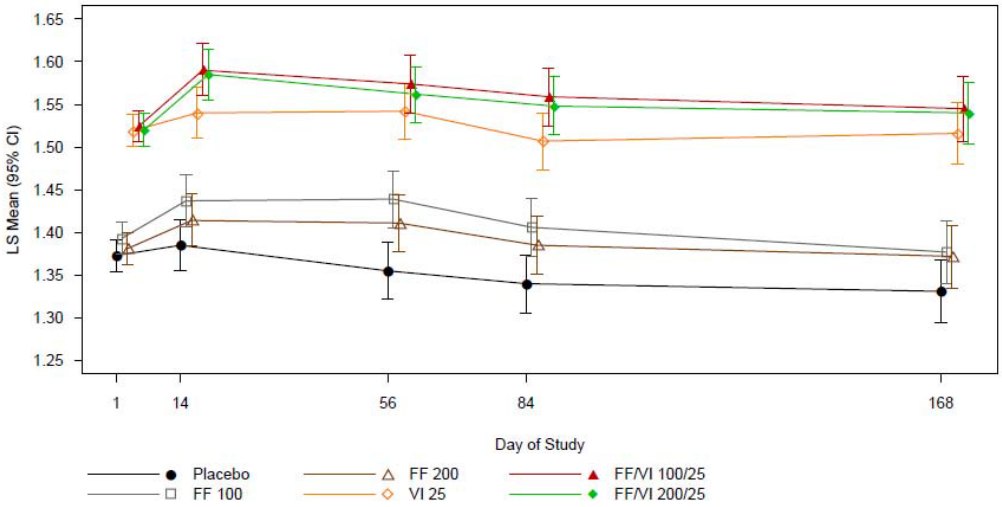
Source: Module 5.3.5.1, CSR HZC112206 and HZC2207, Table 19

Figure 9 Trial 2206: Least squares mean (95% CI) in 0-4h weighted mean FEV1



Source: CSR HZC112206, Module 5.3.5.1.3, Figure 2

Figure 10 Trial 2207: Least squares mean (95% CI) in 0-4h weighted mean FEV1



Source: CSR HZC112207, Module 5.3.5.1.3, Figure 2

- **Trough FEV1**

The change from baseline in mean trough FEV1 was assessed as a primary endpoint in Trials 2206 and 2207. This assessment was intended to demonstrate the benefit of FF/VI over VI alone (the relative contribution of FF). As shown in Table 5, all FF/VI treatment arms showed a numerical benefit over VI alone, ranging from 32 to 62 ml, but none reached statistical significance. No apparent dose response was observed.

Table 5 Trials 2206 and 2207: Mean change from baseline in trough FEV1 at Day 169 (ITT population)							
Treatment	**N**	**LS mean (L)**	**LS mean change**	**Difference from placebo (95% CI)**	**P**	**Difference from VI [95% CI]**	**P**
2206							
FF/VI 100/25	206	1.364	0.151	0.115 (0.060, 0.169)	<0.001	0.048 (-0.006, 0.102)	0.082
FF/VI 50/25	206	1.378	0.166	0.129 (0.074, 0.184)	<0.001	0.062 (0.008, 0.117)	0.025*
VI 25	205	1.316	0.103	0.067 (0.012, 0.121)	0.017	-	-
FF 100	206	1.282	0.070	0.033 (-0.022, 0.088)	0.241	-	-
Placebo	207	1.249	0.037	-	-	-	-
2207							
FF/VI 200/25	205	1.479	0.135	0.131 (0.08, 0.183)	<0.001	0.032 (-0.019, 0.083)	0.224
FF/VI 100/25	204	1.492	0.148	0.144 (0.091, 0.197)	<0.001	0.045 (-0.008, 0.097)	0.093*
VI 25	203	1.447	0.103	0.100 (0.048, 0.151)	<0.001	-	-
FF 100	204	1.392	0.048	0.044 (-0.008, 0.097)	<0.095	-	-
FF 200	203	1.356	0.012	0.008 (-0.044, 0.060)	<0.756)	-	-
Placebo	205	1.347	0.004	-	-	-	-

Source: Module 5.3.5.3, Integrated Summary of Efficacy, Table 14

* Nominal p-value. The p-values reported here do not take into account the testing hierarchy pre-specified in the statistical analysis plan, which required statistical significance for the higher dose prior to testing of lower doses.

The change from baseline in trough FEV1 at week 52 was assessed as a secondary endpoint in the exacerbation trials, 2871 and 2970 (Table 6). The point estimate for the treatment effect of FF (FF/VI compared to VI) ranged from 24 to 64 ml, a similar range as observed in the lung function trials (32 to 62 ml). However, the pre-specified testing hierarchy does not allow for these comparisons given the failure of the primary endpoint for exacerbations (discussed in the following section) in Trial 2871 and the requirement for testing of the higher dose prior to proceeding to lower doses in Trial 2970. In Trials 2871 and 2970, VI 25 alone did not demonstrate a change from baseline trough FEV1, whereas VI 25 demonstrated a mean change of 103 ml in the pulmonary function trials, 2206 and 2207. This observation most likely reflects the treatment of all patients with Advair 250/50 during the run-in periods of Trials 2871 and 2970, so patients started the treatment phase of the trials already bronchodilated. A comparison of FEV1 values at screening and at baseline (mean difference of 77 and 86 ml in the two trials, respectively) supports such an explanation.

