PULMONARY ALLERGY DRUGS ADVISORY COMMITTEE MEETING

FDA Briefing Document

March 7, 2013

NDA 204-275: fluticasone furoate and vilanterol inhalation powder for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)

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 new drug application (NDA) 204-275, fluticasone furoate and vilanterol inhalation powder, for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD), to this 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: February 7, 2013

From: Susan Limb, MD
Medical Team Leader, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for New Drug Application (NDA) 204-275, fluticasone furoate and vilanterol inhalation powder, at a dose of 100/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)

Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on March 7, 2013. As members of the PADAC, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss (NDA) 204-275 from GlaxoSmithKline (GSK), fluticasone furoate and vilanterol inhalation powder at a dose of 100/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). The proposed tradename is Breo Ellipta.

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. 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.

Therefore, the discussion at the PADAC meeting will include a discussion of the data in support of FF and VI individually as well as in combination. As you deliberate on the data submitted in support of the proposed indications, you will be asked to consider 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 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 PADAC meeting will be an important factor in our decision on this application.

The clinical and statistical issues related to the FF/VI clinical trial results are the primary focus of this PADAC meeting. In determining approvability of a product, the Agency takes into consideration other factors in the regulatory decision-making process, including the manufacturing and controls of a product and preclinical data. These will not be the focus of this PADAC meeting.

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, and a summary of the clinical pharmacology program.

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

[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

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 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).

---

[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.

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**

Product Information

Fluticasone furoate/vilanterol inhalation powder is a novel, fixed-dose, combination product administered by oral inhalation. The proposed dose is FF/VI 100/25 mcg once daily. Neither FF nor VI is currently available as an inhalation monotherapy, and as mentioned above, there are currently no plans to market VI commercially. FF, the ICS component of the combination product, is available as a nasal spray suspension, approved for the treatment of symptoms or seasonal and perennial allergic rhinitis in patients 2 years of age and older (Veramyst Nasal Spray).

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.

Nonclinical Pharmacology and Toxicology

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-

[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.

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.

Clinical Pharmacology

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, FF C_{max} and $AUC_{(0-24)}$ were 67% 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.

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	102 102 102 103 102 103	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	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD	Trough FEV1	49 sites (US, Canada, Mexico, E. and W. Europe, S. America, Korea, Philippines)

Table 1 FF, VI, and FF/VI dose selection					
Trial ***Trial period***	**Design**[a]	**N**[b]	**Treatment**[c]	**Endpoint**	**Sites** *% US sites*
		101	Placebo		*50%*
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 $FEV1_{0\text{-}24h}$	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 $FEV1_{0\text{-}24h}$	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. and E. Europe, Philippines, 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

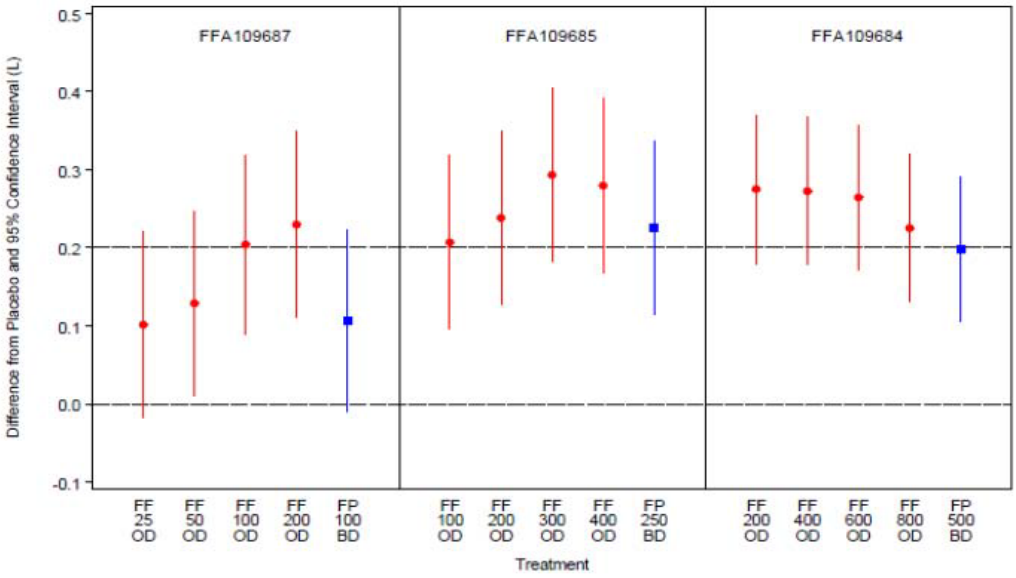
Dose selection

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

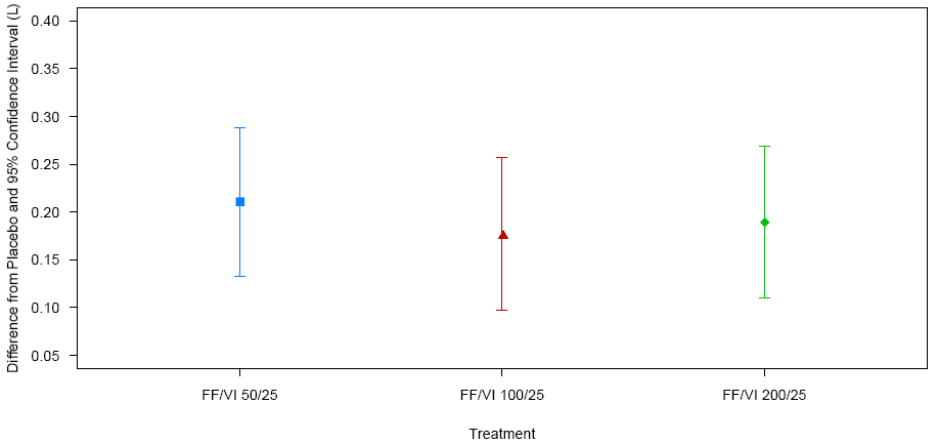
Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
FF 200 QPM	140	2.714	0.221	0.108 (0.064, 0.153)	<0.001
FF 100 BID	142	2.703	0.210	0.098 (0.054, 0.142)	<0.001
FP 200 QD	42	2.693	0.199	0.087 (0.014, 0.161)	0.020
FP 100 BID	43	2.737	0.244	0.132 (0.059, 0.205)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



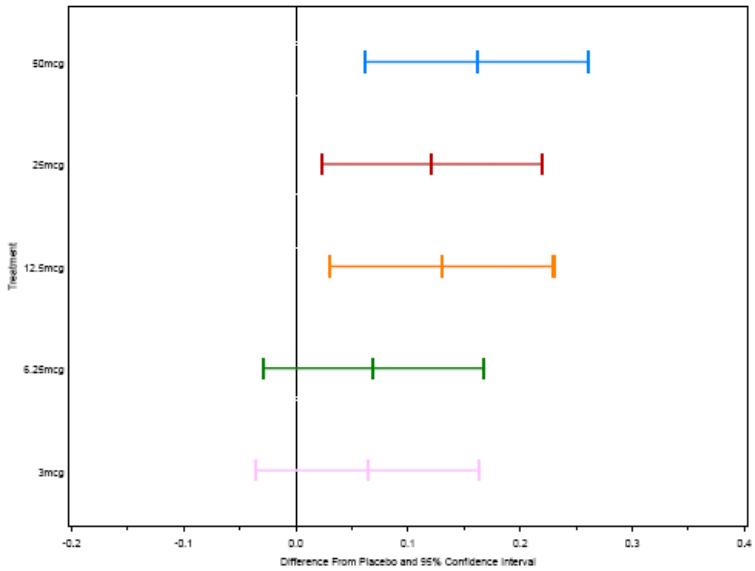
Source: Module 5.3.5.1, CSR, Figure 6.07

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

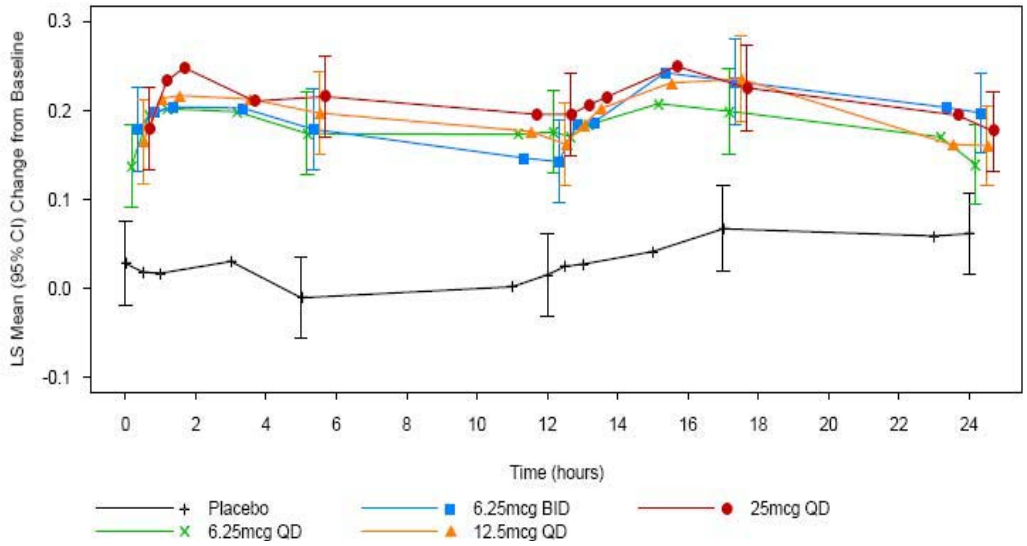


Source: Module 5.3.5.4, CSR, Figure 7.1

- **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



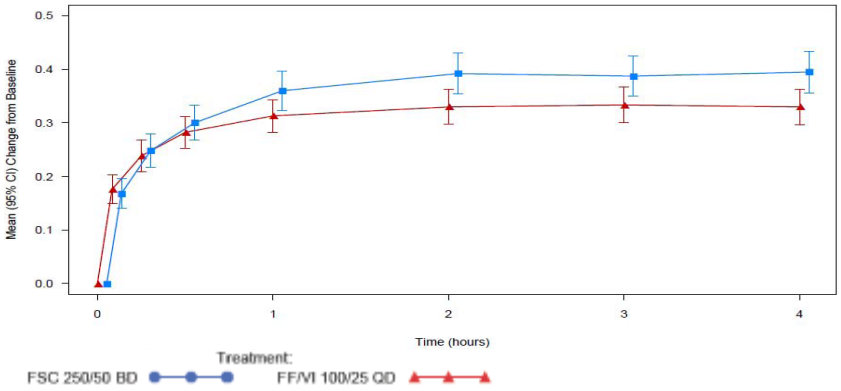
Source: Module 5.3.5.4, Complete Study Report, Figure 6.12

- **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.

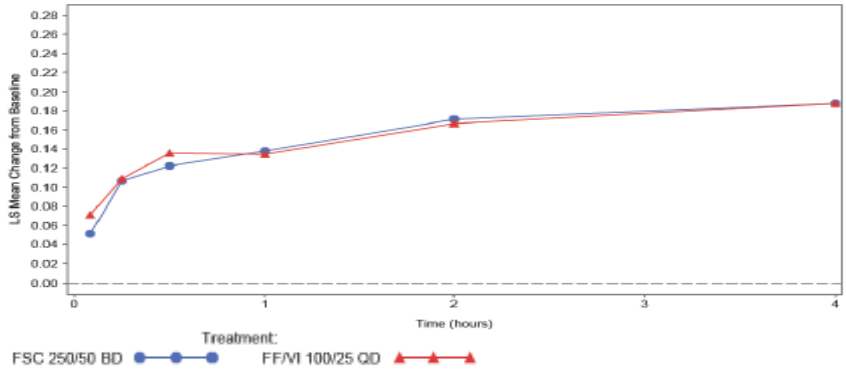
The FF/VI program included other trials with an active comparator to help benchmark the bronchodilatory effects of VI. GSK conducted one trial in asthma (Trial 3091) and two trials in COPD (3109 and 2352) comparing FF/VI 100/25 to Advair 250/50 (fluticasone propionate/salmeterol). Although these trials 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): LS mean 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



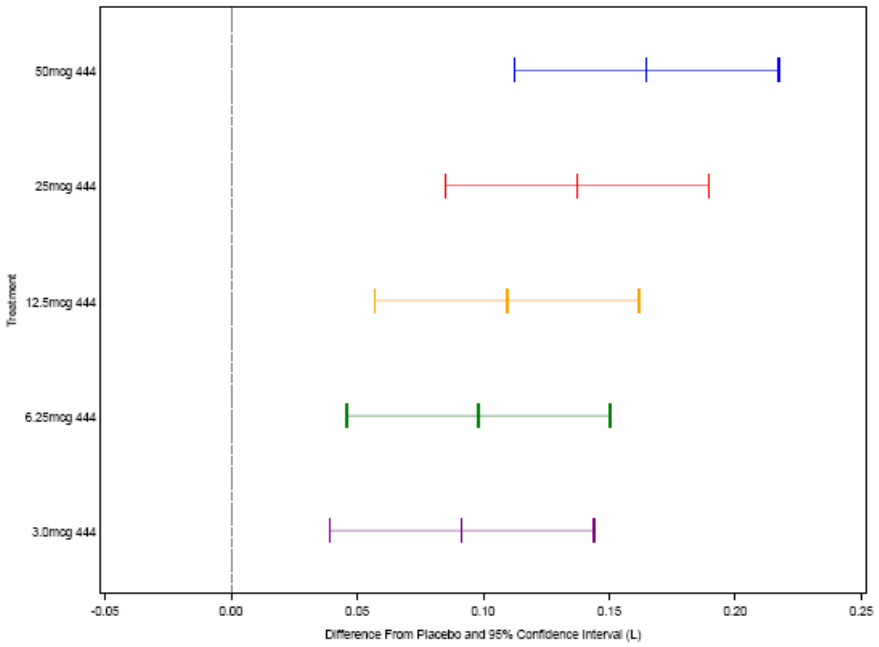
Source: Module 5.3.5, Complete Study Reports, Figure 2

VI component: Dose exploration in COPD

- **Nominal dose selection**

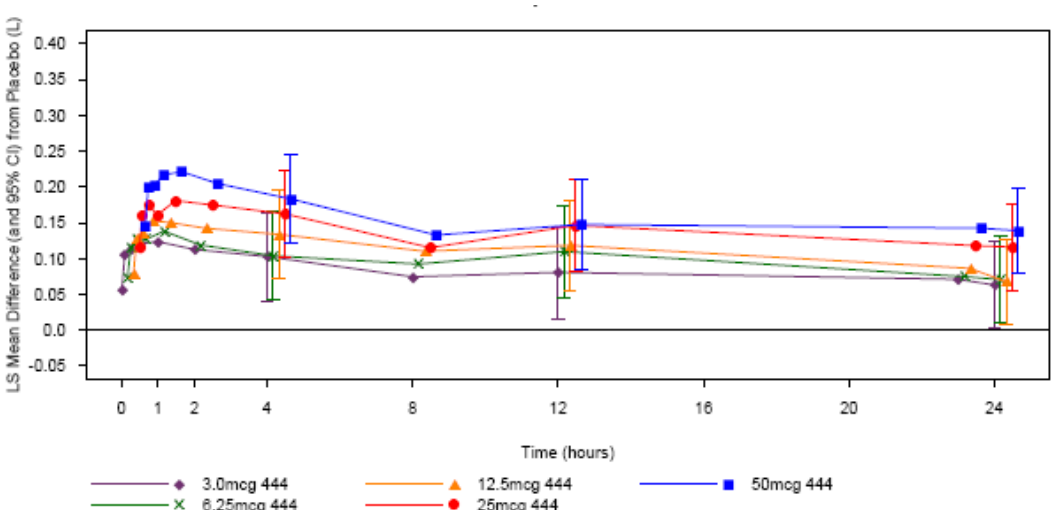
A similar range of nominal doses was evaluated in patients with COPD. Trial 1045 was a 28-day, randomized, double-blind, placebo-controlled, parallel group trial in 602 patients with moderate COPD. Patients were randomized by bronchodilator reversibility at baseline. Patients were randomized to once-daily 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.

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

[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.

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

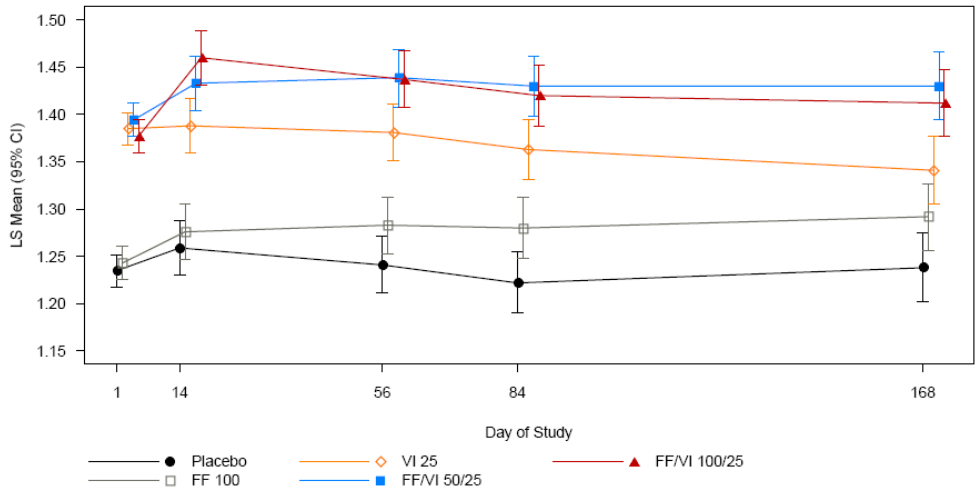
The two lung function trials, 2206 and 2007, included a total of 2,254 patients in the ITT population, of which 410 patients received the proposed FF/VI 100/25 dose. The mean age was 62 years and 70% were male. Twenty-four percent reported at least one exacerbation in the past year that required corticosteroids and/or antibiotics and approximately 8% reported a hospitalization in the past year due to an exacerbation.

In each of the two lung function trials, 2206 and 2007, study completion rates ranged from 27 to 33%, with the highest rate of early discontinuations occurring in the placebo arms. Lack of efficacy was cited as a reason for discontinuation most commonly in the placebo arms. While these rates of discontinuation are fairly high, 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**

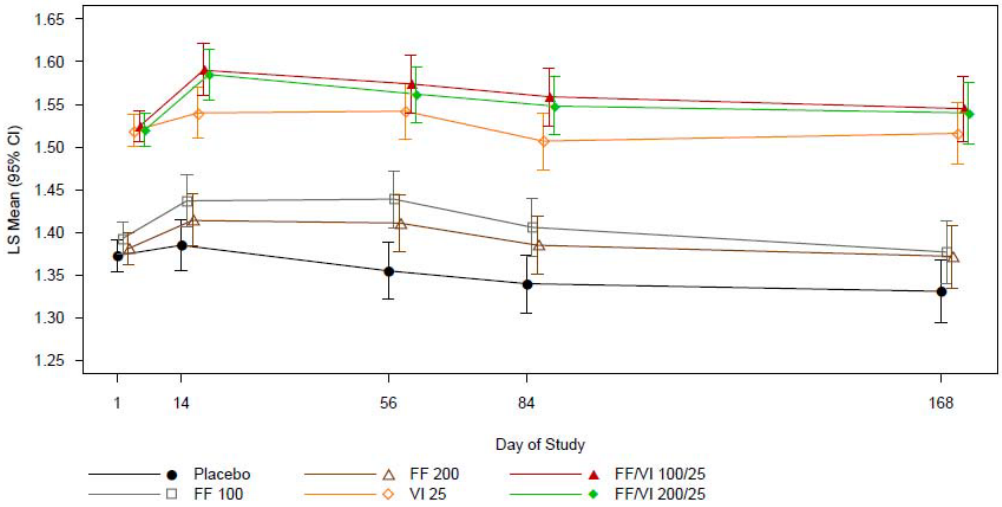
The change from baseline in weighted mean FEV1 0-4 hours (post-dose) at Day 167 was assessed as a primary endpoint in Trials 2206 and 2207. In Trial 2206, a statistically significant result for VI 25 versus placebo was observed ($p<0.001$), as well as for FF/VI 100/25 over FF 100 ($p<0.006$) (Figure 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.