Table 6 Trials 2871 and 2970: Mean change from baseline in trough FEV1 at Week 52 (ITT population)					
Treatment	**N**	**LS mean (L)**	**LS mean change**	**Difference from VI [95% CI]**	**P**
2871					
FF/VI 200/25	402	1.244	0.024	0.064 (0.033, 0.096)	<0.001*
FF/VI 100/25	403	1.238	0.018	0.058 (0.027, 0.09)	<0.001*
FF/VI 50/25	408	1.220	0	0.041 (0.009, 0.072)	0.011*
VI 25	409	1.180	-0.040	-	-
2970					
FF/VI 200/25	409	1.244	0.006	0.026 (-0.006, 0.057)	0.115*
FF/VI 100/25	403	1.242	0.005	0.024 (-0.008, 0.056)	0.143*
FF/VI 50/25	412	1.253	0.015	0.034 (0.003, 0.066)	0.034*
VI 25	409	1.219	-0.019	-	-

Source: Module 5.3.5.3, Integrated Summary of Efficacy, Table 16

* Nominal p-values. The p-values reported here do not take into account the testing hierarchy pre-specified in the statistical analysis plan. Trough FEV1 was designated as a key secondary endpoint and analysis for this endpoint was not to be conducted if the primary endpoint for exacerbations failed.

The application includes exploratory subgroup analyses by gender, ethnicity, age, COPD severity, bronchodilator reversibility, geographical location, and smoking status. While certain analyses were limited by sample size (e.g., ethnic subgroups), the results were generally similar to the efficacy results observed for the population as a whole. The main exception noted was a relationship between reversibility and trough FEV1, with reversible patients generally having higher trough FEV1 values, as might be expected.

COPD exacerbations

The primary support for the proposed COPD exacerbation indication comes from Trials 2871 and 2970. The annual rate of moderate and severe COPD exacerbations was assessed as the primary endpoint, and is presented as an alternative demonstration of the benefit of FF/VI 100/25 over VI 25 alone (contribution of FF). A total of 3,255 patients comprised the ITT population in these two trials, of which 806 patients were randomized to FF/VI 100/25. Study withdrawal rates ranged from 23 to 28% in Trial 2871 and 25 to 31% in Trial 2970. Adverse event and withdrawal of consent were cited as the most common reasons for early discontinuation across the different treatment arms. As in the lung function trials, the results of various imputation analyses for missing data were consistent with the results of the primary analysis described below. Further discussion of missing data can be found in the Agency's statistical briefing document.

In both trials, the prespecified statistical analysis plan required statistical significance at the 0.05 level for the comparison of FF/VI 200/25 to VI 25 prior to the testing of lower doses. As a result, a statistically significant result for FF/VI 100/25 is observed in Trial 2970, while the

p-value reported for the same comparison in Trial 2870 in Table 7 is a nominal p-value. The exacerbation results are a reversal of the lung function results in the two 1-year trials, with a fairly modest treatment difference in terms of trough FEV1 observed in Trial 2970 compared to the larger effect observed in 2871.

Table 7 Trials 2871 and 2970: Moderate and severe COPD exacerbations

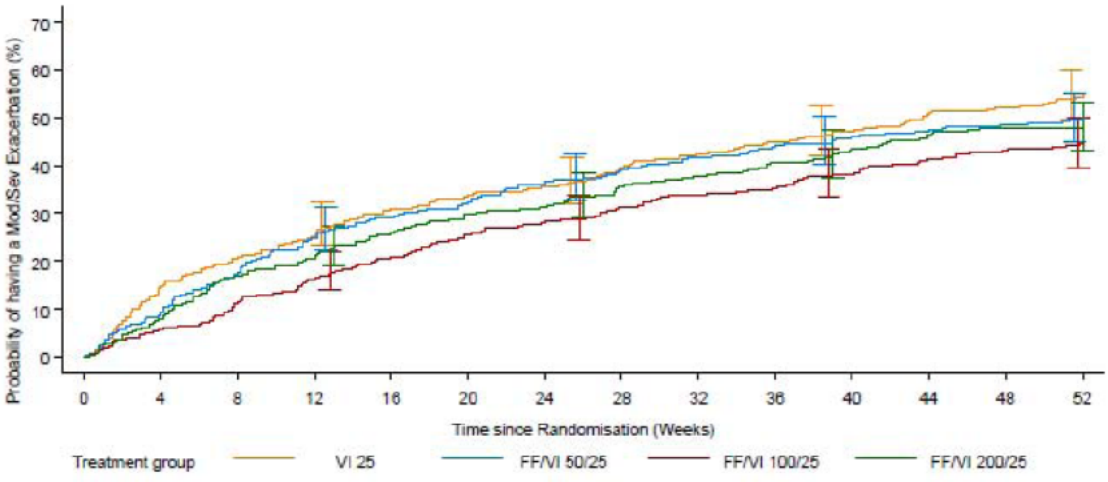
Treatment	N	LS mean annual rate	Ratio vs VI	95% CI	P
2871					
FF/VI 200/25	402	0.90	0.85	(0.70, 1.04)	0.109
FF/VI 100/25	403	0.70	0.66	(0.54, 0.81)	<0.001*
FF/VI 50/25	408	0.92	0.87	(0.72, 1.06)	0.181*
VI 25	409	1.05	-	-	-
2970					
FF/VI 200/25	409	0.79	0.69	(0.56, 0.85)	<0.001
FF/VI 100/25	403	0.90	0.79	(0.64, 0.97)	0.024
FF/VI 50/25	412	0.92	0.81	(0.66, 0.99)	0.040
VI 25	409	1.14	-	-	-

Source: Module 5.3.5, Complete Study Reports

* Nominal p-value. The p-values reported here do not take into account the testing hierarchy pre-specified in the statistical analysis plan, which required statistical significance for the higher dose prior to testing of lower doses.