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 4, 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 4 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 5). 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,

Table 5 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 completion 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 6 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 6 Trials 2871 and 2970: Moderate and severe COPD exacerbations

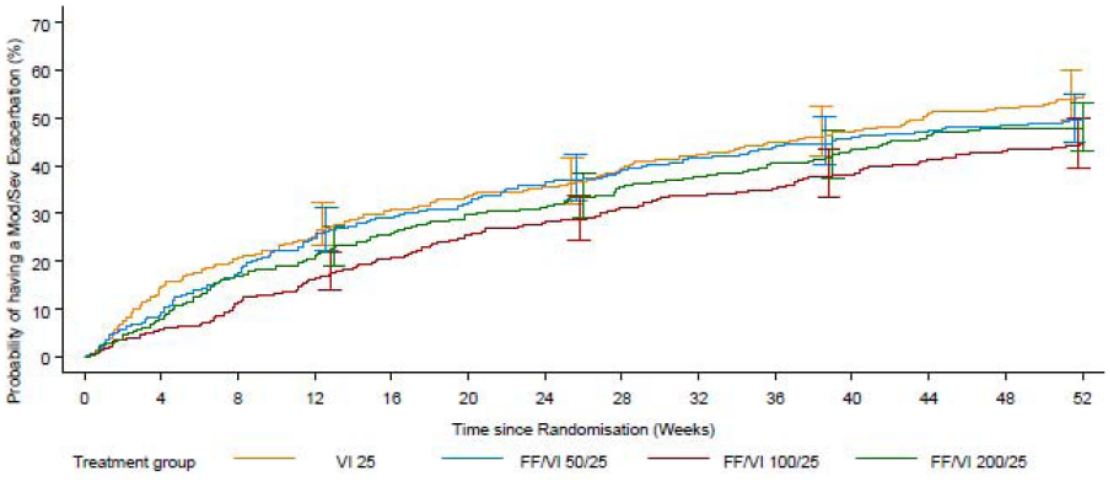
Treatment	N	LS mean annual rate	Ratio vs VI	95% CI	P
2871					
FF/VI 200/25	402	0.90	0.85	(0.70, 1.04)	0.109
FF/VI 100/25	403	0.70	0.66	(0.54, 0.81)	<0.001*
FF/VI 50/25	408	0.92	0.87	(0.72, 1.06)	0.181*
VI 25	409	1.05	-	-	-
2970					
FF/VI 200/25	409	0.79	0.69	(0.56, 0.85)	<0.001
FF/VI 100/25	403	0.90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

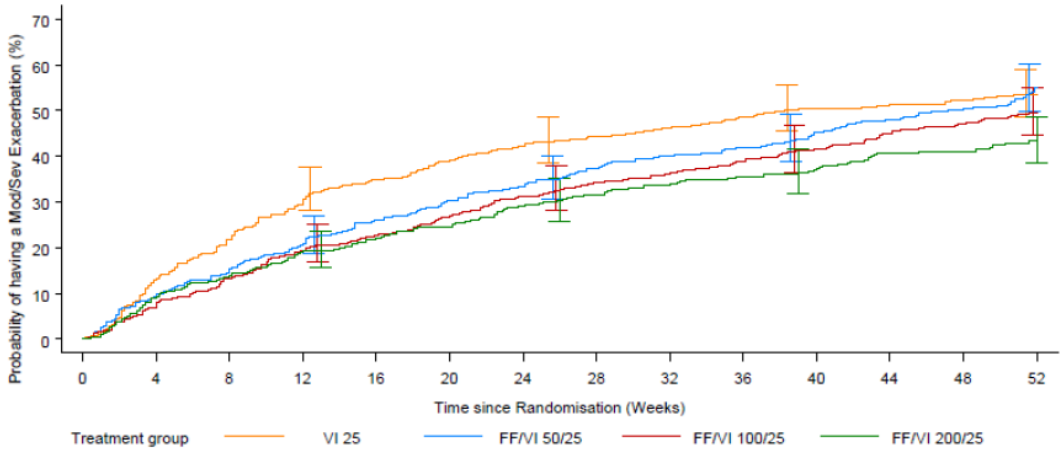
While the testing hierarchy specifies success of the primary endpoint before proceeding to testing of secondary endpoints, examining the exacerbation data in other ways is still informative. The time to first moderate or severe exacerbation showed a dose-related numerical treatment effect for FF/VI 100/25 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.

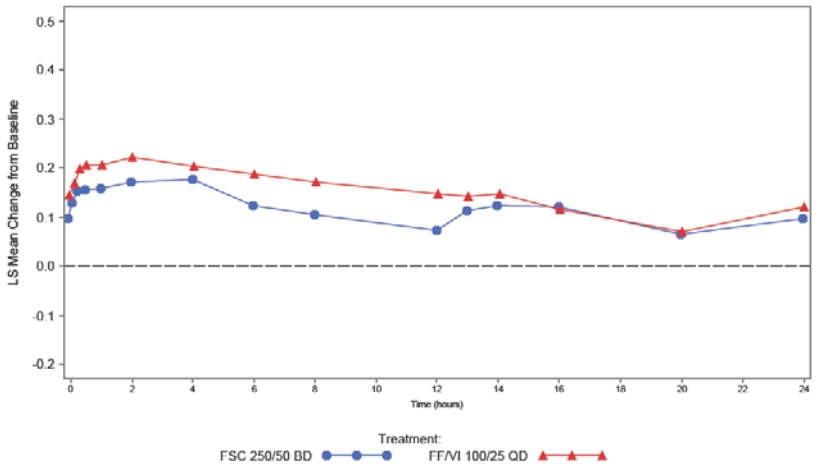
Comparator trials

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, placebo-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.

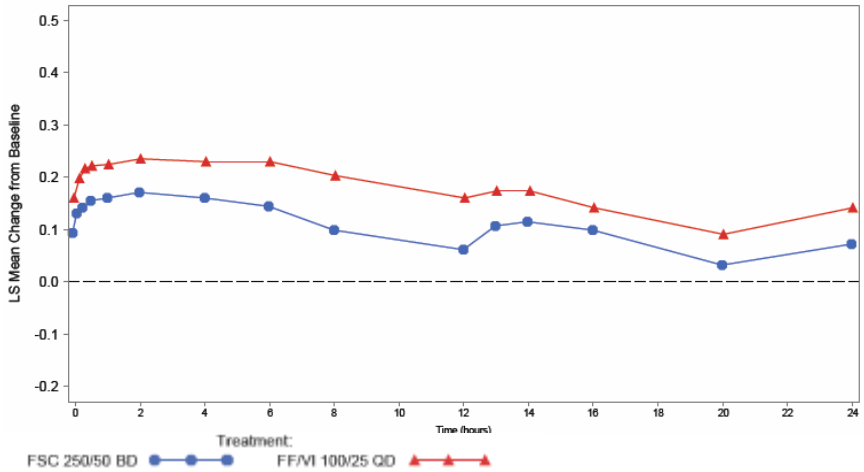
The primary endpoint was the change from baseline trough in 24-hour weighted-mean serial FEV1 at 12 weeks. The results of these trials demonstrated a similar or increased mean change from baseline for FF/VI 100/25 compared to Advair 250/50 or 500/50. Representative results from Trials 2352 and 3019 are 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

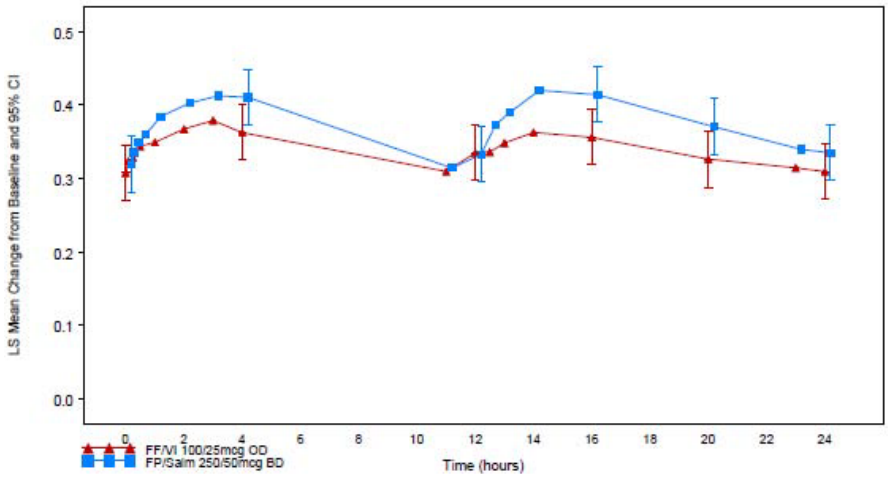
Figure 14 Trial 3109 (COPD): LS mean change from baseline in FEV1 (0-24h) at Day 84



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 ranged from 24 to 58 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 (a nominal p-value of <0.05 was reported for the exacerbation trial, Trial 2871, outside of the testing hierarchy).

On the other hand, the COPD exacerbation endpoint offers an alternative, and perhaps more 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.

Safety findings

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 11%) and placebo (9%) in the lung function trials and across the active treatment arms in the exacerbation trials (6 to 8%).

[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.

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. A greater number of pneumonias were reported as SAEs for FF/VI 200/25 over the other treatment arms; 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 7 Adverse event of interest: pneumonia (Trials 2871 and 2970).

Table 7 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 NNTH (95% CI)	 0.026 39 (22, 191)	 0.030 33 (19, 106)	 0.035 29 (18, 73)	 - -
Patients with more than one pneumonia	5	7	6	1

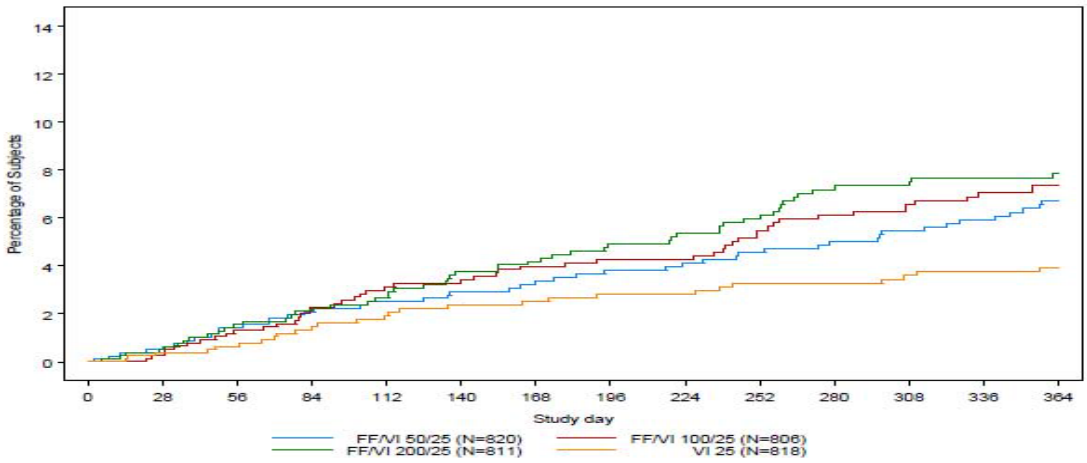
[a] reported as number of subjects (%)

[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 8, an increased risk of fractures was observed with FF/VI compared to VI alone.

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

Table 8 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 9.

Table 9 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)	7 (2)	3 (<1)	1 (<1)	1 (<1)	7 (2)	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 10 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. 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.

Benefit-risk 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 benefit of FF/VI 100/25 over VI 25 alone (relative contribution of FF) in terms of bronchodilation, however, are less robust. 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). While the weighted mean FEV1 values over the duration of the 6-month trials showed separation between FF/VI 100/25 and VI 25, it appears that VI 25 provides the main contribution to FF/VI's bronchodilatory effects.

The COPD exacerbation endpoint offers an alternative, and perhaps more 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. While the submitted data are extensive, the data to support the benefit of FF/VI 100/25 over VI 25 is not entirely consistent. Whether there is substantial evidence of efficacy of FF/VI to balance the identified safety concerns is a topic for discussion at the meeting.

Summary

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by GSK to support the approval of fluticasone furoate/vilanterol 100/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with COPD. The major issues for discussion are: 1) the adequacy of the efficacy data to support the proposed dose of FF/VI 100/25 for the long-term, maintenance treatment of airflow obstruction; 2) the adequacy of the efficacy data to support the proposed dose of FF/VI 100/25 for reducing COPD exacerbations; 3) the adequacy of the safety data to support long-term use of FF/VI 100/25 in COPD patients; and 4) the benefit-risk assessment for FF/VI 100/25 for the proposed indications, particularly the benefit-risk assessment for use of FF/VI 100/25 over a long-acting bronchodilator alone.

At the meeting, GSK will present an overview of the clinical program and the efficacy and safety data. The Agency will follow with its own presentation of the efficacy and safety data. Please consider the questions listed in the following section that will be discussed after you listen to the presentations. Some of the questions are intended for discussions only, while others will be accompanied by a vote.

Draft Topics for Discussion

1. Discuss the efficacy data for fluticasone furoate/vilanterol (FF/VI) 100/25 mcg once daily in comparison to the data for VI 25 mcg alone in support of the two proposed indications:
    - the long-term, maintenance treatment of airflow obstruction
    - the reduction of COPD exacerbations

2. Do the efficacy data provide substantial evidence of a clinically meaningful benefit for FF/VI 100/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction in COPD? **(Voting question)**
    - *If not, what further data should be obtained?*

3. Do the efficacy data provide substantial evidence of a clinically meaningful benefit for FF/VI 100/25 mcg once daily for the reduction of COPD exacerbations? **(Voting question)**
    - *If not, what further data should be obtained?*

4. Discuss the overall safety profile of FF/VI 100/25 mcg once daily.

5. Has the safety of FF/VI 100/25 mcg once daily in COPD been adequately assessed for the proposed indications? **(Voting question)**
    - *If not, what further data should be obtained?*

6. Do the efficacy and safety data provide substantial evidence to support approval of FF/VI 100/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction in COPD? **(Voting Question)**
    - *If not, what further data should be obtained?*

7. Do the efficacy and safety data provide substantial evidence to support approval of FF/VI 100/25 mcg once daily for the reduction of COPD exacerbations? **(Voting Question)**
    - *If not, what further data should be obtained?*

Clinical Review for the Pulmonary and Allergy Advisory Committee Meeting

March 7, 2013

Fluticasone furoate/Vilanterol inhalation powder NDA 204275

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

Proposed indications:
Maintenance treatment of COPD
and reduction in COPD exacerbation

Reviewer: Sofia Chaudhry, MD
Team Leader: Susan Limb, 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

Table of Contents

Table of Tables

Table of Figures

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

GlaxoSmithKline (GSK) has submitted a New Drug Application (NDA) for a new, once-daily, fixed-dose, orally-inhaled corticosteroid (ICS) and long-acting-beta-agonist (LABA) combination product. This product contains fluticasone furoate (FF) as the ICS, and vilanterol (VI) as the LABA. GSK proposes two indications for FF/VI: the maintenance treatment of airflow obstruction and the reduction in exacerbations in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is one oral inhalation of FF/VI 100/25 mcg once daily.

As neither monocomponent is approved as an orally-inhaled formulation, GSK's development program for this combination product is extensive. The application includes dose-ranging and efficacy and safety information for both monocomponents and the combination product. Three doses of FF in combination with a single dose of VI (FF/VI 50/25, 100/25, 200/25) were evaluated in the FF/VI phase 3 COPD trials. GSK conducted two, 24-week, lung function trials [HZC112206 (2206) and HZC112207 (2207)] as well as two 52-week exacerbation trials [HZC102871 (2871) and HZC102970 (2970)]. These four trials are the primary source of efficacy data. In addition, this review utilizes these same four trials as the primary source of safety data, with supplemental safety data from other trials referenced when pertinent.

In terms of efficacy, while the application provides statistically significant results for lung function for VI 25 compared to placebo, the data to support the benefit of FF/VI 100/25 over VI 25 alone is less clear. None of the comparisons of FF/VI to VI for trough FEV1 are statistically significant. However, a numerical treatment benefit for FF/VI 100/25 over VI 25 mcg in trough FEV1 is seen in all of the phase 3 pivotal trials. This benefit ranges from 45 to 58 ml in three of the trials with a smaller treatment effect size in Trial 2871 (24 ml mean improvement). Of note, this treatment effect for FF/VI over VI is generally maintained over time in each of the trials.

The results from the two exacerbation trials are mixed. Trial 2970 demonstrates a statistically significant reduction in exacerbations between all doses of FF/VI and VI, including a 21% reduction between FF/VI 100/25 and VI ($p = 0.024$). While the comparison between FF/VI 100/25 and VI 25 in the other exacerbation trial, Trial 2871, is numerically greater (34% reduction), the result for FF/VI 100/25 over VI are not statistically significant due to the prespecified testing hierarchy which does not permit the assessment of lower doses if the higher dose of FF/VI 200/15 fails (15% reduction, $p = 0.109$).

The safety information for FF/VI is primarily provided by the two 24-week lung function trials (2206 and 2207), and two 52-week exacerbation trials (2871 and 2970). In general, notable safety events for FF/VI are typical of those seen for other ICS/LABA products in COPD, and current product labeling contains warning language regarding these risks. In particular, imbalances in pneumonia, including fatal pneumonia, and

fractures are evident in the FF-containing treatment arms compared to the VI monotherapy arms in the pooled 52-week exacerbation trial data.

Whether the totality of the data supports an added benefit of FF/VI to VI alone will be a major topic for discussion. If the committee feels a benefit is demonstrated, the committee is asked to discuss whether the efficacy benefit provided by FF to the FF/VI combination product balances any safety concerns caused by the FF component.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product is a fixed-dose, combination ICS/LABA dry powder administered by a novel dry powder inhaler. The combination 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 25 mcg of VI. A single FF/VI dose is proposed: 100/25 mcg administered as 1 inhalation once daily. The proposed trade name is Breo Ellipta®.

The sponsor proposes two indications for this new drug product, both of which are currently approved indications for other ICS/LABA products in this patient population.

- "BREO ELLIPTA is a combination inhaled corticosteroid/long-acting beta2 adrenergic agonist (ICS/LABA) indicated for long-term once-daily maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD)."

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1: Approved Treatment of Airflow Obstruction in COPD

Class		Generic Name	Brand Name
Beta$_2$-adrenergic agonist	Short-acting (SABA)*	Albuterol sulfate	Accuneb, ProAir HFA, Proventil HFA, Ventolin HFA
		Levalbuterol tartrate	Xopenex HFA
		Pirbuterol	Maxair autoinhaler
		Terbutaline sulfate	
	Long-acting (LABA)	Salmeterol	Serevent Diskus
		Formoterol	Foradil Aerolizer
		Arformoterol	Brovana
		Formoterol Solution	Perforomist

Class		Generic Name	Brand Name
		Indacaterol maleate	Arcapta Neohaler
Anti-cholinergic	Short-acting	Ipratropium bromide	Atrovent HFA
	Long-acting	Tiotropium bromide	Spiriva Handihaler
		Aclidinium bromide	Tudorza Pressair
Combination	SABA/anti-cholinergic	Albuterol/Ipratropium Albuterol/Ipratropium	Combivent Combivent respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
		Budesonide/Formoterol	Symbicort
Xanthine		Theophylline	Multiple

Table 2: Approved Treatments for Exacerbation Reduction in COPD

Class		Generic Name	Brand Name
Combination	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
Phosphodiesterase Inhibitors	PDE4 Inhibitor	Roflumilast	Daliresp

2.3 Availability of Proposed Active Ingredient in the United States

Neither fluticasone furoate nor vilanterol are approved as orally-inhaled products. While vilanterol is a new molecular entity, fluticasone furoate is approved in an intranasal formulation as Veramyst Nasal Spray at a dose of 110 mcg once daily for patients ≥ 12 years of age and 55mcg once daily for children 2 to 11 years of age. It is approved for the treatment of seasonal and perennial allergic rhinitis[1].

2.4 Important Safety Issues With Consideration to Related Drugs

Previous ICS/LABA development programs in COPD have identified a risk of pneumonia related to the ICS component in a dose-dependant manner.

LABA monotherapy is associated with serious asthma-related adverse events, including death and an increased risk of hospitalization. However, this risk is believed to be restricted to the asthma population and has not been demonstrated in COPD.

Additional risks highlighted in current ICS/LABA product labeling include:

- Localized infections
- Immunosupression
- 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

[1] Veramyst (fluticasone furoate) nasal spray; NDA 022-051 approved April 27, 2007.

- Cautious use in patients with cardiovascular or central nervous system disorders due to beta-adrenergic stimulation

2.5 Other Relevant Background Information

The table below provides a timeline of regulatory interactions with GSK regarding FF/VI and outlines the major discussion points relevant to the COPD program. In addition, discussion highlights pertinent to the COPD indication from the GSK's interactions with the Agency for its asthma program are also highlighted.

Table 3: Milestone Interactions between the Agency and the Applicant

Date	Interaction	Highlights as they pertain to the COPD indication
January 31, 2007	Pre-IND (VI)	• Characterize VI monocomponents prior to developing FF/VI
April 29, 2008	Pre-IND	• Obtain dose regimen and ranging information for VI in COPD • Asthma data may not apply to COPD, each monocomponent must be examined in addition to the combination product • Compare once-daily regimen to twice daily regimen
May 23, 2008	IND	• Safe to proceed
March 31, 2009	EOP2: asthma	• Division noted need to directly compare QD to BID regimens to establish the appropriate dosing frequency
June 17, 2009	EOP2: COPD	• GSK Identified VI 25 mcg as dose to carry into phase 3 trials, FDA could not confirm at the time based on the available data • FDA 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 phase 3 COPD program • Phase 3 trial design options discussed; Division noted that replicate trials were expected to support a bronchodilator claim and an exacerbation claim
December 9, 2009	Type C meeting: COPD mortality	• Bronchodilator dose selection in COPD should be informed by bronchodilator-sensitive population • Discussion of mortality trial design
March 24, 2010	Type C meeting: asthma dose selection	• once daily VI dosing appeared reasonable (HZA113310), with caveat that 12.5 mcg BID was not compared to 25 mcg QD and results from shorter phase trial may not be predictive of a longer phase 3 trial • FDA agreed that 25 mcg VI appeared reasonable for COPD (B2C111045), but that lower doses may be efficacious for asthma
June 8, 2010	Type C meeting: asthma	• Dose selection in COPD should be informed by bronchodilator sensitive population

Date	Interaction	Highlights as they pertain to the COPD indication
	phase 3 asthma	• Bronchodilator dose may differ between asthma and COPD • Asthma safety data should be submitted with COPD NDA to support FF/VI safety in COPD
July 13, 2011	COPD Pre-NDA	• Division noted a lack of consistent benefit of FF/VI over VI alone for spirometry data
October 12, 2012	Asthma Pre-NDA	• Division requested that asthma application be submitted concurrently with COPD application
EOP2 = end of phase 2, IND = investigational new drug, NDA = new drug application		

3 Overview of the Clinical Program

The focus of this review is on the clinical development program conducted in support of FF/VI in COPD. The dose-ranging and dosing frequency data are discussed in Section 4, the efficacy data in Section 6, and the safety data in Section 6.

Traditionally, ICS/LABA combination products in COPD can draw on the experience from the individual monocomponent development programs as well as from the combination product's development program in asthma. As this is the not the case for FF/VI, GSK has provided dose-ranging and regimen data for both FF and VI in asthma and COPD, as well as safety data from its asthma program. The dose selection trials are summarized in Table 4 below. Of note, all of the following trials included the to-be-marketed formulations which were administered via the to-be-marketed novel dry powder inhaler device[2]. The results of these trials are reviewed in Section 4.

Table 4: FF and VI Dose Selection Trials

Trial (dates)	Design	Population (N)	Treatment	Time (weeks)	Primary Endpoint	Sites (Countries)
Vilanterol						
B2C111401 (Apr 08-Oct 08)	R, DB, PC, XO	Asthma (24)	VI 6.25 VI 25 VI 100 GW64244M 6.25 GW64244M 25 GW64244M100 Placebo	single dose	trough FEV1	3: New Zealand, Australia

[2] Trial B2C111401 also included treatment arms containing an older formulation of VI

Trial (dates)	Design	Population (N)	Treatment	Time (weeks)	Primary Endpoint	Sites (Countries)
B2C111045 (Feb 08-Oct 08)	R, DB, PG	COPD (602)	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VQ 50 QD Placebo QD	4	Trough FEV1	49: US, Canada, Mexico, Europe, S. America, Korea, Philippines
B2C109575 (Dec 07-Sep 08)	R, PC, DB, PG,	Asthma (605)	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD Placebo QD	4	Trough FEV1	88: US, Canada, Europe, S. America, Korea, Philippines, Thailand, S. Africa
HZA113310 (Apr 08-Oct 08)	R, PC, DB, 5 per XO	Asthma (75)	VI 6.25 QD VI 6.25 BID VI 12.5 QD VI 25 QD Placebo QD	7 days per Period	Trough FEV1	9: US
Fluticasone furoate						
FFA109687 (Sep 09-Jan 10)	R, PC, DB, PG	Asthma (598)	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo BID	8	Trough FEV1	107: US, Canada, Mexico, Korea, Europe, Peru, Philippines
FFA109685 (Dec 07-Nov 08)	R, PC, DB, PG	Asthma (615)	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo BID	8	Trough FEV1	98: US, Canada, Mexico, Europe, Korea, Philippines
FFA109684 (Dec 07-Sep 08)	R, PC, DB, PG	Asthma (622)	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	8	Trough FEV1	94: US, Canada, Mexico, Europe, Australia, S. Africa, Thailand

Trial (dates)	Design	Population (N)	Treatment	Time (weeks)	Primary Endpoint	Sites (Countries)
FFA112202 (Oct 08-Mar 09)	R, DB, XO	Asthma (190)	1st group FF 200 QD FF 100 BID Placebo BID 2nd group FP 100 BID FP 200 QD Placebo BID	4	Non inferiority margin=110 ml Trough FEV1	16 US
Fluticasone furoate with fixed dose vilanterol						
HZC110946 (Jan 10- Jul 10)	R, DB, XO	COPD	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 Placebo	7 days / period	FEV1 AUC(0-24h)	8 US
GW642444 = M salt of vilanterol (earlier formulation), BID = twice daily, R = randomized, PC = placebo controlled, DB = double blind, PG = parallel group, XO = cross over, QD = once daily, SD = single dose Source: Module 5.2 Tabular listing of all studies and individual CSR						

To demonstrate efficacy, GSK submitted the results of four pivotal phase 3 clinical trials: two replicate 24-week lung function trials (2206 and 2207) and two 52-week exacerbation trials (2871 and 2970). The efficacy trials are summarized in Table 5. The phase 3 trial designs are presented in detail in Section 5, and the efficacy results in Section 6. In addition, supplemental efficacy data is provided by three Advair comparator trials (3107, 3109 and 2352) which are discussed in Section 6.1.9. GSK conducted four pivotal phase 3 trials to support the two proposed indications.

Table 5: Pivotal Phase 3 Trials

Study dates	Design	Population	Wks	Treatments	N	Primary Endpoint	Sites *Countries (n)*
24-week lung function trials: 2206 and 2207							
112206 *Oct 2009 to Feb 2011*	R, DB,PC	COPD	24	FF/VI 50/25 FF/VI 100/25 FF 100 VI 25 PBO	206 206 206 205 207	Trough FEV WM FEV1	*Chile (36), Estonia (58), Germany (132), Japan (42), Korea (124), Philippines (87), Poland (86), Russian Fed. (65), U.S. (400)*
112207 Oct 2009 to Mar 2011	R, DB,PC	COPD	24	FF/VI 100/25 FF/VI 200/25 FF 200 FF 100 VI 25 PBO	204 205 204 203 203 205	Trough FEV WM FEV1	*Czech Republic (77), Germany (282), Japan (47), Poland (103), Romania (270), Russian Fed. (103), Ukraine (34), U.S. (308)*

Study dates	Design	Population	Wks	Treatments	N	Primary Endpoint	Sites *Countries (n)*
52-week exacerbation trials: 2871 and 2970							
102871 *Sept 2009 to Oct 2011*	R, DB,AC	COPD + Recent exacerbation	52	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	408 403 402 409	Annual rate of mod/sev exacerbations	*Argentina (85), Australia (81), Canada (77), Chile (64), Estonia (22), Germany (46), Italy (130), Mexico (86), Netherlands (107), Peru (54), Philippines (129), South Africa (145), Sweden (37), United Kingdom (31), United States (528)*
102970 *Sept 2009 to Oct 2011*	R, DB,AC	COPD + recent exacerbation	52	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 VI 25	412 403 409 409	Annual rate of mod/sev exacerbations	*Argentina (69), Australia (68), Canada (67), Chile (60), Denmark (79), Germany (55), Italy (127), Mexico (83), Netherlands (97), Peru (66), S. Africa (165), Spain (36), Sweden (42), U.K. (39), U.S. (580)*
Source: Module 5.2 Tabular listing of all studies and individual CSR R = randomized, DB = double-blind, PC = placebo controlled; AC = active control WM = weighted mean; S. = South; U.K = United Kindgom U.S. = United States; mod = mod/sev = moderate/severe;							

The safety database for FF/VI in COPD is primarily comprised of data from the four pivotal phase 3 trials (2206, 2207, 2871, and 2970) and is supplemented by data from other shorter COPD trials. The safety review strategy and results are provided in Section 7. Table 6 summarizes the main studies comprising the COPD safety database. Table 65 in Section 7.7 outlines the studies included in the 120-day safety update.

Table 6: COPD Safety Database

Trial	Design	Weeks	Population	Treatment Arms	N
24-week Lung function Trials					
2206	R, DB, PC, PG	24	COPD	Placebo FF 100 VI 25 FF/VI 50/25 FF/VI 100/25	207 206 205 206 206
2207	R, DB, PC, PG	24	COPD	Placebo FF 100 FF 200 VI 25 FF/VI 100/25 FF/VI 200/25	207 204 203 203 204 205
52-week Exacerbation Trials					
2871	R, DB. PG	52	COPD +	VI 25 FF/VI 50/25	409 408

Trial	Design	Weeks	Population	Treatment Arms	N
			Recent exacerbation	FF/VI 100/25 FF/VI 200/25	403 402
2970	R, DB, PG	52	COPD + Recent exacerbation	VI 25 FF/VI 50/25 FF/VI 100/25 FF/VI 200/25	409 408 403 402
Supplemental one month COPD trials					
1045	R, DB, PC, PG	4 week	COPD	VI 3 VI 6.25 VI 12.5 VI 25 VI 50 Placebo	99 101 101 101 99 101
1348	R, DB, PC, PG	4 week	COPD	FF/VI 400/25 Placebo	40 20
946	R, DB, PC, 3-way XO	12 week	COPD + exacerbation within 3 years	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 Placebo	54
Advair Comparator Trials					
3107	R, DB, AC, PG	12 week	COPD: FEV1≤70%, exacerbation within 3 yrs	FF/VI 100/25 FP/Salm 500/50	266 262
3109	R, DB, AC, PG	12 week	COPD: FEV1≤70% exacerbation within 3 yrs	FF/VI 100/25 FP/Salm 250/50	260 259
2352	R, DB, AC, PG	12 week	COPD: FEV ≤ 70%	FF/VI 100/25 FP/Salm 250/50	259 252
Source: Module 5.2 Tabular listing of all clinical studies					

4 Dose Selection

As it is important to determine if appropriate doses and an appropriate dosing regimen were evaluated in the phase 3 program, these data are reviewed first. This is followed by a discussion of the efficacy data (Section 6) and safety data (Section 7).

Overall, it appears that the phase 3 COPD program evaluated appropriate doses of FF (50, 100, and 200 mcg) and VI (25 mcg) as well as an appropriate dosing regimen (once daily) in its phase 3 program. As noted earlier, GSK conducted dose-ranging

trials for VI in both asthma and COPD and for FF primarily in asthma.

4.1 Overview of Dose-Ranging and Dose-Regimen Selection

Traditionally, development of an ICS/LABA combination product for COPD follows the development of orally-inhaled formulations of the monocomponents and of the combination product in asthma. In this case, neither FF nor VI are currently approved in orally-inhaled formulations, nor is the combination FF/VI product approved in asthma. Instead, the sponsor has chosen to pursue development of FF and VI as a fixed-dose combination product in COPD first.

To this end, this NDA application includes dose-ranging information for each of the monocomponents in asthma, as well as dose-ranging information for VI in COPD. Because ICS monotherapy is not thought to be efficacious in COPD, dose-ranging information for FF monotherapy in COPD was not obtained. GSK did conduct a COPD trial containing three FF doses coupled with a fixed dose of VI providing some preliminary COPD FF/VI dose-ranging information. Three FF doses were then carried forward into the phase 3 program to confirm selection of an appropriate FF dose in the combination product.

4.2 VI Dose and Dosing Regimen Selection

Dose selection for VI was primarily based on 4 trials: B2C111401 (1401: single dose asthma trial), B2C111045 (1045: COPD dose-ranging trial), B2C109575 (9575: asthma dose-ranging trial), and HZA113310 (3310: dose-regimen trial).

Historically, dose-ranging for bronchodilator therapy has relied on information derived from an asthmatic population as asthmatic airways are generally more bronchodilator-sensitive than those in COPD. For VI, the sponsor demonstrated pharmacodynamic dose separation in both asthmatic and COPD patient populations. The COPD data is presented first followed by a review of the asthma dose-ranging information. While multiple single-dose trials were conducted with vilanterol, trial 1401 was chosen for review as its treatment arms included various doses of the to-be-marketed formulation of VI administered with the to-be-marketed device, as opposed to earlier formulations of VI.

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

Trial B2C111045: VI Dose-Ranging Trial in COPD

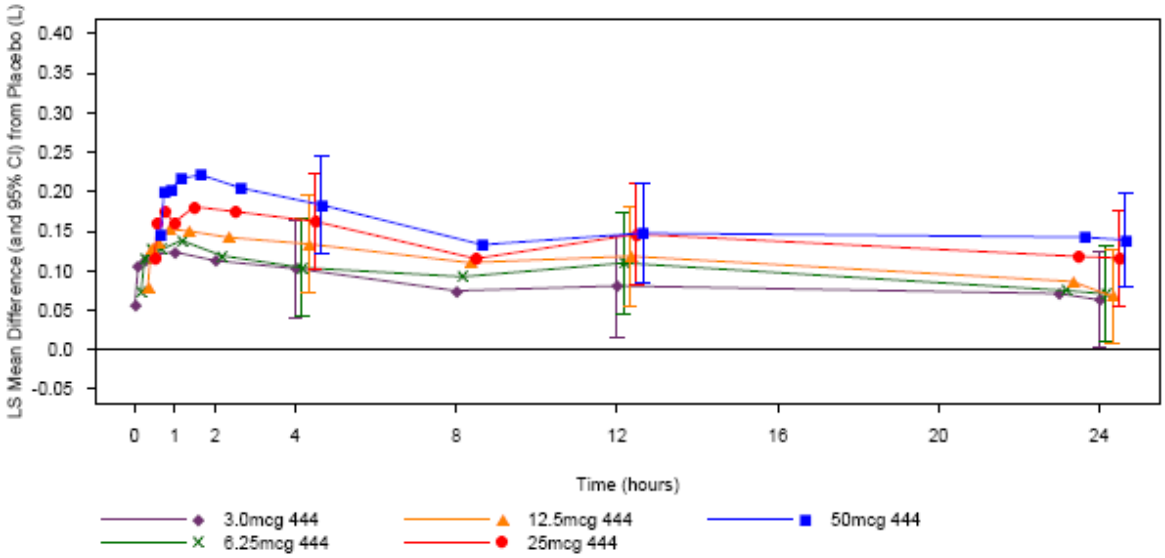
Trial B2C111045 (1045) was a multicenter, double-blind, placebo-controlled, parallel-group trial that evaluated five once-daily doses of VI: 3, 6.25, 12.5, 25, and 50 mcg. A total of 605 adult patients ≥ 40 years of age with COPD with a post-bronchodilator FEV1 ≤ 70% and FEV1/FVC ratio ≤ 0.70 received study drug in the morning for 28 days. The primary endpoint for the trial was the change from baseline in trough FEV1, defined as the mean FEV1 values at 23 and 24 hours post-dosing at the end of the 28 day

treatment period. Secondary support included an evaluation of weighted mean 24-hour serial FEV1 (0-24h) on Days 1 and 28 and the time to an increase ≥ 12% above baseline FEV1 on Day 1 (0-4hr). All SABA therapy was withheld for 6 hours prior to the spirometry assessments, and no other bronchodilator therapy, besides the study drug, was permitted during the trial.

Table 7: VI Dose-Ranging in COPD: 1045

	Placebo N = 101	VI 3 N = 99	VI 6.25 N = 100	VI 12.5 N = 99	VI 25 N = 99	VI 50 N = 99
Primary Efficacy Endpoint: Day 29 Change from baseline in trough FEV1						
LS Mean Change (L)	0.029	0.120	0.127	0.138	0.166	0.194
Difference vs. Placebo (L)		0.092	0.098	0.110	0.137	0.165
p-value		<0.001	<0.001	<0.001	<0.001	<0.001
Secondary Efficacy Endpoint: Change from baseline Weighted Mean Serial FEV1 on 28						
LS Mean Change (L)	0.028	0.085	0.132	0.149	0.178	0.202
Difference vs. Placebo (L)		0.057	0.104	0.12	0.15	0.174
p-value		0.003	<0.001	<0.001	<0.001	<0.001
Source: B2C111045 CSR Tables 14 and 19						

Figure 1: Day 28 Treatment Differences from Placebo in Change from Baseline FEV1: 1045



Note: Analysis performed using repeated measures with covariates of baseline, sex, age, smoking status (at screening), reversibility stratum, time (nominal), treatment and time by treatment and time by baseline interactions
Note: FEV1 is plotted at pre-dose and at 5, 15 and 30 minutes and 1, 2, 4, 8, 12, 23 and 24 hours post dose. At each time point treatments are offset.