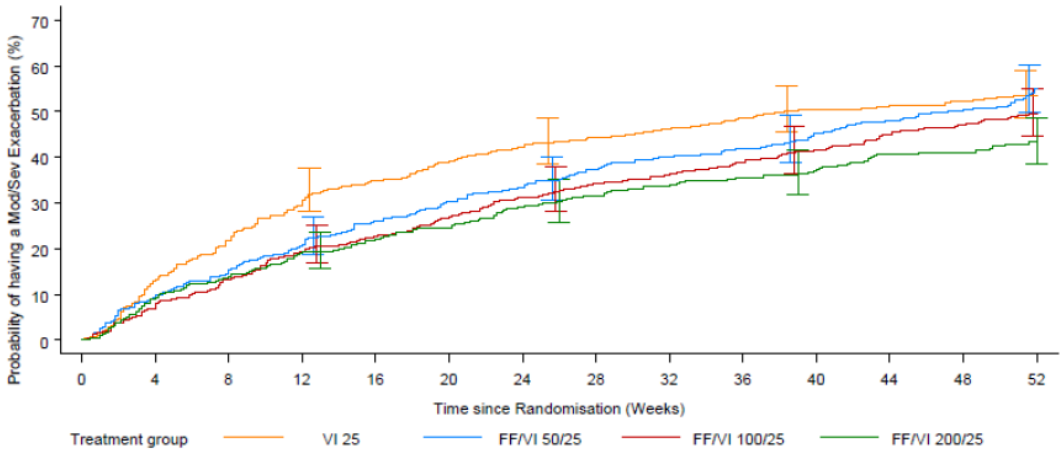
While the testing hierarchy specifies success of the primary endpoint before proceeding to testing of secondary endpoints, examining the exacerbation data in other ways is still informative. The time to first moderate or severe exacerbation showed a dose-related numerical treatment effect for FF/VI 100/25 over VI 25 alone in both trials (Figure 11 and Figure 12). Likewise, an assessment of exacerbations requiring systemic corticosteroids also was numerically supportive of a treatment effect for FF/VI 100/25 over VI 25 alone.

Figure 11 Time to first moderate or severe exacerbation (Trial 2871)



Source: Module 5.3.5.1, Complete study Report HZC102871, Figure 4

Figure 12 Time to first moderate or severe exacerbation (Trial 2970)



Source: Module 5.3.5.1, Complete study Report HZC102970, Figure 4

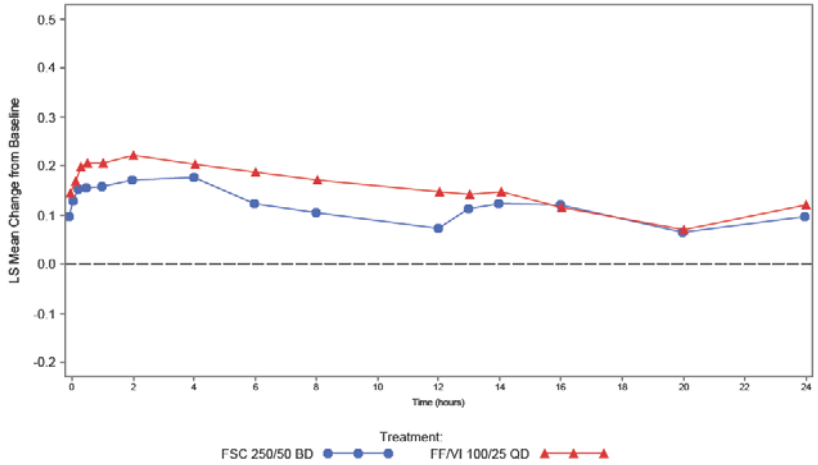
Exacerbation rates were not formally assessed in the pulmonary function trials 2206 and 2207, as patients with moderate and severe exacerbations were withdrawn from the trials. Overall, a slighter larger percentage of patients in the placebo and VI-only arms (5-8%) compared to the FF/VI arms (3-6%) withdrew secondary to an exacerbation in these trials.

Comparator trials

In addition to the two key pulmonary function trials (2206 and 2207) and the two key exacerbation trials (2871 and 2970), the GSK conducted three trials in COPD and one trial in asthma comparing FF/VI to Advair (fluticasone propionate/salmeterol). These trials provide an additional benchmark comparison for FF/VI. The COPD trials (3107, 3109, and 2352) were randomized, double-blind, double-dummy, active-controlled trials that compared FF/VI 100/25 QD to Advair BID. Trials 3109 and 2352 used Advair 250/50, the dose currently approved in the US for the treatment of COPD. Trial 3107 used Advair 500/50, which was previously shown to have similar efficacy to Advair 250/50 but was not approved in the US for COPD due to an increased risk of pneumonia.