Source: B2C111045 CSR Figure 11

Based on the data from this VI dose-ranging trial in COPD, evaluating VI 25 mcg in the phase 3 trials was reasonable. All doses of VI demonstrated a statistically significant

improvement over placebo in a dose-dependent manner for both the primary endpoint, trough FEV1, as well as the secondary endpoint, weighted mean FEV1 (0-24h). However, as shown in Figure 1, the treatment benefit of the 50 mcg dose over the 25 mcg dose appears to diminish towards the end of the 24-hour treatment period, while the treatment benefit for the 25 mcg dose over the 12.5 mcg dose is generally maintained. The Day 1, 14 and 28 FEV1 curves demonstrate similar patterns (data not shown).

Trial B2C111401: Single VI Dose Dose-Ranging Trial in Asthma

Trial B2C111401 (1401) was primarily a PK/PD trial comparing two formulations of vilanterol: a previous formulation (VI + lactose) versus the to-be-marketed formulation (VI + lactose + magnesium stearate). The trial was a single-dose, double-blind, randomized, placebo controlled, five–way cross-over trial evaluating three doses of each formulation (6.25 mcg, 25 mcg, 100 mcg) versus placebo. A total of 24 patients with mild to moderate persistent asthma were randomized to receive four of the six available active treatments and placebo. Serial FEV1 measurements were obtained and the primary endpoint of trough FEV1 was calculated from the 23- and 24-hour post dosing measurements.

All of the treatments, with the exception of the 6.25 mcg VI + lactose treatment arm, were statistically superior to placebo. Focusing the analysis on the to-be-marketed formulation, separation is seen between the 6.25 mcg and 25 mcg doses; however the treatment effect is similar between the 25 mcg and 100 mcg. Compared to placebo, the 6.25 mcg dose provides a 0.13 L improvement over placebo (P = 0.0067), the 25 mcg dose a 0.22 L improvement over placebo (P < 0.0001), and the 100 mcg group a 0.23 L improvement over placebo (P < 0.0001). These data suggest that appropriate doses of VI were evaluated in the multiple-dose dose-ranging trials.

Trial B2C109575: VI Dose-Ranging in Asthma

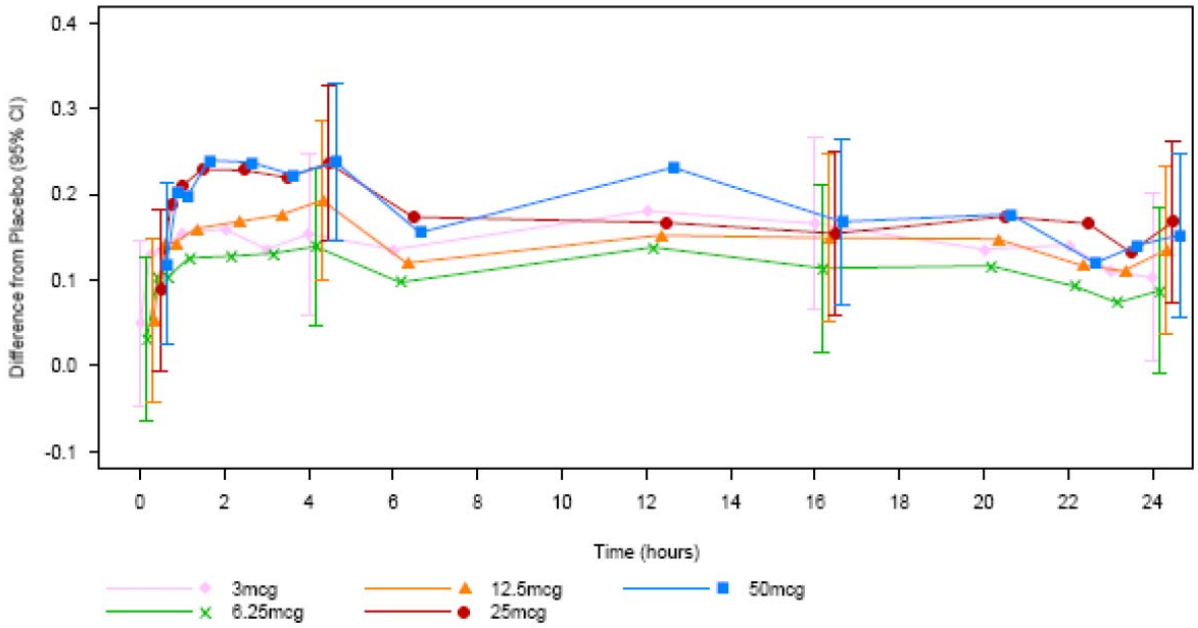
Study B2C109575 (9575), was a randomized, double-blind, placebo-controlled, parallel group, dose-ranging trial evaluating the efficacy and safety of five doses of VI (3, 6.25, 12.5, 25, and 50 mcg) administered once-daily compared with placebo. A total of 607 adult and adolescent patients ≥ 12 years of age with persistent asthma uncontrolled on ICS alone received double-blind treatment for 28 days. Patients were permitted to continue their baseline ICS therapy throughout the duration of the trial, and a SABA rescue inhaler was provided. No other bronchodilator therapy besides the study drug was permitted. The primary efficacy endpoint was the mean change from baseline trough FEV1 at the end of 28 days of treatment.

Table 8: VI Dose-Ranging in Asthma: 9575

	Placebo N = 95	VI 3 N = 98	VI 6.25 N = 99	VI 12.5 N = 97	VI 25 N = 99	VI 50 N = 100
LS Mean (L)	2.388	2.452	2.458	2.518	2.509	2.55
Change from placebo (L)		0.064	0.069	0.13	0.121	0.162
p-value		0.208	0.169	0.011	0.016	0.001

	Placebo N = 95	VI 3 N = 98	VI 6.25 N = 99	VI 12.5 N = 97	VI 25 N = 99	VI 50 N = 100
Source: CSR B2C109575 Table 12						

Figure 2: Day 28 Treatment Differences from Placebo in Change from Baseline FEV1: 9575



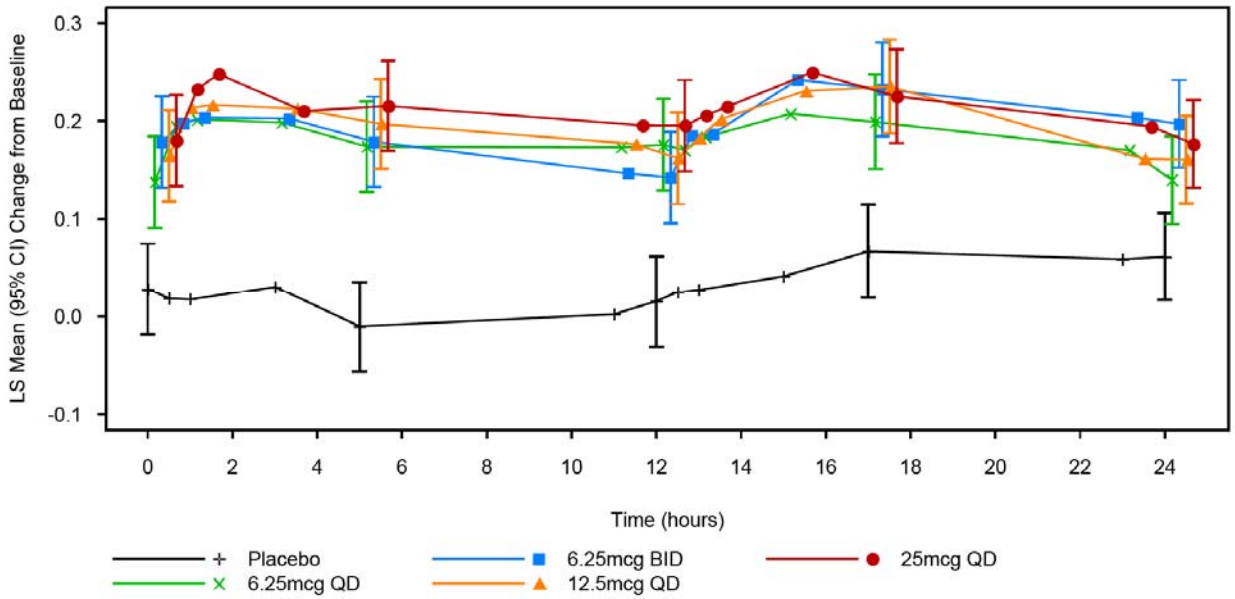
Source: CSR B2C109575 Figure 14

The FEV1 time curve is suggestive of a dose-dependent effect, although the trough FEV1 point estimate for the 50 mcg dose is lower than the 25 mcg dose. These results provide additional support to the VI dose information obtained in trial 1045.

Trial HZA113310: VI Dose-Regimen Trial in Asthma

Trial HZA113310 (3310) was a multicenter, randomized, double-blind, placebo-controlled, five-period, cross-over trial that evaluated the dosing interval of VI in 75 patients ≥ 18 years of age with persistent asthma. Patients received each treatment for 7 days followed by a 7-day washout period between treatments. All patients remained on their baseline ICS and rescue SABA treatment was permitted throughout the trial (to be withheld 6 hours prior to any spirometry assessments). There were five treatment sequences in the trial comparing 6.25 mcg VI once a day, 6.25 mcg VI twice a day, 12.5 mcg VI once a day, 25 mcg VI once a day and placebo. All patients took blinded treatment every 12 hours. The primary efficacy endpoint was the change from baseline in trough FEV1 at the end of each 7-day treatment period and the secondary endpoint was the weighted mean 24-hour serial FEV1 on Day 7. Spirometry measurements were taken at 30 and 60 minutes pre-dose and 3, 5, 11, 12, 12.5, 13, 15, 17, 23, and 24 hours post-dose.

Figure 3: Day 7 Mean Change from Baseline in FEV1: 3310



Source: CSR HZA113310 Figure 6.12

Table 9: VI Dose Regimen in Asthma: 3310

	6.25 QD N = 73	6.25 BID N = 74	12.5 QD N = 73	25 QD N = 73
Trough FEV1: day 7 change from baseline				
LS mean change from placebo (L)	0.094	0.140	0.102	0.125
P value	<0.001	<0.001	<0.001	<0.001
Weighted mean FEV1 (0-24h): day 7 change from baseline				
LS mean change from placebo (L)	0.153	0.166	0.168	0.185
P value	<0.001	<0.001	<0.001	<0.001

Source: CSR HZA113310 Tables 13 and 14
QD = once daily, BID = twice daily

All doses and dosing-regimens demonstrate a statistically significant improvement over placebo. The 6.25 mcg twice-daily dose demonstrates a similar treatment effect as the 25 mcg once-daily dose at the end of 24-hour treatment period. However, as evidenced in Figure 3, the 25 mcg dose provides a more consistent effect over the 24-hour time period. For the weighted mean FEV1 (0-24h) data, the 25 mcg once-daily dose demonstrates the largest treatment effect, with the 6.25 mcg twice-daily and 12.5 mcg once-daily doses demonstrating similar results.

While a direct comparison of 12.5 mcg twice-daily to 25 mcg once-daily would have been preferable, the data suggest that a once-daily regimen is similar to a twice-daily regimen in this dose range. Given the potential benefit of once-daily versus twice-daily dosing on patient compliance and the similar efficacy results demonstrated above, carrying forward the once-daily dose of VI into the phase 3 trials was not unreasonable.

4.3 FF Dose and Dose-Regimen Selection

Since asthmatics patients are thought be more steroid sensitive, dose-ranging for FF monotherapy was primarily conducted in asthmatics. The FF asthma trials are discussed first followed by an evaluation of the single FF/VI dose-ranging trial conducted in COPD. Based on the results of these trials, carrying forward once-daily FF doses of 50, 100 and 200 mcg into the phase 3 COPD program for final FF dose selection was not unreasonable.

Trials FFA109687 and FFA109685: Asthma FF Dose-ranging

Trial FFA109687 (9687) was a randomized, double-blind, double-dummy, placebo-controlled, parallel-group, dose-ranging trial evaluating four doses of once-daily fluticasone furoate (25 mcg, 50 mcg, 100 mcg and 200 mcg), 100 mcg fluticasone propionate (FP) twice-daily, and placebo. A total of 601 adult and adolescent patients with persistent asthma, uncontrolled on non-ICS maintenance therapy, received treatment for eight weeks. The primary endpoint was a change from baseline in trough FEV1 at Week 8. All doses except the 25 mcg dose demonstrated a statistically significant benefit over placebo.

Trial FFA109685 (9685) was similarly designed to 9687; however 9685 evaluated higher doses of FF. This resulted in a different comparator FP treatment arm and enrollment of an asthmatic population uncontrolled on low-dose ICS therapy. The primary endpoint data from both trials are summarized in Table 10.

GSK conducted an additional dose-ranging trial for FF in asthma, FFA109684 (9684), that evaluated even higher dosage strengths of FF: 200, 400, 600 and 800 mcg once-daily compared to 500 mcg FP twice-daily and placebo. As the proposed 100 mcg FF dose was not included in this trial, the data are not reviewed here.

Table 10: FF Dose-ranging in Asthma: 9685 and 9687

		FF once daily						FP twice daily	
	PBO	25	50	100	200	300	400	100	250
Trough FEV1: change from baseline at week 8									
Trial 9687									
N	93	94	97	109	94			101	
LS mean change from Placebo (L)		0.101	0.129	0.204	0.23			0.106	
P value		0.095	0.033	<0.001	<0.001			0.074	
Trial 9685									
N	106			102	101	102	97		99
LS mean change from Placebo (L)				0.207	0.238	0.293	0.279		0.225

		FF once daily						FP twice daily	
	PBO	25	50	100	200	300	400	100	250
Trough FEV1: change from baseline at week 8									
Trial 9687									
P value				< 0.001	< 0.001	< 0.001	< 0.001		< 0.001
Source: CSR 109687,109685 Table 11 FP = fluticasone propionate, PBO = placebo,									

Overall, the treatment benefit compared to placebo is fairly consistent between the two trials. In addition, the higher doses (300-400 mcg) of FF appear to offer minimal additional benefit. Based on the results of these trials, carrying forward FF 50, 100 and 200 mcg once-daily into the phase 3 trials for final dose selection was reasonable.

Trial FFA11202: Asthma Dose Regimen Trial

Trial FFA11202 (1202) was a multicenter, randomized, double-blind, cross-over trial evaluating once daily dosing of FF versus twice daily dosing of FF in 190 adult and adolescent patients 12 years of age and older. Additional treatment arms included 200 mcg of fluticasone propionate (FP), 100 mcg FP twice daily and placebo. The once-daily dosing was given approximately every 24 hours, and the twice daily dosing every 12. Patients were randomized 7:2 so that seven patients were randomized to a FF sequence for every two randomized to a FP sequence. Patients randomized to a FF sequence were given double-blinded NDPI containing either FF or placebo and a double-blinded discus if randomized to an FP sequence. Thus, while possible to detect if a patient was receiving FF or FP for a particular sequence, the study medication was still double-blinded to placebo. The study included a two-week run-in period to assess compliance followed by three 28-day treatments periods, each separated by a two-week washout period. The primary efficacy endpoint was the change from baseline in trough FEV1 at the end of each 28-day treatment period. Spirometry was measured prior to the evening dose of study medication at each PM clinic visit at the end of the 28 day treatment period.

The data are summarized in Table 11 below.

Table 11: FF Dose Regimen in Asthma: 1202

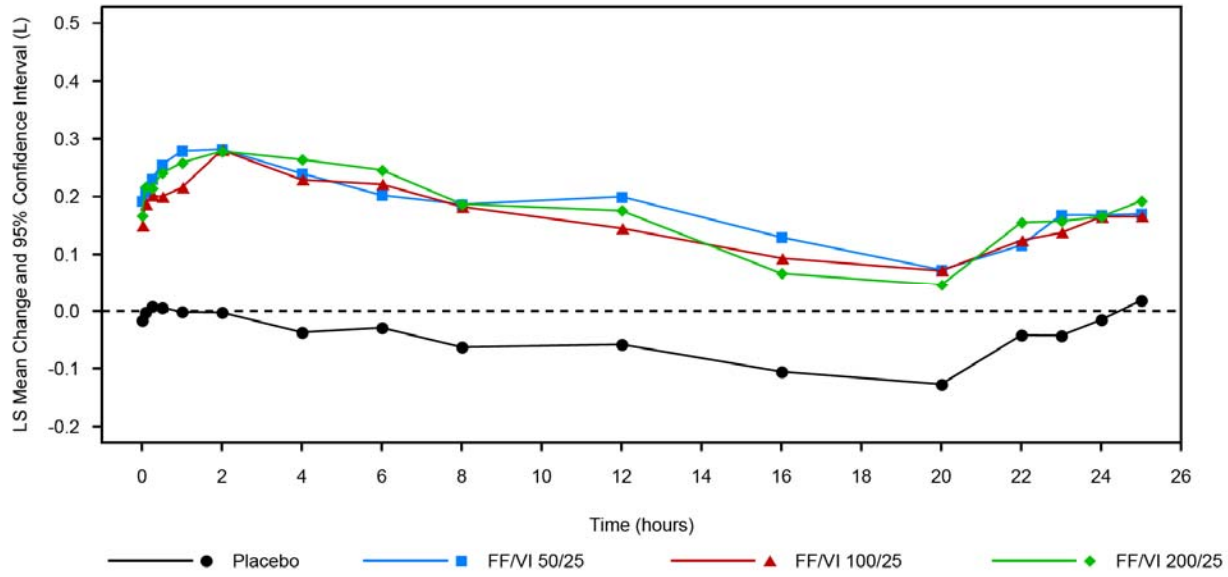
	FF 200 QD N=140	FF 100 BID N = 142	FP 200 QD N = 42	FP 100 BID N = 43
Trough FEV1: LS mean change from baseline at Day 28				
LS mean change from placebo (L)	0.108	0.098	0.087	0.132
P value	<0.001	<0.001	<0.001	<0.001
LS mean change from FF 100 BID (L)	0.011			
P value	0.641			
Source: CSR FFA112202 BID = twice a day, FP = fluticasone propionate, QD = once a day				

A similar treatment effect (approximately 100 ml) is demonstrated for the once daily and twice daily regimens with no statistically significant difference between the two (P=0.641). These data support the choice to carry forward once-daily dosing into the phase 3 trials.

Trial HZC110946: Preliminary FF/VI Dose Selection in COPD

Trial HZC110946 (0946) was a three-way, incomplete block crossover study to evaluate the effect on 24-hour pulmonary function of three dosage strengths of FF/VI compared with placebo at the end of a 28-day treatment period. The trial was a multicenter, randomized, placebo-controlled trial in 54 adult patients with COPD. Following the first treatment period, patients had a two-week washout period, prior to receiving the second of the treatment regimen. This was followed by a second washout period followed by treatment with the third investigational agent. Each treatment period was 28 days and patients administered double-blind medication once a day in the morning, with inhalation of single-blind treatment once every day during the run-in and two washout periods. A SABA inhaler was provided for rescue treatment and use of short-acting ipratropium bromide was also permitted provided the dose remained stable throughout the study. The primary efficacy endpoint was weighted-mean serial FEV1 (0-24 h) at the end of each 28-day treatment period. Secondary efficacy measures included change from baseline in clinic trough FEV1. Spirometry assessments at the end of each treatment period were performed at -30 and -5 minutes pre-dose, and at 5, 15, 30 and 60 minutes and at 2, 4, 6, 8, 12, 16, 20, 22, 23, and 24 hour post-dose.