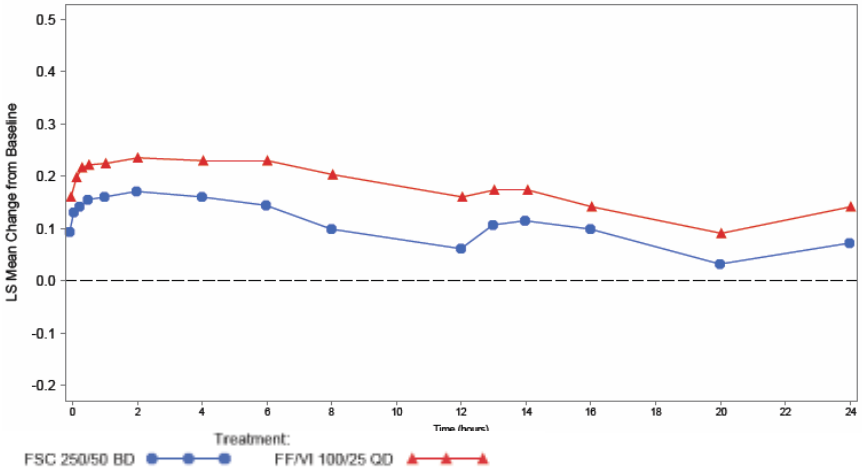
The primary endpoint was the change from baseline trough in 24-hour weighted-mean serial FEV1 at 12 weeks. The results of these trials demonstrated a similar or increased mean change from baseline for FF/VI 100/25 compared to Advair 250/50 or 500/50. Representative results from Trials 2352 and 3019 are shown in Figure 13 and Figure 14, respectively. Similar results were observed when analyzed using the observed data (data now shown). Results for the mean change from baseline FEV1 (0-4h) on the first day of dosing were discussed above in the section regarding dose selection for the VI component.

Figure 13 Trial 2352 (COPD): LS mean change from baseline in FEV1 (0-24h) at Day 84



Source: Module 5.3.5, Complete Study Reports, Figure 4

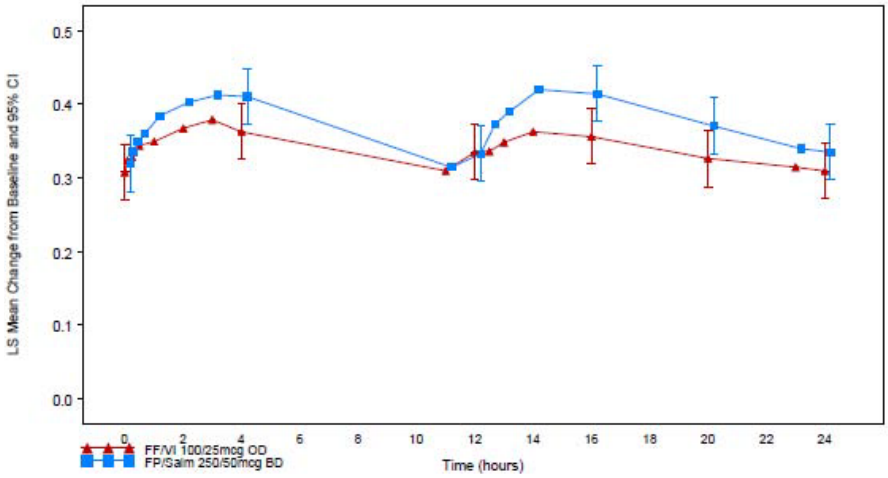
Figure 14 Trial 3109 (COPD): LS mean change from baseline in FEV1 (0-24h) at Day 84



Source: Module 5.3.5, Complete Study Reports, Figure 4

A similar active comparator trial was conducted in asthma, comparing FF/VI 100/25 to Advair 250/50 BID at 24 weeks. In contrast to the COPD trials, Advair numerically outperformed FF/VI at most timepoints (Figure 15). The interpretation of these findings in the context of the COPD results is somewhat uncertain.

Figure 15 Trial 3091 (asthma): Mean change from baseline in FEV1 at Week 24



Source: Module 5.3.5, Clinical Study Report HZA113091, Figure 4

Efficacy summary

The application includes replicate, statistically significant results for the efficacy of VI 25 alone versus placebo and FF/VI 100/25 versus FF 100 in terms of lung function (weighted mean FEV1 and trough FEV1). These data support the relative contribution of VI 25 to the efficacy of the FF/VI combination. The data to support the benefit of FF/VI 100/25 over VI 25 alone in terms of bronchodilation are less robust. The mean treatment difference for the change from baseline trough FEV1 in the lung function trials was fairly consistent (45 and 48 ml) in favor of FF/VI 100/25 over VI 25, but there was no consistent dose response, and the results were not statistically significant based on the pre-specified testing strategy. The weighted mean FEV1 values over the duration of the 6-month trials did show separation between FF/VI 100/25 and VI 25, but it appears that VI 25 provides the main contribution to FF/VI's immediate lung function effects. FF/VI 100/25 as a whole appears to have a similar effect on lung function as another ICS/LABA product, fluticasone propionate/salmeterol, which is currently approved for the same indication.

The COPD exacerbation endpoint offers an alternative, clinically meaningful assessment of the benefit of FF/VI 100/25 over VI 25 alone. While similar issues regarding the testing hierarchy for lower doses were encountered in Trial 2871, a statistically significant result for FF/VI 100/25 was observed in Trial 2970 with a comparable numerical result in Trial 2871. In both trials, the mean rate of moderate to severe exacerbation in the VI 25 arm was approximately 1 exacerbation per year; the mean reduction observed with FF/VI was about a quarter to a third of an event in one year with FF/VI 100/25. Analyses of the time to exacerbation and exacerbations requiring systemic corticosteroids were also supportive. When reviewed in totality, the weight of the evidence supports a clinical benefit for FF/VI 100/25 in terms of an improvement in lung function and a reduction in exacerbations. The data indicate that VI 25 provides the primary benefit for lung function while the FF 100 component acts in the combination to reduce the frequency of COPD exacerbations.

8. Safety

Overview of the safety database

The safety database for FF/VI 100/25 centers on the two 6-month lung function trials (2206 and 2207) and the two 1-year exacerbation trials (2871 and 2970), supplemented by shorter dose-ranging trials for the combination and the individual monocomponents and the active comparator trials. Safety information from ongoing trials in COPD and the concurrent asthma development program for FF/VI were also included in the application.

The application has pooled the COPD safety database into several groups for analysis:

1. The two placebo-controlled, 6-month lung function trials (2206 and 2207)
2. The two 1-year exacerbation trials (2871 and 2970)
3. The "integrated COPD" database, comprised of the four main efficacy and safety trials (2206, 2207, 2871, 2970) plus three shorter-term trials (0946, 1045, and 1348). Trials 0946 and 1045 were dose-ranging trials of FF/VI and VI, respectively, with 4-week treatment periods; the designs of these trials are discussed in the preceding section on dose selection. Trial 1348 was a 4-week Phase 2 trial that evaluated the safety and tolerability of a higher dose, FF/VI 400/25, versus placebo.
4. The "integrated COPD" database plus patients from the three, 12-week active comparator trials (3107, 3109, and 2352)

The seven integrated COPD trials and three active comparator trials (analysis group #4) include a total of 7700 unique patients, of whom 2034 patients have received at least one dose of the proposed FF/VI 100/25, and 1087 patients have received higher doses of FF/VI. Given differences in treatment exposure, the severity of the underlying patient populations, and relative sample sizes, the clinical review has focused on the analysis groups #1 and #2 and considered the other studies separately.

The demographic characteristics of the patients in the lung function and exacerbation studies were fairly similar in terms of race (84-85% White), gender (57-70% male), and age (62-64 years). In the lung function trials, the majority of patients demonstrated reversibility at baseline (69%) and were categorized as GOLD Stage III (44%) or IV (9%). In the exacerbation trials, the rate of reversibility was much lower (30%), and the population overall was skewed to greater severity given the enrollment requirement for a history of exacerbation (GOLD Stage III 46% and GOLD Stage IV 15%). In general, patients in the exacerbation trials had a longer reported duration of disease and a history of more frequent and severe exacerbations. Approximately 21% of patients had at least one exacerbation requiring hospitalization in the past year, in contrast to 9% of patients in the lung function trials.

In the lung function trials, the different treatment arms had similar mean days of exposure (136 to 146 days). Likewise, the mean days of exposure was similar across the treatment arms in the exacerbation trials too (295 to 308 days). Mean compliance rates were similarly high in the Phase 3 studies (approximately 97%), as assessed by patient diary.

Deaths

Given a relatively older population with comorbidities, deaths are expected in a COPD program. In the lung function trials, a total of 8 deaths were reported during the treatment period and 3 deaths in the post-treatment follow-up period (1 week after the last dose). With the exception of zero deaths in the FF 200 arm, the deaths were evenly distributed across the other active treatment arms and placebo (placebo, n=2 [<1%]; FF/VI 50/25, n=2 [<1%]; FF/VI 100/25, n=2 [<1%]; FF/VI 200/25, n=1 [<1%]; VI 25 n=3 [<1%], FF 100, n=1 [<1%]). In the exacerbation trials, 43 deaths were reported during treatment and 10 deaths were reported in the post-treatment period. The deaths were evenly distributed across the treatment arms in these trials too. The most commonly cited causes of death in the clinical program were myocardial infarction and COPD, which are consistent with the disease population and typical comorbid conditions. There was no apparent dose effect in terms of the total number of fatal cases or specific causes cited, with the exception of pneumonia, which appeared to occur most frequently in the FF/VI 200/25 arm. The risk of pulmonary infection with increasing doses of inhaled corticosteroid is discussed separately in further detail below.

Serious adverse events (SAE)[17] and discontinuations due to adverse events

Overall rates for early withdrawal due to an AE and the reported System Organ Class for these AEs were fairly similar across active treatment arms (7 to 10%) and placebo (8%) in the lung function trials and across the active treatment arms in the exacerbation trials (6 to 8%).

In terms of SAEs, a wide range of events were reported in the clinical program. In most cases, one or two events in an individual AE category were reported for a given treatment arm, making it difficult to identify a specific safety signal or to assess causality. Overall, the most commonly reported SAEs were COPD and pneumonia. The risk of pneumonia is discussed in further detail in the following section.

Other adverse events of interest

Adverse events of interest included local and systemic corticosteroid effects, hypersensitivity, tremor, metabolic effects, and cardiovascular effects related to adrenergic stimulation. In general, the pattern of AEs did not indicate a specific safety signal, with the exception of dose-related pneumonia.

- **Pneumonia**

As mentioned previously, an increased risk of pneumonia has been observed with higher doses of inhaled corticosteroid in previous COPD programs. A similar pattern was observed in the FF/VI program, most prominently in the exacerbation trials, which were longer in duration and enrolled a more severe population at baseline. The analysis of pneumonia in Trials 2871 and 2970 shows an increased risk for all doses of FF/VI over VI alone, with a numerically higher number of fatal pneumonias observed in the FF/VI 200/25 arm (Table 8 Adverse event of interest: pneumonia (Trials 2871 and 2970).