Figure 4: Day 28-29 LS mean change from baseline in serial FEV1: 0946



Source: Figure 6.10 from CSR HZC110946

Table 12: FF/VI Dose-ranging in COPD: 0946

	FF/VI once a day		
	50/25 N = 34	100/25 N = 33	200/25 N = 31

Trough FEV1: LS mean change from baseline at Day 29			
LS mean change from placebo (L)	0.211	0.177	0.189
P value	< 0.001	< 0.001	< 0.001
Source: CSR Table HZC110946 Table 16			

The data from this trial demonstrates the efficacy of the combination product over placebo; however no dose response is evident between the three FF doses. This may be indicate that the chosen doses are within the plateau phase of the dose response curve.

Another trial, trial HZA114624, evaluated the effects of AM versus PM dosing of FF/VI 100/25 in 26 patients with asthma. This trial was a single, center 14-day, randomized, double-blind, placebo controlled trial with the primary endpoint of weighted mean FEV1 (0-24h). These results (data not shown) indicate that AM versus PM dosing was similar.

5 Pivotal Phase 3 Trial Design

5.1 24-weeek Lung Function Trials: 2206 and 2207

Trials 2206 and 2207 were similarly designed trials initiated in 2009 and completed in February and March of 2011 respectively. The only difference between the two trials was the three FF/VI dosage strengths and corresponding FF comparator arms evaluated. Trial 2206 evaluated FF/VI 50/25 and 100/25 with FF 100 mcg and 2207 evaluated FF/VI 100/25 and 200/25 with corresponding FF 100 and 200 mcg comparator arms. In addition to FF/VI and FF treatment arms, both trials also evaluated a VI 25 mcg arm and placebo. The protocol for 2206 is detailed below. Details of the protocol for 2207 are not provided given the similarity to 2206.

Overall, the studies were appropriately designed to assess the effects of FF/VI compared to FF, VI, and placebo for airflow obstruction. Similar trial designs have been used by previous ICS/LABA COPD programs to support a maintenance treatment of airflow obstruction indication.

HCZ112206 (2206)

Study Title: A 24-Week Study to Evaluate the Efficacy and Safety of Fluticasone Furoate (GW685698)/GW642444 Inhalation Powder and the Individual Components Delivered Once Daily (AM) Via a Novel Dry Powder Inhaler Compared with Placebo in Subjects with Chronic Obstructive Pulmonary Disease (COPD)

Objectives/Rationale

Primary:

- Efficacy and safety of 50/25 and 100/25 FF/VI, 100 mcg FF and 25 mcg VI and

placebo over 24 week treatment period in COPD

Secondary:

- Population PK of FF and VI
- PK-PD between FF and VI systemic exposure and systemic PD endpoints

Study Design and Conduct

Overview:

This trial was a 24-week, randomized, multicenter, placebo-controlled, double-blind, parallel-group study evaluating two once-daily dosage strengths of FF/VI (50/25 and 100/25 mcg) compared to FF 100 mcg once daily, VI 25 mcg once daily, and placebo.

Eligible patients entered a 2-week, single-blind (placebo) run-in period to assess baseline parameters and compliance with study procedures. Patients who remained eligible were randomized, stratified by smoking status, and then entered the 24-week treatment period. All patients stopped their conventional COPD treatment during the run-in period and double-blind treatment period. Rescue albuterol/salbutamol therapy was provided throughout the study duration. All treatment groups received once daily administration of the study drug in the morning via the to-be-marketed novel dry powder inhaler (NDPI). Clinic visits occurred at screening, randomization, and at weeks 1, 2, 4, 8, 12, 16, 20 and 24. A follow-up phone call was made one week after completion of the trial or after an early withdrawal visit.

Spirometry:

A minimum of three spirometry attempts was attempted at each clinic visit using equipment meeting ATS guidelines and performed between 6 and 10 am. Spirometry was performed prior to administration of any AM study dosing. Rescue medication was withheld for ≥ 4 hours at all clinic visits during the study. In addition, patients were instructed to refrain from exercising 2 hours prior to visit, avoid cold air for 15 minutes prior and not smoke for 1 hour prior to each visit.

Table 13: Time and Events Table: 2206

Visit	1	2	3	4	5	6	7	8	9	10	11	12	Early WD	Follow up
Day[1]	-14	1	2	7	14	28	56	84	112	140	168	+1		+7
Week	-2			1	2	4	8	12	16	20	24			
IC	X													
PG sample								X			X			
History	X													
mMRC	X													
PE	X										X		X	
Reversibility testing	X													
Smoking status	X							X				X	X	
Smoking cessation counseling	X							X				X	X	
Safety Assessments														

Visit	1	2	3	4	5	6	7	8	9	10	11	12	Early WD	Follow up
Day[1]	-14	1	2	7	14	28	56	84	112	140	168	+1		+7
Week	-2			1	2	4	8	12	16	20	24			
CXR	X													
VS	X	X	X	X	X	X	X	X	X	X	X	X	X	
OP exam	X	X	X	X	X	X	X	X	X	X	X	X	X	
Laboratory tests	X	X						X			X		X	
Serum glucose, K+								X			X			
Serum HCG	X							X			X		X	
Urine HCG														X
24-hr urine supplies dispensed	X													
24-hr urine collection returned		X									X			
ECG	X	X						X			X		X	
24-hour holter	X	X						X			X			
Exacerbation		X	X	X	X	X	X	X	X	X	X	X	X	X
AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy Assessment														
Spirometry	X												X	
Serial spirometry		X			X		X	X			X			
Trough spirometry			X	x	X	X	X	X	X	X	X	X		
Additional Assessments														
Resource utilization		X	X	X	X	X	X	X	X	X	X	X		
PK sampling								X			X			
Medication														
Concurrent med assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense SABA	X	X	X	X	X	X	X	X	X	X	X			
Collect SABA		X	X	X	X	X	X	X	X	X	X	X		
Dispense SB IP	X													
Collect SB IP		X												
Dispense DB IP		X												
Collect DB IP						X	X	X	X	X	X		X	
Diary														
Dispense PEF meter	X													
Collect PEF meter												X	X	
Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	
Collect/review diary		X	X	X	X	X	X	X	X	X	X	X	X	

Source: CSR2206 Table 5

[1] (±2) for each day except Day 1(Visit 1)

WD = withdrawal; IC = informed consent; PG = pharmacogenomic; CXR = chest xray, VS = vital signs, PE = physical exam, OP

Visit	1	2	3	4	5	6	7	8	9	10	11	12	Early WD	Follow up
Day[1]	-14	1	2	7	14	28	56	84	112	140	168	+1		+7
Week	-2			1	2	4	8	12	16	20	24			

= oropharyngeal, AE = adverse event; PE = physical exam; VS = vital signs; ECG = electrocardiogram; SABA = short acting bronchodilator therapy, SB = single blind, DB = double blind, PEF = peak expiratory flow,

Study Population

Inclusion Criteria

- Male of female subjects ≥ 40 years of age
    - Female subjects eligible if she was of non-childbearing potential or has negative pregnancy test on screening and agreed to use of an acceptable form of birth control
- COPD diagnosis per ATS/ERS definition with
    - FEV1/FVC ≤ 0.70
    - Post SABA FEV1 ≤ 70% of predicted
- Current of prior history ≥ 10 year pack year history of cigarette use
- ≥ 2 on mMRC scale at screening

Exclusion Criteria

- Hospitalization due to poorly controlled COPD within 6 weeks of screening
- Lower respiratory tract infection that required use of antibiotics within 6 weeks of screening
- Asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease, or other active pulmonary disease
- Lung volume reduction surgery within 12 months of screening
- CXR (or CT scan) with clinically significant abnormality not due to COPD. CXR had to be taken at screening or within 6 months of screening.
- Uncontrolled, clinically significant, peptic ulcer disease, hypertension
- All cancer had to be in remission for a minimum of 5 years. Carcinoma-in-situ of cervix, squamous cell and basal cell carcinoma were excluded if the patient was considered cured
- Hypersensitivity to any study medications. Subjects with a history of severe milk protein allergy were excluded per physician judgment.
- Drug/alcohol abuse within last 2 years
- Inability to withhold SABA or ipratropium for the 4 hour period prior to spirometry testing at each study visit.
- Use of the any of the following medications within the following time intervals prior to screening or during the study:

Medication	No use within the following time intervals prior to Screening (Visit 1) and thereafter at any time during the study
Depot corticosteroids	12 weeks
Systemic, oral, parenteral (intra-articular) corticosteroids	6 weeks
Antibiotics (for lower respiratory tract infection)	6 weeks
Cytochrome P450 3A4 strong inhibitors including but not limited to antiretrovirals (protease inhibitors) (e.g., indinavir, nelfinavir, ritonavir, saquinavir, atazanavir); imidazole and triazole anti-fungals (e.g., ketaconazole, itraconazole, voriconazole); clarithromycin, telithromycin, troleandomycin , mibefradil, cyclosporin , nefazodone.	6 weeks Grapefruit is allowed up to Visit 1, then limited to no more than one glass of grapefruit juice (250 mL/8 ounces) or one grapefruit per day
Inhaled corticosteroids	4 weeks
Inhaled ICS/LABA combination products	4 weeks
Long-acting anticholinergics (e.g., **tiotropium**)	1 week
Theophylline preparations	48 hours
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Inhaled long acting beta$_2$-agonists (LABA) (e.g., salmeterol)	48 hours
Oral beta-agonists Long-acting Short-acting	 48 hours 12 hours
Inhaled sodium cromoglycate or nedocromil sodium	24 hours
Ipratropium/albuterol (salbutamol) combination product	4 hours
Inhaled short-acting beta$_2$-agonists[1]	4 hours (albuterol/salbutamol will be supplied for rescue during the study)
Short-acting anti-cholinergics (e.g., **ipratropium bromide**[2])	4 hours (stable dose of ipratropium alone is allowed during the study but must be withheld 4 hours prior to each study visit)
Any other investigational drug	30 days or 5 half lives, whichever is longer

1. Use of study-provided albuterol/salbutamol is permitted throughout the study; however, it must be withheld for 4 hours prior to and during each clinic visit.
2. Ipratropium bromide alone is permitted, provided that the subject is on a stable dose from Screening (Visit 1) and remains on the stable dose throughout the study; however, it must be withheld for 4 hours prior to and during each clinic visit.

- Long term or nocturnal oxygen therapy for ≥ 12 hours a day with the exclusion of as needed oxygen use
- Clinically significant sleep apnea
- Pulmonary rehabilitation within 4 weeks of screening or plants to enter a program during the study. Patients in maintenance phase of rehabilitation program were not excluded.
- Prior use of study medication or other investigational drugs
- Clinically significant disease, in investigator's opinion, that would affect efficacy or safety evaluation or place the patient at risk

<u>Randomization Criteria:</u>

- COPD exacerbation/lower respiratory tract infection during run-in

- Abnormal, clinically significant laboratory finding at screening
- Abnormal, clinically significant 12-lead ECG at screening as reviewed by independent, centralized cardiologist. Abnormal changes included but were not limited to:
    - Sinus bradycardia < 45 bpm or sinus tachycardia ≥ 110 bpm (confirmed by additional 2 reading 5 min apart)
    - Multifocal atrial tachycardia
    - PR > 240 msec
    - Evidence of mobitz II or third degree heart block
    - Pathological q wave
    - Ventricular ectopic couplets, bigeminy, trigeminy, or multifocal PVC
    - QTc unsuitable for QT measurements (confirmed by additional 2 readings 5 minutes apart)
    - ST-T wave abnormalities (excluding non specific changes)
    - Clinically significant conduction abnormalities
    - Clinically significant arrhythmia
- Abnormal clinically significant 12-lead Holter finding conducted at screening, including but not limited to:
    - PVCs > 1000 in 24 hour period
    - Sustained ventricular tachycardia > 100 bpm, > 30 beats
    - Atrial fibrillation with rapid ventricular response (rate > 100 bpm)
    - Atrial flutter
    - Mean heart rate < 40 or > 120 bpm for 4 consecutive hours
    - Fixed 2nd degree heart block or third degree
    - Sinus pause ≥ 2 seconds (p wave to p wave)
- Non-compliance

<u>Withdrawal Criteria:</u>

- Subject or investigator discretion
- COPD exacerbation defined as acute worsening of symptoms requiring use of antibiotics, systemic corticosteroids, and/or emergency treatment of hospitalization
- Clinically important change in laboratory parameter
- Pneumonia (presumptive diagnosis or radiographically confirmed)
- Clinically significant ECG changes or 24 hour Holter finding
- Pre-defined liver stopping criteria
- Pregnancy

<u>Permitted Medications and non-drug therapy during screening or treatment period</u>

- Study-supplied albuterol/salbutamol (MDI or nebules)
- Ipratropium at stable dosage from Screening (Visit 1) throughout the study (must be withheld for 4 hours prior to clinic visits with spirometry)
- Mucolytics at constant dosage
- PRN oxygen for ≤ 12 hours a day
- Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers.

- Antihistamines and nasal decongestants
- OTC cough suppressants (for short term treatment ≤7 days)
- Intranasal cromolyn or nedocromil
- Intranasal, ophthalmic and topical corticosteroids
- Antibiotics that are not strong inhibitors of cytochrome P450 3A4 for short term treatment (≤14 days) of acute non-respiratory tract infections and for the treatment of pneumonia and COPD exacerbations.
- Influenza and pneumonia vaccines
- Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs).
- Diuretics
- Smoking cessation medications
- All medications for other disorders as long as the dose remains constant wherever possible and their use would not be expected to affect lung function.

Investigational Treatments:
Treatment Groups:

- FF/VI 50/25 mcg once daily in the am
- FF/VI 100/25 mcg once daily in the am
- FF 100 mcg once daily in the am
- VI 25 mcg once daily in the am
- Placebo once daily in the am

All treatments were double-blinded and the FF/VI formulation and novel DPI were the to-be marketed products. For the monotherapy treatment arms and placebo, the NDPI contained the same foil packs with removal of the active drug moieties; all other excipients remained the same.

Compliance
Compliance was assessed at each treatment visit and any unscheduled visit by reviewing the dose counter on the device. Any subject who fell to ≤ 80% or ≥ 120% was reeducated on treatment compliance.

Efficacy Endpoints
Co-Primary Endpoint:

- Weighted mean clinical visit FEV1(0-4) post dose on treatment day 168
- Change from baseline in clinic visit trough FEV1 on treatment day 169

Secondary Endpoints:

- Peak FEV1 on treatment day 1
- Time to onset (increase > 100 ml above baseline in FEV1) on treatment day 1

Other Endpoints:

- CRQ-SAS dyspnea domain
- Time to 12% change from baseline in FEV1 on Day 1
- Percentage of symptom-free 24-hour periods during each week and over the

entire 24 week treatment period
- Percentage of rescue free 24-hour periods each week and over the entire 24 week treatment period
- Symptom scores averaged over each week and over the entire 24 week treatment period
- Number of occasions rescue albuterol/salbutamol used during a 24-hour period each week and over the entire 24 week treatment period
- Percentage of nights with no nighttime awakenings requiring albuterol/salbutamol during each week of treatment and over the entire 24 week treatment period
- Number of nighttime awakenings requiring albuterol/salbutamol averaged over each week of treatment and over the entire 24-week treatment period
- Mean AM PEF
- CRQ-SAS other domains and total score

Safety Endpoints
- Incidence of AEs: defined as any untoward medical occurrence in a patient temporally associated with the use of medicinal product.
- Serious adverse event (SAE): defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly
- Incidence of COPD exacerbations: defined as requiring use of systemic corticosteroids, antibiotics and/or emergency treatment of hospitalization
    - Moderate exacerbation = systemic corticosteroids and/or antibiotics
    - Severe = requiring hospitalization
- Incidence of all pneumonias
    - Consider radiographic confirmation, but not required
- Change from baseline in pulse rate, systolic and diastolic blood pressure on treatment day 1, 2, 7, 14, 28, 56 and 84, 112, 140, 160 and 169
- Change from baseline in 12-lead ECG assessments on day 1, 84, and 168
- Change from baseline in clinical chemistry and hematology parameters on day 84 and 168
    - Including serum glucose and potassium
- Change from baseline in oropharyngeal exam finding at each treatment visit
- Change from baseline in oropharyngeal exam finding at each treatment visit
- Change from baseline in Holter reading assessment at day 1, 84, 168 (subset of 100 patients)
- Change from baseline in urinary cortisol excretion at day 168 (subset of 100 subjects)

Statistical Plan
A sample size of 146 subjects per arm was estimated to provide 90% power to detect an 80ml difference between FF/VI and VI in trough FEV1 on day 169.

The primary population used for efficacy and safety endpoints was the Intent-to-Treat population defined as all subjects who were randomized and received at least one dose

of study medication.

Each of the co-primary endpoints was analyzed using a mixed models repeated measures (MMRM) analysis and the following treatment comparisons were designated as primary:

- Weighted mean FEV1(0-4) for VI vs placebo (efficacy of VI)
- Trough FEV1 for VI vs placebo (24 hour duration of VI)
- Trough FEV1 for each FF/VI combination versus placebo (efficacy of combination dose at the end of dosing interval lung function)
- Weighted mean FEV1(0-4) for each FF/VI combination versus placebo (efficacy of a combination dose on post-dose lung function)
- Weighted mean FEV1(0-4) FF/VI 100/25 vs FF 100 (contribution of LABA)
- Trough FEV1 for each FF/VI dose versus VI alone (contribution of FF)

Protocol Amendment
A single protocol amendment was made to protocol 2206, the changes of which are reflected in the protocol description above. This amendment clarified the general sleep apnea exclusion criteria and the ECG exclusion criteria for patients with right bundle branch block. In addition, other minor editorial changes were made. None of the changes altered the study design or conduct in a major fashion.

Protocol Results
The efficacy results for this trial are found in Section 6 and the safety results in Section 7 of this review.

5.2 52-week Exacerbation trials: 2871 and 2970

Trials 2871 and 2970 were replicate trials initiated at the same time and both completed in October 2011. The protocol for 2871 is detailed below and serves as the protocol description for both trials. Similar trial designs have been used in other COPD exacerbation programs. Of note, the sponsor's definition and classification for exacerbations include objective parameters, which decrease the impact of local practice patterns.

HCZ102871 (2871)

Study Title: A 52-Week efficacy and safety study to compare the effect of three dosage strengths of fluticasone furoate/GW642444 inhalation powder with GW642444 on the annual rate of exacerbations in subjects with chronic obstructive pulmonary disease

Objectives/Rationale
Primary:

- To evaluate the safety and efficacy of FF/VI 50/25 mcg, 100/25 mcg, and 200/25 mcg versus VI 25 mcg on the annual rate of moderate and severe exacerbations in subjects with COPD over a 52 week treatment period

Secondary:

- To evaluate long term safety
- To evaluate other efficacy assessments
- To further investigate any reported cases of pneumonia

Study Design and Conduct

Overview:

This trial was a randomized, double-blind, parallel-group, multi-center trial evaluating three once-daily dosage strengths of FF/VI compared to VI 25 mcg. The trial duration was approximately 57 weeks, consisting of a 4-week run-in-period, 52-week treatment period and a 1-week follow-up period.

Eligible patients underwent a 4-week run-in period during which all subjects received open-label Advair 250/50. During this run-in period, all additional COPD medications, with the exception of PRN short-acting anticholinergics, were discontinued. Patients who met randomization criteria were then randomized 1:1:1:1 to one of four treatment groups: FF/VI 50/25 mcg, FF/VI 100/25 mcg, FF/VI 200/25 mcg or VI 25 mcg. Patients were stratified based on smoking status. All treatment groups received once-daily, morning administration of the study drug via the to-be-marketed NDPI. Clinic visits occurred at screening, randomization, and after 2, 4, 8, 12, 20, 28, 36, 33, and 52 weeks of treatment. A safety follow-up phone contact occurred one week after completion of randomized treatment or after an early withdrawal visit. All patients were provided with supplemental albuterol/salbutamol MDI and/or nebules to be used on an as needed basis.

COPD Exacerbation Assessment:

Exacerbations were identified based on an IVRS diary review which patients completed daily via telephone. In the daily diary, patients were asked to provide the following information:

- Number of night time awakening due to COPD symptoms
- Use of rescue medication (albuterol/salbutamol)
- Major symptoms concerning the subject's dyspnea, sputum volume, sputum purulence
- Minor symptoms of cough, wheeze, sore throat, colds (nasal discharge and/or congestion) fever without other cause

Patients who experienced worsening of COPD symptoms for greater than 24 hours were told to contact the study investigator and report to the clinic as required. In the event that patients were unable to contact the study investigator, they were instructed to contact their primary care physician, while continuing to record symptoms and rescue albuterol/salbutamol usage in their daily diary. If the patient required emergent/acute care for COPD, the patient was instructed to inform the study investigator as soon as possible.

A COPD exacerbation was defined using the following criteria:

- worsening of two or more of the following major symptoms for at least two

consecutive days:
    - Dyspnea
    - Sputum volume
    - Sputum purulence

  OR
- Worsening of any one major symptom outlined above plus any one of the following minor symptoms for at least two days:
    - Sore throat
    - Colds (nasal discharge and/or nasal congestions)
    - Fever without other cause
    - Increased cough
    - Increased wheeze

The severity of a COPD exacerbation was categorized using the definitions outlined below. If an exacerbation started off mild but progressed in severity, the exacerbation was classified by its highest level of severity. Two mild exacerbations could be combined into one if the two exacerbations were separated by no more than three exacerbation free days. This was left to investigator discretion.

- Mild exacerbation: worsening symptoms that are self-managed by the subject, and not associated with use of oral corticosteroids or antibiotics.
- Moderate exacerbation worsening symptoms that require treatment with oral corticosteroids and/or antibiotics
- Severe: worsening symptoms of COPD that require treatment with in-patient hospitalization.

Specific guidelines for COPD exacerbation treatment were outlined in the protocol. Investigators were instructed not to record exacerbations as AEs unless the definition of a SAE was met.

- Oral corticosteroid use:
    - Duration should be ≤ 14 days (dose and type per local practice) unless approval given by sponsor or representative
    - Any course of steroid started within 7 days of finishing a previous course was considered treatment for a single exacerbation
- Antibiotic use:
    - Duration of treatment should be 7 to 14 days (dose and type per local practice). If first line treatment fails and an additional antibiotic is used, duration should not exceed 30 days unless approved.
    - Any course of antibiotics started within 7 days of finishing a previous course was considered treatment for a single exacerbation.
    - Antibiotic treatment for upper or lower respiratory infections were not considered COPD exacerbations unless the symptoms met the COPD exacerbation definition outlined above.

<u>Pneumonia Identification</u>
The protocol specified that a CXR should be down within 48 hours of the identification of

a moderate or severe exacerbation. All CXRs were over-read by a central site to determine if there were radiographic findings consistent with pneumonia. Confirmed diagnoses of pneumonia were recorded as adverse events. Any suspected pneumonia required confirmation by the presence of new infiltrate on CXR plus at least two of the following signs and symptoms:

- Increased cough
- Increased sputum purulence or production
- Adventitious breath sounds on auscultation
- Dyspnea or tachypnea
- Fever
- Elevated WBC
- Hypoxemia

Spirometry:

The spirometric assessments followed the same procedures outlined for the airflow obstruction trial 2206.

Table 14: Time and Events Table: 2871

Visit	1	2	3	4	5	6	7	8	9	10	11	Early WD	Follow up
Day1	-28	1	14	28	56	84	140	196	252	308	364		
Week	-4		2	4	8	12	20	28	36	44	52		
Procedures													
IC	X												
PG IC	X												
Demography and History	X												
Inclusion/Exclusion Criteria	X												
Concomitant Meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Smoking Status	X							X			X	X	
Randomization criteria		X											
Efficacy Assessments													
Spirometry	X	X	X	X	X	X	X	X	X	X	X		
Reversibility	X												
Diary Review		X	X	X	X	X	X	X	X	X	X	X	
Exacerbation	X	X	X	X	X	X	X	X	X	X	X	X	
Healthcare utilization		X	X	X	X	X	X	X	X	X	X	X	
Safety Assessments													
AE	X	X	X	X	X	X	X	X	X	X	X	X	X
PE	X	X						X			X	X	
VS	X	X	X	X	X	X	X	X	X	X	X	X	
ECG	X	X				X		X			X	X	
OP exam	X	X	X	X	X	X	X	X	X	X	X	X	
CXR	X												
Pulse oximetry		X											

Visit	1	2	3	4	5	6	7	8	9	10	11	Early WD	Follow up
Day1	-28	1	14	28	56	84	140	196	252	308	364		
Week	-4		2	4	8	12	20	28	36	44	52		
Laboratory Assessments													
Hematology and Chemistry	X	X				X		X			X	X	
Bone metabolism		X									X	X	
Hepatitis B and C	X												
Serum pregnancy	X	X				X		X			X	X	
Urine Pregnancy							X		X	X			X
PGx sampling		X											
Study supplies And Investigational Product (IP)													
Dispense OL product													
Collect OL													
Dispense IP													
Assess compliance													
Collect IP													
Dispense rescue SABA													
Collect rescue SABA													

Source: Protocol 2871 Table 3 Time and Events Table
1 (±2) for each day except Day 1(Visit 1)
WD = withdrawal; IC = informed consent; PG = pharmacogenomic; AE = adverse event; PE = physical exam; VS = vital signs; ECG = electrocardiogram;OP = oropharyngeal; CXR = chest xray; OL = open Label; IP = investigational product;

Study Population

Key Inclusion Criteria:

Trial 2871 enrolled a similar patient population as trial 2206. However instead of a requirement for baseline symptoms of dyspnea, patients had to have a documented history of ≥ 1 COPD exacerbation within 12 months of screening.

Key Exclusion Criteria

Trial 2871 had similar exclusion criteria as 2206, with the following additions and modifications.

- CXR abnormality, not due to COPD, including pneumonia, that would preclude the ability to detect an infiltrate on CXR
    - All subjects had CXR screen at visit 1 which was over-read by a central radiologist
- Pneumonia risk factors including immune suppression, neurological disease affecting control of upper airway such as Parkinson's, Myasthenia Gravis, etc
- Moderate or severe COPD exacerbation without resolution within 14 days of screening and at least 30 days since last dose of oral corticosteroids
- Pneumonia and/or moderate or severe COPD exacerbation at Visit 1

Key Randomization Criteria: patients were not randomized if any of the following were

met:

- Pneumonia and/or moderate or severe COPD exacerbation during screening or run-in period
    - These subjects were not randomized, but were allowed to be rescreened at a later time
- Clinically significant abnormal laboratory findings in liver chemistry, hematology, or chemistry tests
- Clinically significant abnormalities on ECG, included but not limited to:
    - Sinus bradycardia (<45 bpm) or tachycardia (>110 bpm) confirmed by two additional readings at least 5 minutes apart
    - Multifocal atrial tachycardia
    - PR interval > 240 msec
    - 2nd degree Mobitz block of 3rd degree AV block
    - Pathological q waves unless unchanged from a previous ECG obtained at least 12 months prior
    - Evidence of ventricular ectopic couplets, bigeminy, trigeminy, or multifocal PVCs
    - ECG unsuitable for QT measurements
    - ST-T wave abnormalities
    - Clinically significant conduction abnormalities or arrhythmias

Withdrawal criteria

- Subject or investigator discretion
- Clinically important changes in laboratory parameters, including liver stopping criteria
- Clinically significant ECG abnormality identified during the study

Withdrawal due to COPD exacerbation and/or pneumonia

- Any pneumonia/exacerbation during screening or run-in were not to be randomized
- Subjects with mild, moderate or severe exacerbation were to remain in study if possible
- If withdrawn due to exacerbation, the exacerbation was sub-classified under lack of efficacy, and was only recorded as adverse event if it met the definition of SAE
- Subjects could discontinue study medication for ≤ 14 days due to an exacerbation

Permitted Medications and non-drug therapy

The permitted medications and non-drug therapy were the same as in trial 2206, except that oral corticosteroids and antibiotics (short course ≤14 days) for the short term treatment of COPD exacerbations were allowed in trial 2871. These medications were not allowed in 24-week lung function trials and any COPD exacerbation in resulted in patient withdrawal.

Investigational Treatment:

Treatment Groups:

- FF/VI 50/25 mcg once daily in the am
- FF/VI 100/25 mcg once daily in the am
- FF/VI 200/25 mcg once daily in the am
- VI 25 mcg once daily in the am

Similar to trial 2206, this trial used the to-be-marketed formulation of FF/VI in the to-be-marketed NDPI. For the VI monotherapy, the same formulation was used with removal of the micronized FF from the second strip. All other excipients remained the same.

Compliance
Compliance was assessed at each treatment visit and any unscheduled visit by reviewing the dose counter on the device. Any patient who fell to ≤ 80% or ≥ 120% was reeducated on treatment compliance.

Efficacy Parameters
Primary Efficacy Endpoint:
- Annual rate of moderate and severe exacerbations

Secondary Efficacy Endpoints:
- Time to first moderate or severe exacerbation
    - Date of onset is the first of ≥ 2 consecutive days of symptoms
- Annual rate of exacerbations requiring oral/systemic corticosteroids
- Trough FEV1

Other Efficacy:
- Annual rate of severe exacerbations
- Annual rate of all exacerbations (mild, moderate, severe)
- Time to onset of multiple moderate and severe exacerbations
- Nighttime awakening due to symptoms of COPD
- Occasions of supplemental use of albuterol/salbutamol
- Percentage of rescue free days
- Mean dyspnea score
- Percentage of days with increased sputum
- Percentage of days with increase in yellow/green sputum color

Safety Endpoints
- Incidence of adverse events: defined as any untoward medical occurrence in a subject temporally associated with the use of medicinal product.
- Incidence of Serious adverse event (SAE): defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in disability/incapacity, is a congenital anomaly
- Incidence of pneumonia
- Time to first pneumonia
- Time for first hospitalization for pneumonia

- Deaths due to pneumonia
- Incidence of bone fractures
- Hematological and clinical chemistry parameters
    - including serum glucose and potassium levels
- Vital sign measurements
    - including pulse and blood pressure measurements
- ECG measurements
- Oropharyngeal examinations
- Biochemical markers of bone metabolism

Per the draft Guidance for Industry, Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment (November 2007) a drug development program targeting an improvement in exacerbation should address the frequency, time to first exacerbation, duration, and severity of an exacerbation over an appropriate timeframe.

GSK's 52-week exacerbation protocols specified the frequency of exacerbations as the primary endpoint and assessed the time to first exacerbation and severity as secondary or additional endpoints; however, exacerbation duration was not explicitly assessed as an endpoint.

Statistical Plan
A sample size of 390 patients provided 90% power to detect a 25% reduction in annual rate of moderate and severe exacerbations of the FF/VI compared to VI alone. The sponsor estimated sample size for this trial based on an assumed annual rate of moderate and severe exacerbations of 1.4, which was based on estimates from the salmeterol arms of the previously conducted Advair exacerbation trials.

The primary population used for efficacy and safety endpoints was the Intent-to-Treat population. This definition was defined as all subjects who were randomized and received at least one dose of study medication.

The primary comparison of interest was the pairwise comparison of each dose regimen of FF/VI versus VI alone. To account for multiplicity, a step-down testing procedure dependent upon statistical significance for the previous tests in the hierarchy was used. The highest dose of FF/VI versus VI for the primary endpoint was the first comparison, with continued testing for the middle and low dose FF/VI combinations if significance was achieved. The secondary endpoints were nested under the primary endpoint for each dose group.

Protocol Amendments
A single protocol amendment was made to the original protocol. None of the changes altered the study design or conduct in a major fashion, and the protocol description above reflects the amended protocol.

The protocol amendment clarified the corticosteroid use defining an exacerbation to include systemic corticosteroids in addition to oral corticosteroids. Additional changes

included clarification of exclusion, randomization and withdrawal criteria for patients with right bundle branch block, revision of the list of excluded cytochrome P450 3A4 medications. In addition, other minor editorial changes were made.

Protocol Results
The efficacy results for this trial are found in Section 6 and the safety results in Section 7 of this review.

6 Review of Efficacy

Efficacy Summary

GSK has proposed two indications for the use of FF/VI 100/25 mcg once daily in patients with COPD:

- Long-term, once-daily, maintenance treatment of airflow obstruction
- Reducing exacerbations

To support the airflow obstruction indication, data is drawn from two, 24-week lung function trials (2206 and 2207) with co-primary endpoints of change from baseline in trough FEV1 and weighted mean FEV1 (0-4). These data are supplemented with trough FEV1 data, designated as a secondary endpoint, from the two 52-week exacerbation trials (2871 and 2970).

Data for the reduction in exacerbation indication is drawn from the replicate, 52-week exacerbation trials (2871 and 2970).

In addition to these trials, GSK conducted three active-controlled trials comparing FF/VI 100/25 to Advair (fluticasone/salmeterol). Trial HZC113107 (3107) compared once-daily FF/VI 100/25 to twice-daily Advair 500/50. Trial HZC113109 (3109) and trial HZC112352 (2352) compared once-daily FF/VI 100/25 to twice-daily Advair 250/50 mcg. Of note, in the United States, Advair is approved for both of the proposed indications at a dose of 250/50 mcg twice daily. While these trials provide a general assessment of the efficacy of FF/VI, they do not assess whether the efficacy of FF/VI is driven by VI alone.

Detailed analyses of the lung function data and exacerbation data are presented in Sections 6.1 and 6.2, respectively. The primary endpoint data for the Advair comparator trials is discussed separately in Section 6.1.9.

Overall, the data support the efficacy of FF/VI 100/25 over placebo in all four pivotal phase 3 trials. In addition, the efficacy of the LABA component, evidenced by a FF/VI to FF comparison on weighted mean FEV1 is demonstrated in both 2206 and 2207. However, the benefit of the FF/VI combination product over VI monotherapy, assessed

by a comparison of FF/VI to FF on trough FEV1, is less clear.

A numeric improvement in trough FEV1 is seen for FF/VI 100/25 over VI 25 in trials 2206 and 2207 (45 and 48 ml, respectively) and in trials 2871 and 2970 (58 ml and 24 ml respectively). However, none of these results are statistically significant with the results of many these comparisons descriptive only due to failure in the statistical hierarchical testing procedures.

Of note, the numeric increase in trough FEV1 of FF/VI over VI monotherapy is generally maintained at all of the evaluated time points in all four pivotal phase 3 trials. In addition, an FF/VI to VI comparison of weighted mean FEV1 demonstrates a 71 ml and 29ml improvement in favor of FF/VI 100/25 in trials 2206 and 2207 respectively. While not traditionally used to demonstrate the efficacy of an ICS, and not pre-specified for either trial, there data provide supplemental data indicating a numeric treatment benefit for FF/VI over VI.

For the reduction in exacerbation indication, which is traditionally ascribed to the steroid component of the combination ICS/LABA products, both exacerbation trials demonstrate a numeric improvement in the number of moderate and severe exacerbations for FF/VI 100/25 compared to VI monotherapy (2871: 34% reduction, 2970: 21% reduction). However, due to statistical hierarchical testing procedures and the failure of FF/VI 200/25 in demonstrating a statistically significant difference in trial 2871, only the comparison for 2970 is statistically significant.

Finally, an analysis of the Advair comparator trials provides an overall assessment for the efficacy of the combination product compared to a combination ICS/LABA product already approved for both proposed indications. Two of the three Advair trials, 3107 and 2352, compared FF/VI 100/25 to the U.S. approved dose of Advair 250/50. In both of these trials, FF/VI 100/25 demonstrates a numerically superior change from baseline in weighed mean FEV1 (0-24h) after 12 weeks of treatment compared to Advair 250/50. While trial 3107 demonstrates a statistically significant difference between the two treatments, the comparison from trial 2352 is not statistically significant. However, as noted above, these data do not provide an assessment of whether FF/VI provides an additional treatment benefit over VI treatment alone.

Whether the totality of the efficacy results from this development program demonstrates a benefit of the FF/VI combination product over VI monotherapy is a major point of discussion point for this Advisory Committee.

6.1 Indication: Airflow Obstruction

6.1.1 Methods

Section 6.1 discusses the efficacy trial results for the maintenance treatment of airflow obstruction. The majority of data is drawn from trials 2206 and 2207; however, the trough FEV1 data from the exacerbation trials 2871 and 2970 is also presented in

Section 6.1.4 and the active comparator trial data is summarized in Section 6.1.9.

6.1.2 Demographics

Overall, the gender, age, and race distribution across the treatment groups are comparable in both trials. The trials primarily enrolled subjects with GOLD[3] Stage 2 and 3 COPD. Of note, the GOLD guidelines reserve the addition of the ICS to a LABA for patients with Stage 3 disease who have a history of exacerbations. A discussion of the efficacy results stratified by GOLD stage is found in Section 6.1.7 and in Table 31.

Overall, an underrepresentation of subjects of African heritage and overrepresentation of those of Asian descent compared to the US population is evident; however the demographics are similar to other ICS/LABA combination development programs for approved products.

Table 15: Demographic and Baseline Characteristics: 2206

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N = 206	Total N = 1030
Age						
Mean	62.1	62.7	63.4	62.8	62.3	62.7
Median	63	63	64	62.5	62	63
Min - Max	41-85	42-83	40-84	43-84	42-85	40-85
Sex						
Female	66 (32)	74 (36)	65 (32)	71 (34)	69 (33)	345 (33)
Male	141 (68)	132 (64)	140 (68)	135 (66)	137 (67)	685 (67)
Race						
African Heritage	7 (3)	3 (1)	7 (3)	6 (3)	9 (4)	32 (3)
Amer. Indian or Alaska Native	1 (<1)	0	0	1 (<1)	1 (<1)	3 (<1)
Asian	44 (21)	64 (31)	57 (28)	43 (21)	46 (22)	254 (25)
White	155 (75)	139 (67)	141 (69)	156 (76)	150 (73)	741 (72)
Duration of COPD						
<1 year	19 (9)	17 (8)	11 (5)	19 (9)	19 (9)	85 (8)
≥1 to <5 years	72 (35)	92 (45)	82 (40)	81 (39)	79 (38)	406 (39)
≥5 to <10 years	72 (35)	55 (27)	64 (31)	59 (29)	63 (31)	313 (30)
≥10 to <15 years	26 (13)	23 (11)	25 (12)	26 (13)	31 (15)	131 (13)
≥15 to <20 years	11 (5)	11 (5)	11 (5)	10 (5)	5 (2)	48 (5)
≥20 to <25 years	4 (2)	5 (2)	6 (3)	5 (2)	7 (3)	27 (3)
≥25 years	3 (1)	3 (1)	6 (3)	6 (3)	2 (<1)	20 (2)
Smoking Status at screening						
Current Smoker	112 (54)	111 (54)	111 (54)	111 (54)	111 (54)	556 (54)

[3] Global Strategy for Diagnosis, Management, and Prevention of COPD: Global Initiative for Chronic Obstructive Lung Disease (GOLD) report revised 2011.