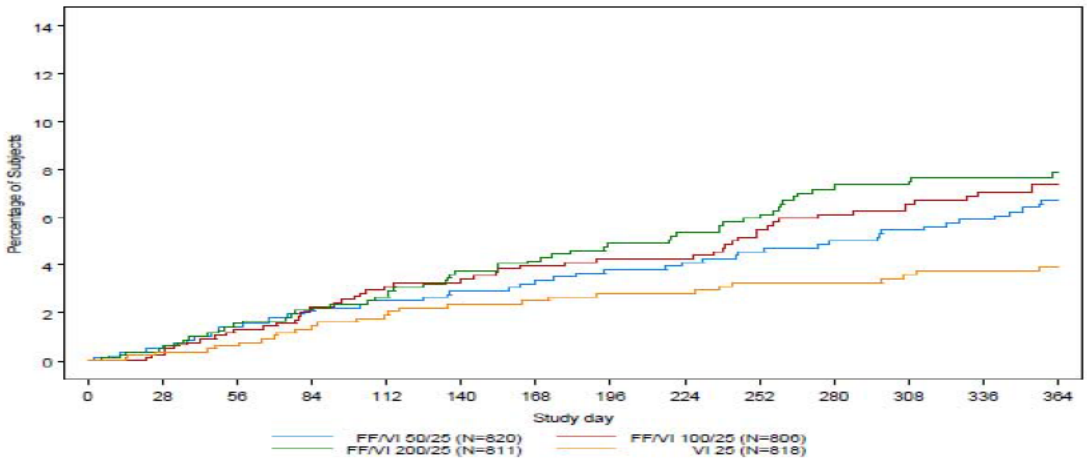
[17] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient 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.

Table 8 Adverse event of interest: pneumonia (Trials 2871 and 2970)[a]				
	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Total number of pneumonia events, n (%)	54 (7)	58 (7)	65 (8)	28 (3)
Total number of patients with pneumonia	48 (6)	51 (6)	55 (7)	27 (3)
Deaths: pneumonia	0	1 (<1)	6 (<1)	0
Pneumonia reported as SAE	24 (3)	25 (3)	23 (3)	8 (<1)
Pneumonia leading to early discontinuation from trial	3 (<1)	5 (<1)	8 (<1)	3 (<1)
Pneumonia[b]				
Absolute risk difference	0.026	0.030	0.035	-
NNTH (95% CI)	39 (22, 191)	33 (19, 106)	29 (18, 73)	-
Patients with more than one pneumonia	5	7	8	1

[a] reported as number of subjects (%)
[b] absolute risk difference and number-needed-to-harm relative to VI 25
Source: Module 5.3.5.3.28, Integrated Summary of Safety, Table 69 and Table 2.144 and Agency's statistical review

Kaplan-Meier analysis of time to first on-treatment pneumonia shows a similar dose-related increase (Figure 16).

Figure 16 Time to first on-treatment pneumonia (Trials 2871 and 2970)



Source: Module 5.3.5.3.28, Integrated Summary of Safety, Figure 13

A dose-related trend was also observed in the lung function trials, although the separation among doses was less pronounced and the overall number of events was much lower, which is expected since Trials 2206 and 2007 were shorter in duration and enrolled a milder population (data not shown).

While there are limitations to cross-study comparisons, such as different screening and diagnostic criteria for pneumonia, it is worth noting the relative imbalances observed in controlled trials for Advair Diskus and Symbicort. In two 52-week trials in 1,579 patients, a higher rate of pneumonia was observed for Advair 250/50 (7%) compared to salmeterol (3%)[1].

In the three-year TORCH mortality trial (n=6,184), a rate of 16% was observed for Advair 500/50 compared to 9% in the placebo arms. In a 6-month trial in 1,704 patients, the incidence of pneumonia was reported to be similar between Symbicort 160/4.5 (1%) and placebo (1%), but the rate of other lung infections (e.g., bronchitis, viral lower respiratory infections) was higher in the Symbicort 160/4.5 arm (8%) compared to formoterol alone (5%)[18]. In a 12-month trial in 1,964 patients, the rates for other lung infections were 8% and 7%, respectively.

- **Bone disorders**

The Applicant assessed bone disorders as another category of adverse events of special interest. This category included a range of terms related to decreases in bone density and fracture, which are included as drug class labeling for other inhaled corticosteroid products. As shown in Table 9, an increased risk of fractures was observed with FF/VI compared to VI alone.

Table 9 Adverse event of interest: bone fractures (Trials 2871 and 2970)[a]

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Fractures[b]	14 (2)	19 (2)	14 (2)	8 (<1)
Absolute risk difference[c]	0.007	0.014	0.008	-
NNTH (95% CI)	137 (51, ∞)	72 (36, 857)	134 (50, ∞)	-

[a] reported as number of subjects (%)
[b] composite safety endpoint of preferred terms related to bone disorders
[c] absolute risk difference and number-needed-to-harm relative to VI 25
Source: Module 5.3.5.3.28, Integrated Summary of Safety, Table 69 and Table 2.144 and Agency's statistical review

Bone disorder data was also assessed in the TORCH trial. Bearing in mind the limitations of a comparison of rates across studies, the rates observed were 5% for Advair 500/50 compared to 4% for salmeterol[1]. The Division also obtained an internal consultation for assessment of fracture risk data with FF/VI. The consultation reviewed the available literature for inhaled corticosteroids and fracture risk and noted a lack of consensus with both positive and negative studies reported. In terms of the FF/VI data, the consultation noted that while there appeared to be a small, dose-dependent increase in fractures in one of the exacerbation trials, Trial 2871, this finding was not observed in the other exacerbation trial, Trial 2970, when safety data were not pooled. The consultation also commented that a study to confirm the effect of FF on fractures would likely pose challenges in terms of feasibility and may not provide definitive results.

Common adverse events

In the lung function studies, the overall rates of AEs varied among the treatment arms (47 to 55%), although there was no apparent dose-relationship. The placebo arm had an overall rate of 48% for comparison. Adverse events occurring in ≥3% and more commonly than in placebo are summarized in Table 10.

[18] Symbicort Inhalation Aerosol prescribing information, AstraZeneca. Retrieved from http://www1.astrazeneca-us.com/pi/symbicort.pdf on February 7, 2013.

Table 10 Adverse events occurring in ≥3% and more commonly than in placebo (Trials 2206 and 2207)							
Preferred term	**Placebo N=412**	**FF/VI 50/25 N=206**	**FF/VI 100/25 N=410**	**FF/VI 200/25 N=205**	**VI 25 N=408**	**FF 100 N=410**	**FF 200 N=203**
Any AE	196 (48)	114 (55)	203 (50)	93 (45)	196 (48)	201 (49)	96 (47)
Nasopharyngitis	31 (8)	14 (7)	35 (9)	13 (6)	41 (10)	32 (8)	20 (10)
Upper respiratory tract infection	13 (3)	16 (8)	29 (7)	7 (3)	20 (5)	16 (4)	5 (2)
Headache	20 (5)	12 (6)	29 (7)	15 (7)	36 (9)	30 (7)	11 (5)
Oral candidiasis	3 (<1)	8 (4)	12 (3)	4 (2)	5 (1)	7 (2)	5 (2)
COPD	8 (2)	0	9 (2)	5 (2)	11 (3)	2 (<1)	2 (<1)
Hypertension	7 (2)	3 (1)	3 (<1)	1 (<1)	1 (<1)	3 (1)	7 (3)

Source: Module 5.3.5.28, Integrated Summary of Safety, Table 2.13

In the exacerbation trials, the overall rate of AEs was similar in the FF/VI arms (76-77%), which was higher than the VI 25 arm (70%). This difference was attributable mainly to a discrepancy in the number of infections.

Table 11 Adverse events occurring in ≥5% (Trials 2871 and 2970)				
Preferred term	**FF/VI 50/25 N=820**	**FF/VI 100/25 N=806**	**FF/VI 200/25 N=811**	**VI 25 N=818**
Any AE	620 (76)	621 (77)	622 (77)	575 (70)
Nasopharyngitis	112 (14)	128 (16)	158 (19)	112 (14)
Upper respiratory tract infection	84 (10)	90 (11)	75 (9)	78 (10)
Oral candidiasis	78 (10)	73 (9)	76 (9)	50 (6)
Bronchitis	41 (5)	38 (5)	47 (6)	42 (5)
Sinusitis	47 (6)	42 (5)	40 (5)	36 (4)
Pneumonia	46 (6)	49 (6)	45 (6)	23 (3)
COPD	53 (6)	56 (7)	53 (7)	53 (6)
Headache	61 (7)	57 (7)	67 (8)	60 (7)
Back pain	40 (5)	54 (7)	37 (5)	53 (6)

Source: Module 5.3.5.28, Integrated Summary of Safety, Table 2.89

The application included subgroup analysis of AEs by age, gender, race, and COPD severity. The overall rate of adverse events trended higher with age in the lung function trials but not in the longer, exacerbation trials, and the distribution of AEs was similar to the profile observed in younger patients. No consistent differences by gender, baseline disease severity (GOLD stage), or cardiovascular history were observed, and subgroup analysis by race was limited by the low number of non-White patients.

Other safety parameters

Other safety assessments performed in the clinical program included laboratory parameters, vital signs, and ECG evaluations. While some clinically relevant shifts were observed in a few individuals, the overall distribution did not indicate a specific safety signal for FF/VI 100/25.

Safety in asthma

The package inserts for currently approved LABA products describe an increased risk of severe asthma-related adverse events. While a similar safety concern has not been specifically raised for COPD, the clinical experience with VI in an asthma population is of interest as secondary safety information and as confirmation of the proposed dose. Therefore, the application provided a summary of safety data from the asthma development program for FF/VI, which includes data from approximately 10,000 patients, of which over 2,500 have received FF/VI. The summary included an adjudicated assessment by an independent, blinded committee of a composite safety endpoint for asthma-related hospitalizations, intubations, and deaths, which did not suggest an increased risk of a severe asthma-related AE associated with VI alone or in combination with FF. A total of three deaths were reported in the program (1 in FF/VI 100/25, FF 100, and placebo arms each), but none were adjudicated as asthma-related. In terms of asthma-related hospitalizations, no events were reported for placebo, FF/VI 200/25, or salmeterol plus ICS, and rates of <1% were reported for FF/VI 100/25 (n=11 cases), FF 100 (n=7), FF 200 (n=1), fluticasone propionate 1000 (n=2), and VI 25 plus other ICS (n=1). A total of 3 intubations were reported for the FF 100 treatment group, but no asthma-related intubations were reported in any of the treatment arms.

Safety summary

The safety database for FF/VI is large and includes safety information for the individual components, FF and VI, as well as for the combination from both COPD and asthma populations. The nature of the adverse events identified for FF/VI appears generally consistent with the general safety profile of similar combination products. In particular, a dose-related risk of respiratory infections and a lesser risk of fractures were identified. While a direct, head-to-head comparison of long-term safety with other approved ICS/LABA combination products is not available, safety data for other ICS/LABA products relative to the corresponding LABA monotherapies is available. The proportion of events appears similar to the proportion observed in the FF/VI program. This information provides some context for the relative safety of FF/VI 100/25 compared to VI 25 alone. Safety information from the parallel asthma development program provides secondary support, including support for the selection of an appropriate VI dose.

9. Advisory Committee Meeting

A meeting of the PADAC was scheduled for March 7, 2013, but was postponed to April 17, 2013, due to inclement weather. The anticipated major issues for discussion are the strength of the data to support the benefit of the FF/VI 100/25 combination over the VI component alone and the risk-benefit balance associated with the addition of an ICS.