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N = 206	Total N = 1030
Former Smoker	95 (46)	95 (46)	94 (46)	95 (46)	95 (46)	474 (46)
Baseline Lung Function						
Mean pre-bronchodilator FEV1 percent predicated	42.4	41.5	44.5	42.5	42.3	42.6
GOLD Stage at Baseline						
≥80% (Stage I) ≥50% (Stage II) ≥30% (Stage III) <30% (Stage IV)	0 94 (46) 93 (45) 18 (9)	0 94 (46) 88 (43) 24 (12)	0 108 (53) 83 (40) 14 (7)	0 102 (50) 84 (41) 19 (9)	0 89 (43) 97 (47) 19 (9)	0 487 (47) 445 (43) 94 (9)
Reversibility						
Reversible Non-Reversible	77 (38) 128 (62)	71 (34) 135 (66)	64 (31) 140 (69)	73 (36) 131 (64)	66 (32) 138 (68)	351 (34) 672 (66)
Concomitant Medications						
Short acting anticholinergics Other respiratory medications	62 (30) 26 (13)	53 (26) 19 (9)	40 (20) 26 (13)	44 (21) 24 (12)	46 (22) 11 (5)	245 (24) 106 (10)
Source: CSR 2206 Tables 8, 9, 10, 11, 12,14						

Table 16: Demographic and Baseline Characteristics: 2207

	Placebo N=207	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N = 205	Total N = 1224
Age							
Mean Median Min - Max	61.9 62 40-81	61.8 61.5 41-84	61.8 62 40-85	61.2 62 41-80	61.9 62 41-84	61.1 61 42-83	61.6 62 40-85
Sex							
Female Male	53 (26) 152 (74)	54 (26) 150 (74)	52 (26) 151 (74)	52 (26) 151 (74)	60 (29) 144 (71)	68 (33) 137 (67)	339 (28) 885 (72)
Race							
African Heritage Amer. Indian or Al. Native Asian White	0 0 8 (4) 197 (96)	2 (<1) 0 5 (2) 197 (97)	5 (2) 1 (<1) 14 (7) 183 (90)	3 (1) 0 4 (2) 196 (97)	4 (2) 2 (<1) 8 (4) 190 (93)	2 (<1) 0 11 (5) 192 (94)	16 (1) 3 (<1) 50 (5) 1155 (94)
Duration of COPD							
<1 year ≥1 to <5 years ≥5 to <10 years ≥10 to <15 years ≥15 to <20 years	24 (12) 79 (39) 57 (28) 30 (15) 8 (4)	22 (11) 77 (38) 69 (34) 24 (12) 5 (2)	29 (14) 79 (39) 49 (24) 31 (15) 12 (6)	19 (9) 76 (37) 57 (28) 25 (12) 14 (7)	18 (9) 78 (38) 62 (30) 30 (15) 10 (5)	18 (9) 77 (38) 70 (34) 21 (10) 8 (4)	130 (11) 466 (3) 364 (30) 161 (13) 57 (5)

	Placebo N=207	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N = 205	Total N = 1224
≥20 to <25 years ≥25 years	2 (<1) 5 (2)	5 (2) 2 (<1)	2 (<1) 1 (<1)	6 (3) 6 (3)	5 (2) 1 (<1)	6 (3) 5 (2)	26 (2) 20 (2)
Smoking Status at Screening							
Current Former	108 (53) 97 (47)	114 (56) 90 (44)	112 (55) 91 (45)	111 (55) 92 (45)	109 (53) 95 (47)	112 (55) 93 (45)	666 (54) 558 (46)
Baseline Lung Function							
Mean Percent Predicted pre-bronchodilator FEV1	43.5	44.6	42.7	43.7	43.8	43	43.6
GOLD Stage at Baseline							
≥80% (Stage I) ≥50% (Stage II) ≥ 30% (Stage III) <30% (Stage IV)	0 94 (46) 96 (47) 13 (6)	0 95 (47) 91 (45) 15 (7)	0 85 (42) 101 (50) 16 (8)	0 102 (50) 81 (40) 19 (9)	1 (<1) 93 (46) 90 (45) 18 (9)	1 (<1) 91 (45) 89 (44) 22 (11)	2 (<1) 560 (46) 548 (45) 103 (8)
Reversibility							
Reversible Non-Reversible	61 (30) 142 (70)	57 (29) 142 (71)	54 (27) 147 (73)	60 (30) 140 (70)	58 (29) 142 (71)	54 (27) 144 (73)	344 (29) 857 (71)
Concomitant Medications							
Short acting anticholinergics Other respiratory medications	41 (20) 13 (6)	35 (17) 5 (2)	39 (19) 11 (5)	42 (21) 9 (4)	41 (20) 10 (5)	46 (22) 13 (6)	244 (20) 61 (5)
Source: CSR 2207 Tables 8, 9, 10, 11, 12, 14							

6.1.3 Patient Disposition

A total of 1,030 patients were randomized in trial 2206 and 1,224 in 2207. The most common reason for subject withdrawal is withdrawal due to adverse events. An increase in withdrawals due to lack of efficacy and exacerbation is seen in the placebo arms; this may indicate efficacy of the active treatment arms.

Table 17: Patient Disposition: 2206

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total N=1030
Completed	138 (67)	145 (70)	142 (69)	147 (71)	151 (73)	723 (70)
Withdrawn	69 (33)	61 (30)	63 (31)	59 (29)	55 (27)	307 (30)
Primary reason for withdrawal						
Adverse event	15 (7)	23 (11)	24 (12)	17 (8)	14 (7)	93 (9)

	Placebo N=207	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Total N=1030
Lack of Efficacy	20 (10)	18 (9)	15 (7)	12 (6)	12 (6)	77 (7)
Exacerbation	17 (8)	16 (8)	13 (6)	9 (4)	12 (6)	67 (7)
Protocol Deviation	3(1)	4(2)	2(<1)	1(<1)	4(2)	14(1)
Lost to Follow-up	4 (2)	0	2 (<1)	1 (<1)	3 (1)	10 (<1)
Source: CSR 2206 Table 6						

Table 18: Patient Disposition: 2207

	Placebo N=205	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N=205	Total N=1224
Completed	146 (71)	155 (76)	160 (79)	161 (79)	144 (71)	158 (77)	924 (75)
Withdrawn	59 (29)	49 (24)	43 (21)	42 (21)	60 (29)	47 (23)	300 (25)
Primary Reason for Withdrawal							
Adverse event	18 (9)	12 (6)	15 (7)	15 (7)	17 (8)	19 (9)	96(8)
Lack of efficacy	12 (6)	5 (2)	6 (3)	11 (5)	8 (4)	7 (3)	49 (4)
Exacerbation	12 (6)	2 (<1)	5 (2)	11 (5)	7 (3)	7 (3)	44 (4)
Protocol deviation	7(3)	7(3)	2(<1)	3(1)	8(4)	4(2)	31(3)
Lost to follow-up	3 (1)	2 (<1)	0	0	2 (<1)	1 (<1)	8 (<1)
Source: CSR 2207 Table 6							

Compliance:
Compliance was assessed through a review of device dose counters. Overall, rates were high across all treatment groups in both studies (2206: > 98% and 2207: > 97%).

6.1.4 Analysis of Co-Primary Endpoint(s): weighted mean FEV1 (0-4h) and trough FEV1

The two 24-week lung function trials, 2206 and 2207, evaluated weighted-mean FEV1 (0-4) and trough FEV1 as co-primary endpoints. In addition, the two exacerbation trials, 2871 and 2970, evaluated trough FEV1 as a secondary endpoint. All four trials evaluated these measures at additional time points, designating these as "other" endpoints. Typically, trough FEV1 is used to evaluate the efficacy of an ICS, and post-dosing FEV1 is used for assessment of bronchodilator activity, as was done in this development program. As the evaluation of these data is pertinent to the proposed airflow obstruction indication, all of these data are presented and analyzed in this section of the review. In addition, the comparison of FF/VI to VI for weighted mean FEV1 is also presented below as this provides an additional assessment of whether FF provides a treatment benefit for the FF/VI combination.

For both co-primary endpoints, both bronchodilator trials, 2206 and 2207, demonstrate the benefit of the combination product over placebo ($p < 0.001$ for all FF/VI to placebo comparisons). The efficacy of VI in the combination product is also demonstrated through a comparison of the FF/VI treatment arms to the respective FF doses for

weighted mean FEV1 (2206: FF/VI 100/25 to FF 100: p = 0.003; 2207: FF/VI 200/25 to VI 25: p < 0.001). The result for the FF/VI 100/25 to FF 100 comparison in trial 2207 has a nominal p value of < 0.001; this is descriptive only due to failure of higher dose comparison in trough FEV1. Of note, the treatment effect appears to be maintained throughout the course of the trial (see Figure 6).

The lung function trials (2206 and 2207) demonstrate an approximate 100 ml improvement from baseline for VI monotherapy and 150 ml for the combination FF/VI 100/25 therapy. Similar increases from baseline are not seen for the exacerbation trials (2871 and 2970) for either VI or FF/VI therapy. This is likely due to the different run-in procedures for the two trials. For the lung function trials, baseline values were obtained after a 2-week run-in which all maintenance COPD medications were stopped. For the exacerbation trials, the baseline values were obtained after a 4-week run-in during which all patients took Advair 250/50. It is likely that the absolute treatment benefits from baseline are lower in the exacerbation trials as baseline values were obtained while patients were already bronchodilated.

While the absolute improvements from baseline are not consistent across the four trials, the relative benefit of the combination therapy to VI monotherapy is generally maintained (24 ml-58ml improvement).The difference in treatment effect between FF/VI and VI for trough FEV1 is consistently demonstrated in 2206 and 2207 (48 ml and 45 ml); however neither result is statistically significant. Similarly, the trough FEV1 results from the exacerbation trial 2871 and 2970 also demonstrate a numeric benefit for the combination product compared to VI monotherapy; however, neither of these results is statistically significant.

While not a designated comparison, a comparison of the change from baseline in weighted mean FEV1 for FF/VI 100/25 to VI also demonstrates a numeric treatment benefit in favor of FF/VI 10025 for both 2206 (0.71 ml) and 2207 (0.29 ml).

Table 19: Change from Baseline in Trough FEV1: 2206, 2207, 2871 and 2970

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Day 169 LS mean change	0.037	0.07		0.103	0.166	0.151	
Difference from placebo P value		0.033 0.241[3]		0.067 0.017	0.129 <0.001	0.115 <0.001	
Difference from VI 25 mcg P value					0.062 0.025[2]	0.048 0.082	
Difference from FF 100 P value						0.082 0.003	
Trial 2207							
N[1]	205	204	203	203		204	205
Day 169 LS mean change	0.004	0.048	0.012	0.103		0.148	0.135

Difference from placebo P value		0.044 0.095[3]	0.008 0.756[3]	0.1 <0.001		0.144 <0.001[2]	0.131 <0.001
Difference from VI 25 mcg P value						0.045 0.093[2]	0.032 0.224
Difference from FF 100 P value						0.1 <0.001[3]	
Difference from FF 200 P value							0.123 <0.001[3]
Trial 2871							
N[1]				409	408	403	402
Week 52 LS mean change				-0.04	0.00	0.018	0.024
Difference from VI 25 P value					0.041 0.011[2]	0.058 <0.001[2]	0.064 <0.001[2]
Trial 2970							
N[1]				409	412	403	409
Week 52 LS mean change				-0.019	0.015	0.005	0.006
Difference from VI 25 P value					0.034 0.034[2]	0.024 0.143[2]	0.026 0.115[2]
Source: Table 21 CSR 2206 and 2207 and Table 18 CSR 2871 and 2970 [1] number randomized 2 nominal p values only due to statistical hierarchal testing procedures							

Table 20: Change from Baseline in Weighted Mean FEV1 (L): 2206 and 2207

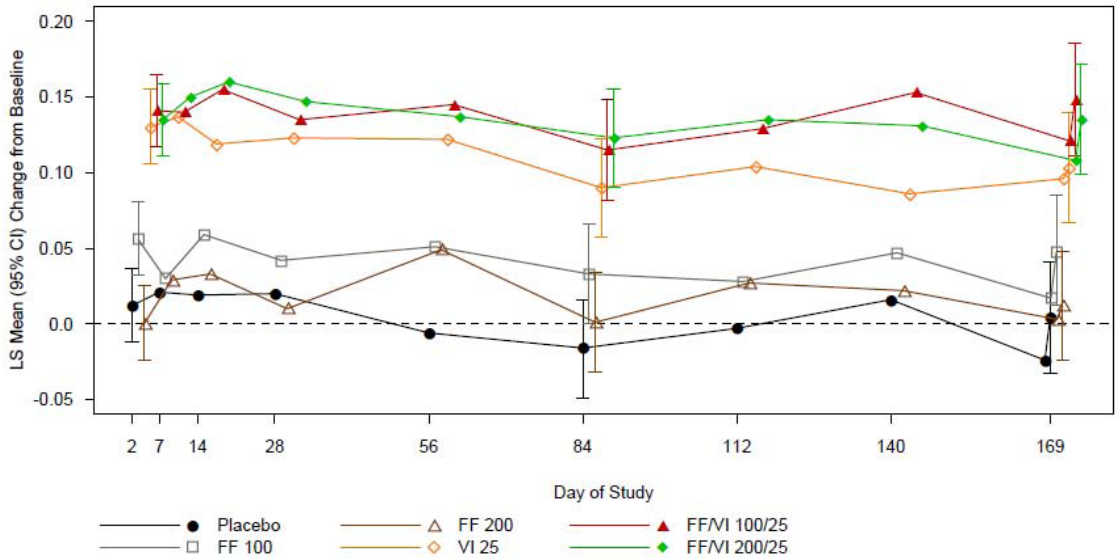
	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Day 169 LS mean change	0.029	0.098		0.139	0.239	0.205	
Difference from placebo P value		0.053 0.04[3]		0.103 <0.001	0.192 <0.001[2]	0.173 <0.001	
Difference from VI 25 mcg P value					0.090 <0.001[23]	0.071 0.006[3]	
Difference from FF 100 P value						0.120 <0.001	
Trial 2207							
N[1]	205	204	203	203		204	205
Day 169 LS mean change	-0.012	0.033	0.026	0.181		0.221	0.205
Difference from placebo P value		0.046 0.085[3]	0.041 0.123[3]	0.185 <0.001		0.214 <0.001	0.209 <0.001
Difference from VI 25 mcg P value						0.029 0.274[23]	0.024 0.357[3]
Difference from FF 100 P value						0.168 <0.001[2]	

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Difference from FF 200 P value							0.168 <0.001

Source: CSR 2206 and 2207 Table 19
[1] number randomized
[2] nominal p values only due to statistical hierarchal testing procedures
[3] comparison not included in statistical hierarchal testing procedures

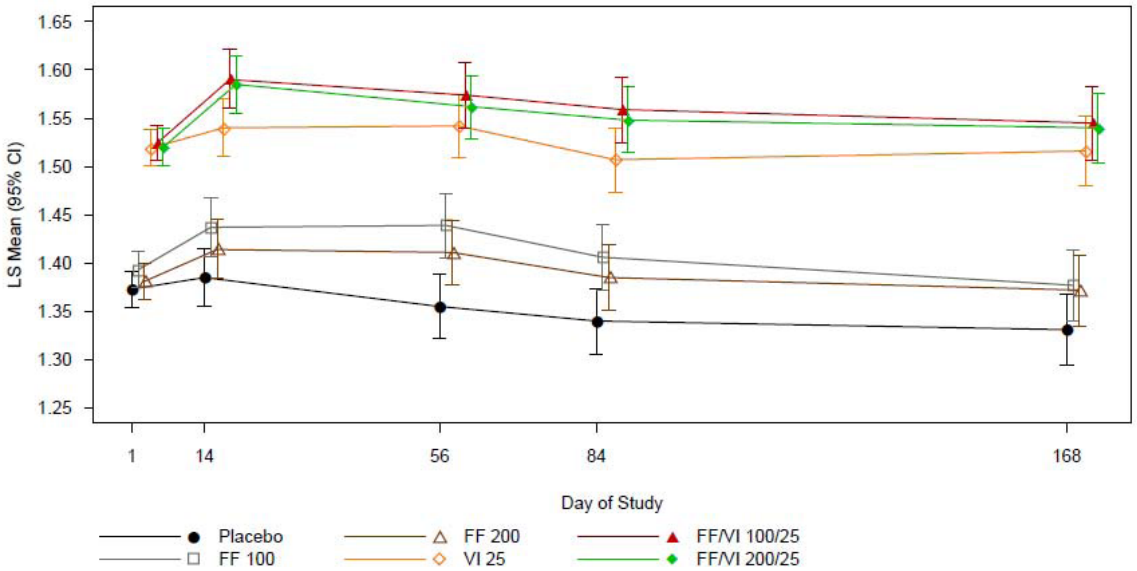
In addition to the weighted mean FEV1 data and trough FEV1 data obtained at the end of the treatment periods, all four trials evaluated these same measures at additional time points throughout the trials. In general, the separation between FF/VI and VI is maintained throughout the course of each study. Figure 5 displays the change from baseline in trough FEV1 for trial 2207, Figure 6 the change from baseline in weighted mean for trial 2207 and Figure 7 the change from baseline in trough FEV1 from 2871. These figures are representative of data from the other trials.

Figure 5: LS Mean Change from Baseline in Trough FEV1: 2207



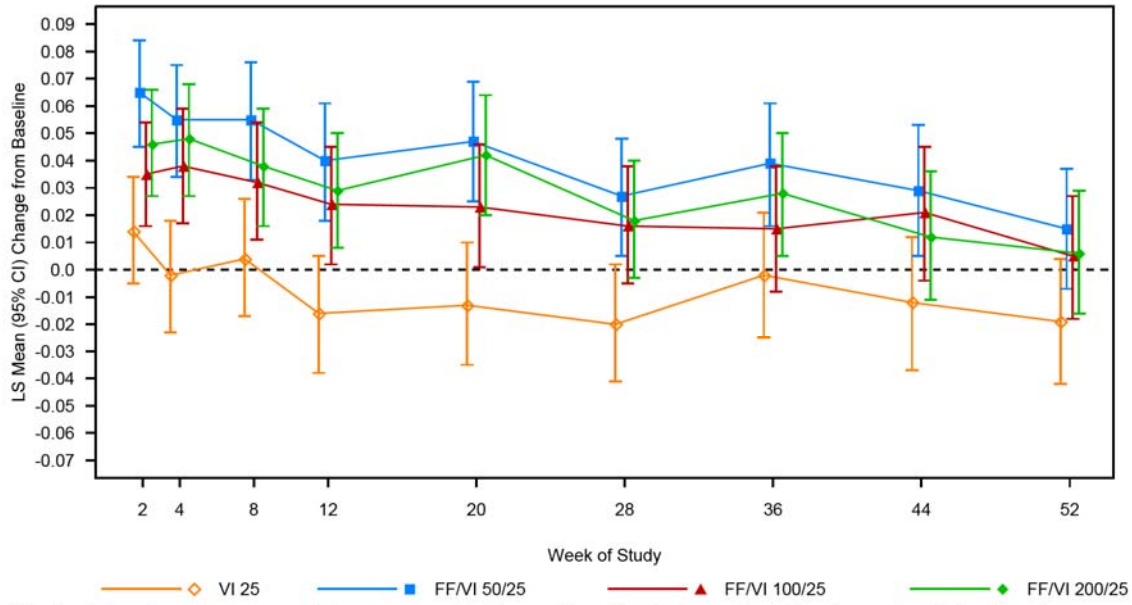
Source: CSR 2207 Figure 3; data presented are the LS means with 95% confidence intervals in trough FEV1 for the ITT using a repeated measures model

Figure 6: LS Mean Change from Baseline in Weighted Mean FEV1: 2207



Source: CSR 2207 Figure 2; data presented are the LS means with 95% confidence intervals in 0-4h weighted mean FEV1 for the ITT population using the mixed model repeated measures analysis

Figure 7: LS Mean Change from Baseline in Trough FEV1: 2970



Source: CSR 2970 Figure 6.09

6.1.5 Analysis of Secondary Endpoints(s)

The bronchodilator trials specified two secondary endpoints: peak FEV1 on Day 1 and time to onset > 100 ml above baseline on Day 1. In addition, GSK specified the time to a

12% increase from baseline in FEV1 as an "other" efficacy parameter. The data for all of these endpoints are presented in detail below. Due to failure of the primary endpoint to win, none of comparisons are permitted in the statistical testing procedures. Thus, the results below are for descriptive purposes only. As such, the p-values for these comparisons are not provided.