10. Pediatrics

As COPD is largely a disease of adults, the requirement for pediatric trials under the Pediatric Research Equity Act (PREA) was waived. The Pediatric Research Committee (PeRC) concurred with the waiver.

11. Other Relevant Regulatory Issues

The Applicant conducted the clinical trials using Good Clinical Practices and provided the required financial disclosure information for investigators, which did not suggest a conflict of interest that would have impacted the overall conclusions of the review. A DSI audit was requested of three study sites that enrolled a higher number of patients: Richard Martinez, MD (Boerne, TX), Joven Roque Gonong, MD (Quezon City, Philippines), and Edward Kerwin, MD (Medford, OR). Dr. Gonong's site was also notable as a site of 7 fatal pneumonias in the development program. Aside from sporadic protocol deviations at each site, no irregularities were noted that would have been likely to impact the main efficacy and safety conclusions. The ORA field staff noted in the report of Dr. Gonong's site that in each of the 7 deaths, patients' relatives had refused further diagnostic testing or patient intubation, which may have limited the medical interventions performed.

12. Labeling

This section provides a high level overview of labeling, which remains pending at the time of this memorandum. The proposed tradename is Breo Ellipta, which has been found acceptable by DMEPA. Consults from OPDP and OSE were received and included in the labeling process. Carton and container labeling were also reviewed. Regarding the package insert, the following are high level revisions proposed for the product label:

- Highlights: Revise to conform with labeling for other LABA-containing products
- Section 2: Dosage and Administration: Remove (b) (4) information
- Section 5, Warnings and Precautions: Inclusion of clinical trial data relevant to the warnings and precautions statements regarding the risk of pneumonia, bone disorders, and glaucoma
- Sections 8, 10, and 12: Removal of unnecessary information and revision to maintain consistency with other ICS/LABA products.
- Section 14, Clinical Studies: Addition of dose-ranging information for both the individual FF and VI components, include serial time curves at Day 1 and Day 28 from the VI dose-ranging trial in COPD, Trial 1045. Inclusion of separate sections featuring results from the two lung function trials, 2206 and 2207, and the exacerbation trials, 2871 and 2970.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is Approval, pending resolution of the outstanding CMC issues and satisfactory inspections and the upcoming discussion at the PADAC meeting.

- Risk Benefit Assessment

The application includes replicate, statistically significant results for the efficacy of VI 25 alone versus placebo and FF/VI 100/25 versus FF 100 in terms of lung function (weighted mean FEV1 and trough FEV1). These data support the bronchodilatory contribution of VI 25 to the combination. The data to support the lung function benefit of FF/VI 100/25 over VI 25 alone (relative contribution of FF), however, are less robust. While the magnitude of the change in trough FEV1 in the lung function trials (45 and 48 ml) was consistent for FF/VI 100/25 between the two lung function trials, there was no consistent dose response, and the results were not statistically significant based on the pre-specified testing strategy (a nominal p-value of <0.05 was reported for the exacerbation trial, Trial 2871, outside of the testing hierarchy). The weighted mean FEV1 values over the duration of the 6-month trials did show separation between FF/VI 100/25 and VI 25, but it appears that VI 25 provides the main contribution to FF/VI's immediate lung function effects. FF/VI 100/25 as a whole appears to have a similar effect on lung function as another ICS/LABA product, fluticasone propionate/salmeterol, which is currently approved for the same indication.

The COPD exacerbation endpoint offers an alternative, clinically meaningful assessment of the benefit of FF/VI 100/25 over VI 25 alone. While similar issues regarding the testing hierarchy for lower doses were encountered in Trial 2871, a statistically significant result for FF/VI 100/25 was observed in Trial 2970 with a comparable numerical result in Trial 2871. In both trials, the mean rate of moderate to severe exacerbations in the VI 25 arm was approximately 1 exacerbation per year; the mean reduction observed with FF/VI was about a quarter to a third of an event in one year with FF/VI 100/25. Analyses of the time to exacerbation and exacerbations requiring systemic corticosteroids were also supportive.

The safety profile for FF/VI 100/25 appears similar to the safety profile described for other ICS/LABA products approved for COPD. An increase in pneumonias related to the dose of the FF component was observed. There also appeared to be an increased risk of fractures associated with use of the FF/VI combination over VI alone. Other commonly observed adverse events included nasopharyngitis, upper respiratory tract infection, and oral candidiasis.

In summary, GSK has conducted an extensive program to evaluate the efficacy and safety of FF/VI. Because neither VI nor FF is approved as a monotherapy for patients with asthma or COPD, GSK was asked to provide data to support the nominal dose and dosing frequency for each of the components and data demonstrating the relative efficacy contributions of each to justify the combination for the treatment of COPD. The totality of the data supports the benefit of FF/VI 100/25 in terms of an improvement in lung function and a reduction in exacerbations. The data indicate that VI 25 provides the primary benefit for lung function while the FF 100 component acts in the combination to reduce the frequency of COPD exacerbations. Based on these considerations, the CDTL review makes a conditional recommendation for Approval, pending resolution of the outstanding CMC issues and the discussion at the upcoming Advisory Committee meeting.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies (REMS) are recommended for this application. The Applicant included a REMS proposal in the original submission comprised of a medication guide and communication plan that was consistent with the REMS programs previously required of other LABA-containing products. As the REMS programs for these other products have since been removed, and no new risks have been identified that would warrant a REMS, the CDTL review does not recommend a REMS for this application.

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing requirements or commitments are recommended for this application.

- Recommended Comments to Applicant

None.

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/s/

SUSAN L LIMB
04/01/2013