Time to Peak FEV1

Time to peak FEV1 was defined as the maximum post dose-FEV1 obtained at the 5, 15, 30 minute and 1, 2, 4 hour time points. The combination product consistently demonstrates a difference in peak FEV1 on Day 1 compared to placebo in both trials. In addition, the FF/VI doses also demonstrate a difference from the FF comparators in both trials. As expected, given that the immediate bronchodilator effect is likely driven by the LABA component, a consistent difference in time to peak FEV1 between the FF/VI doses and VI comparator is not seen.

Table 21: Time to Peak FEV1: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Peak FEV1 on Day 1	0.106	0.118		0.247	0.253	0.24	
Difference from placebo		0.012		0.142	0.148	0.139	
Difference from VI 25 mcg					0.006	-0.003	
Difference from FF 100						0.127	
Trial 2207							
N[1]	205	204	203	203		204	205
Peak FEV1 on Day 1	0.12	0.03	0.11	0.21		0.33	0.23
Difference from placebo		-0.09	-0.01	0.09		0.21	0.11
Difference from VI 25 mcg						0.12	0.02
Difference from FF 100						0.3	
Difference from FF 200							0.12

Source: CSR 2206 and 2207 Table 25
[1] number randomized

Time to Onset

The median time to onset for both FEV1 >100 ml ranges between 16 and 17 minutes for all VI containing treatment arms in both trials. The time to 12% change in FEV1 from baseline is more variable, ranging between 30 and 61 minutes for both trials with the highest tested dose of FF/VI in both trials having the longest median times for each trial (59 minutes for FF/VI 100/25 and 61 minutes for FF 200/25).

Table 22: Time to Onset: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N[1]	207	206		205	206	206	
Time to 100 ml increase							
Number events, n(%)	90 (43)	97 (47)		175 (85)	174 (85)	175 (85)	
Number censored[2], n (%)	117 (57)	109 (53)		30 (15)	31 (15)	31 (15)	
Median[3], min				16	17	17	
Time to 12% change from baseline							
Number events, n (%)	65 (31)	75 (36)		156 (76)	152 (74)	149 (72)	
Number censored[2], n (%)	142 (69)	131 (64)		49 (24)	53 (26)	57 (28)	
Median[3], min				32	30	59	
Trial 2207							
N[1]	205	204	203	203		204	205
Time to 100 ml increase							
Number events, n (%)	101 (50)	118 (58)	106 (52)	180 (90)		172 (85)	177 (86)
Number censored[2], n (%)	103 (50)	85 (42)	96 (48)	21 (10)		31 (15)	28 (14)
Median[3], min		231	242	17		16	17
Time to 12% change from baseline							
Number events	63 (31)	71 (35)	70 (35)	148 (74)		152 (75)	144 (70)
Number censored[2], n (%)	141 (69)	132 (65)	132 (65)	53 (26)		51 (25)	61 (30)
Median[3], min				35		33	61

Source: CSR 2206 and 2207 Table 27, 29

[1] number randomized

[2] censored defined as a subject who had at least one post-dose measurement but did not meet criteria.

[3]If more than 50% of subjects are censored, median time was not given.

6.1.6 Other Endpoints

The sponsor specified eight additional endpoints as “other efficacy endpoints”.

- Symptom scores
- Rescue medication use
- Night-time awakenings
- Peak expiratory flow
- Serial FVC
- CRQ-SAS dyspnea domain
- Symptom free 24-hour periods
- Rescue-free 24 hour periods

In general, the data support the overall efficacy of the combination product over placebo. In addition, a benefit for FF/VI over VI monotherapy is seen for many, but not all of these endpoints. As discussed above, due to statistical testing procedures the results of these comparisons are for descriptive only and p values are not reported.

Symptom Scores

The FF/VI treatment arms appear to demonstrate an improvement in cough, sputum production, and breathlessness in both trials compared to placebo. In general, numeric improvements for the combination therapy over the monotherapy VI and FF products are also seen.

Table 23: Symptom Scores over Weeks 1-24: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Cough Scores							
LS Mean	1.48	1.39		1.35	1.27	1.28	
Difference from placebo		-0.09		-0.13	-0.21	-0.2	
Difference from VI 25 mcg					-0.08	-0.07	
Difference from FF 100						-0.11	
Sputum Scores							
LS Mean	1.32	1.24	1.26	1.18	1.21	1.32	
Difference from placebo		-0.07		-0.05	-0.13	-0.11	
Difference from VI 25 mcg					-0.08	-0.06	
Difference from FF 100						-0.04	
Breathlessness Scores							
LS Mean	1.72	1.6		1.52	1.42	1.4	
Difference from placebo		-0.12		-0.19	-0.3	-0.31	
Difference from VI 25 mcg					-0.11	-0.12	
Difference from FF 100						-0.19	
Trial 2207							
N[1]	205	204	203	203		204	205
Cough Scores							
LS Mean	1.46	1.43	1.4	1.39		1.33	1.31
Difference from placebo		-0.03	-0.06	-0.07		-0.13	-0.15
Difference from VI 25 mcg						-0.06	-0.08
Difference from FF 100						-0.1	
Difference from FF 200							-0.09
Sputum Scores							
LS mean	1.31	1.28	1.24	1.29		1.17	1.2
Difference from placebo		-0.03	-0.07	-0.02		-0.14	-0.12
Difference from VI 25 mcg						-0.12	-0.09
Difference from FF 100						-0.11	
Difference from FF 200							-0.04
Mean Breathlessness Scores							
LS mean	1.81	1.71	1.68	1.62		1.5	1.49
Difference from placebo		-0.09	-0.13	-0.19		-0.31	-0.32
Difference from VI 25 mcg						-0.12	-0.13

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Difference from FF 100						-0.21	
Difference from FF 200							-0.19
Source: CSR 2206 and 2207 Table 32, 33, 34 [1] number randomized							

Rescue Medication Use

The FF/VI treatment arms and VI monotherapy arm demonstrate improvement over placebo in rescue medication use in both trials. In trial 2206, the 100/25 FF/VI treatment arm demonstrates a decrease in rescue medication use compared to VI monotherapy. A similar result is seen for the 100/25 FF/VI to VI treatment comparison in 2207, however in this trial the higher 200/25 dose demonstrates a smaller treatment effect.

Table 24: Occasions of Rescue Medication Use per 24 hours over Week 1-24: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
LS mean # occasions/24 hrs	1.95	1.59		1.41	1.23	1.06	
Difference from placebo		-0.36		-0.55	-0.72	-0.89	
Difference from VI 25					-0.17	-0.34	
Difference from FF 100						-0.53	
Trial 2207							
N[1]	205	204	203	203		204	205
LS mean # of occasions/24 hrs	1.78	1.6	1.62	1.34		1.07	1.28
Difference from placebo		-0.17	-0.15	-0.43		-0.71	-0.49
Difference from VI 25						-0.27	-0.06
Difference from FF 100						-0.53	
Difference from FF 200							-0.34
Source: CSR 2206 and 2207 Table 35 [1] number randomized							

Night-time Awakenings

The FF/VI treatment arms demonstrate improvement in the number of nighttime awakenings requiring rescue medication use over placebo in both trials and the FF/VI arms demonstrate numeric improvement over the VI monotherapy arm as well. In addition, the VI and FF monotherapy arms demonstrate improvement over placebo in both trials.

Table 25: Percentage of Awakenings Requiring Rescue Medication over Week 1-24: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N[1]	207	206		205	206	206	
LS mean % awakenings requiring medication/24 hrs	0.37	0.31		0.31	0.24	0.23	
Difference from placebo		-0.06		-0.06	-0.13	-0.14	
Difference from VI 25					-0.08	-0.08	
Difference from FF 100						-0.08	
Trial 2207							
N[1]	205	204	203	203		204	205
LS mean % of awakenings requiring medication/24 hrs	0.41	0.3	0.37	0.3		0.21	0.26
Difference from placebo		-0.11	-0.03	-0.11		-0.2	-0.15
Difference from VI 25						-0.08	-0.03
Difference from FF 100						-0.08	
Difference from FF 200							-0.11

Source: CSR 2206 and 2207 Table 37
[1] number randomized

Peak Expiratory Flow

All active treatment arms demonstrate improvement in mean AM peak expiratory flow for Week 1 to 24 over placebo and the FF monocomparators in both trials. However, in general, the FF/VI provides for a lower effect over VI monotherapy and no dose-response is evident. The FF comparator arm also demonstrate an improvement over placebo in both trials, however a smaller benefit over placebo compared to the VI-containing treatment arms is seen.

Table 26: Mean AM Peak Expiratory Flow over Week 1-24: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
LS mean	217.6	225.1		237.1	241.2	242.8	
Difference from placebo		7.5		19.5	23.6	25.2	
Difference from VI 25					4.1	5.7	
Difference from FF 100						17.7	
Trial 2207							
N[1]	205	204	203	203		204	205
LS mean	230.1	239.1	239.8	246		251.8	250.1
Difference from placebo		9	9.7	15.9		21.7	20.1
Difference from VI 25						5.8	4.1
Difference from FF 100						12.7	
Difference from FF 200							10.4

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Source: CSR 2206 and 2207 Table 38 [1] number randomized							

Serial FVC

In general, the results for the change from baseline for 4-hour post-dosing serial FVC at day 168 for trials 2206 and 2207 demonstrate improvement in FVC compared to placebo for all of the VI-containing treatment arms. However, a consistent effect for FF monotherapy is not seen between trials.

Table 27: Day 168 Change from Baseline in FVC (ml): 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Predose	35	83		76	185	107	
5	42	65		147	242	151	
15	38	81		141	224	170	
30	49	94		135	270	162	
1	34	116		156	300	171	
2	57	95		185	294	182	
4	68	123		178	302	199	
Trial 2207							
N[1]	205	204	203	203		204	205
Predose	-30	-11	-47	133		113	37
5	-53	-36	-57	203		164	92
15	-56	-27	-74	222		191	145
30	-34	-22	-64	244		182	119
1	-41	-26	-31	240		242	152
2	-11	34	-2	245		248	190
4	0	73	2	239		265	195
Source: CSR 2206 and 2207 Table 39 [1] number randomized							

Chronic Respiratory Questionnaire (CRQ)

Dyspnea Domain:

While CRQ was defined as a secondary endpoint for other international sites, in the US this endpoint was designated as an “other endpoint”. This questionnaire has not been validated for an evaluation of dyspnea by the FDA. For both 2206 and 2207, numeric improvements for both FF/VI dosage strengths compared to placebo and the respective FF monotherapy are seen; however these differences fail to exceed the minimal

clinically important difference of > 0.5 reported in the literature[4].

Table 28: CRQ Dyspnea Domain: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Day 168 LS mean change from baseline	0.23	0.29		0.37	0.42	0.53	
Difference from placebo		0.06		0.14	0.19	0.3	
Difference from VI 25					0.05	0.16	
Difference from FF 100						0.24	
Trial 2207							
N[1]	205	204	203	203		204	205
Day 168 change from baseline	0.21	0.10	0.21	0.28		0.45	0.31
Difference from placebo		-0.12	-0.01	0.07		0.24	0.1
Difference from VI 25						0.17	0.03
Difference from FF 100						0.36	
Difference from FF 200							0.1

Source: 2206 and 2207 CSR Table 23
[1] number randomized

Other domains and Total Score
Similar to the CRQ-SAS Dyspnea Domain, none of the comparisons for CRQ other domains and CRQ total score exceed the minimal clinically important difference of > 0.5.

Percentage of Symptom-Free 24 hour Periods:

In general, numeric improvement in the percentage of symptom free 24-periods for the combination product over placebo and to a lesser extent over the monotherapy arms are seen.

Table 29: Symptom Free Periods: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Total Symptom free, mean % Baseline, Week 1-24	 3 6.1	 2.8 7		 5 10.1	 1.8 9.7	 5 8.4	

[4] Jones, PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. *Eur Respir J* 2002; 19:398-404.

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Cough Free							
Baseline	13.8	14.3		13.3	13.1	11.7	
Week 1-24	17.2	18		20.3	23.9	19.2	
Sputum Free							
Baseline	16.2	18.6		21	18.9	16.5	
Week 1-24	19.3	22.2		26.1	26.2	21.4	
Breathlessness Free, mean %							
Baseline	8.9	7		11.6	8.7	12.5	
Week 1-24	10.2	12.1		16.3	16.3	18.9	
Trial 2207							
N[1]	205	204	203	203		204	205
Total Symptom Free, mean %							
Baseline	3.1	3.1	2.9	1.8		2.6	2.3
Week 1-24	3.7	4.2	5.5	4.5		6.8	6
Cough Free, mean %							
Baseline	14	11.7	13.5	12.3		13.4	11.9
Week 1-24	14.2	16.6	17.5	16.1		18.7	18.4
Sputum Free, mean %							
Baseline	19.4	19.8	21.9	17.7		19.5	18.3
Week 1-24	18.5	22	23.6	19.7		23.9	21.4
Breathlessness Free, mean %							
Baseline	6.6	7.5	8.3	4.7		5.5	8.2
Week 1-24	6.6	10.1	11.4	7.7		11.4	12.7

Source: CSR 2206 and 2207 Table 30
[1] number randomized

Rescue-Free 24 hour periods

In both trials, the largest percentage of rescue-free 24 hour periods over the 24 weeks of treatment is seen in the FF/VI treatment arms. The VI monocomparator arms also show an increase, albeit smaller, in both trials.

Table 30: Rescue Free 24 hour Periods: 2206 and 2207

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2206							
N[1]	207	206		205	206	206	
Baseline	34.1	35.6		33.7	36.4	40.9	
Week 1-24	33	40		43.2	49.1	56.5	
Trial 2207							
N[1]	205	204	203	203		204	205
Baseline	37.4	38.2	40.7	35.7		31.9	38.8
Week 1-24	39.5	40	44	43.5		48.9	51.3

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Source: CSR 2206 and 2207 Table 31 [1] number randomized							

6.1.7 Subpopulations

The sponsor provided summary statistics for the following subgroup analyses of the primary endpoints for the pooled data from trial 2206 and 2207:

- percent predicted FEV1
- age
- race
- gender
- smoking status
- geographical region
- reversibility
- cardiovascular history and risk.

As the efficacy of FF contribution to FF/VI remains unclear, the table below specifically summarizes the difference from VI in change from baseline in trough FEV1 for the FF/VI treatment arms by GOLD stage for the combined data from trials 2206 and 2207. Of note, the majority of patients in the trials had GOLD stage 2 and 3, with each stage responsible for approximately half of the enrollment. Patients with GOLD 2 stage disease in the FF/VI treatment arm demonstrate a 27 to 47 ml improvement over VI compared to a 36 to 82 ml improvement for patients with GOLD stage 3. This analysis suggests a possible increase in efficacy for patients in GOLD stage 3. However this trend is not maintained in patients with Stage 4 COPD (the most severe patients enrolled). These patients had a 3 to 31 ml improvement in trough FEV1 over VI therapy alone, although interpretation is limited by the relatively few number of patients with GOLD stage 4 disease.

Table 31: Trough FEV1 by GOLD Stage: 2206 and 2207

	FF/VI 50/25 N=206	FF/VI 100/25 N=410	FF/VI 200/25 N=205
GOLD Stage 1 and 2[1]			
Difference from VI	0.047	0.027	0.033
P value	0.153	0.332	0.32
GOLD Stage 3			
Difference from VI	0.07	0.082	0.036
P value	0.056	0.005	0.315
GOLD Stage 4[2]			
Difference from VI	0.031	0.003	0.031
P value	0.714	0.960	0.678

Source: Table 120.04 provided in GSK response to Information Request dated December 3, 2012
[1] No patients with GOLD stage 1 were enrolled
[2] 10 to 26 patients per treatment arm with GOLD stage IV were enrolled in the two trials

In general, the results for the other subpopulation analyses are similar to the primary analyses.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

Tachyphylaxis of bronchodilation is of particular concern with LABA therapy. As discussed in Section 4.4.2.1, the dose-ranging trial of VI in COPD did not demonstrate tachyphylaxis over the first month of treatment (see Table 7). In addition, the spirometric data from the four phase 3 trials does not display any evidence of clinically relevant tachyphylaxis over the course of the treatment periods (see Figure 6). Similarly, no tolerance effect is seen for the fluticasone furoate component (see Figure 7).

6.1.9 Additional Efficacy Issues/Analyses

As noted in the efficacy summary above, GSK conducted four active comparator trials comparing the once-daily FF/VI 100/25 to Advair. Three of these trials were conducted in COPD (3109, 2352 and 3107) and the remaining trial (HZA113091: 3091) was conducted in asthma.

Trials 3109 and 2352 compared FF/VI 100/25 to the U.S. approved dose of Advair 250/50 and trial 3107 compared it to Advair 500/50. These three trials were conducted in COPD. Of note, Advair 250/50 is approved for both a maintenance treatment of COPD and a reduction in exacerbation indication in the United States. Advair 500/50 was not approved due to an increased risk of pneumonia without a substantial increase in efficacy to balance this safety concern.

While these comparator trials do not provide a specific sense of the efficacy of the combination product compared to the monotherapy components, a general sense of the efficacy of the product compared to an already marketed product can be gained.

Trials 3109 and 2352 were randomized, double-blind, 12-week, parallel-group study comparing the FEV1 of 100/25 mcg of FF/VI once-daily to twice-daily Advair 250/50 in patients with COPD. Trial 3107 was a similarly designed study; however, it compared twice-daily Advair 500/50 to FF/VI 100/25 mcg once-daily. These Advair comparator trials were 12 weeks in duration and assessed an effect on lung function only. The primary endpoint was the change from baseline trough in 24-hour weighted-mean serial FEV1 at the end of the 12 weeks of treatment. The effect on exacerbations was not assessed.

For trial 3109, 519 patients with COPD were equally randomized into the two treatment groups and followed for the 12 weeks. The LS mean change from baseline in weighted mean 24-hour FEV1 is 174 ml for the FF/VI 100/25 once-daily group and 94 ml for the Advair 250/50 twice-daily group providing for a treatment difference of 80 ml in favor of FF/VI 100/25 which was statistically significant (p<0.001) per the sponsor's analysis.

A total of 511 subjects were evaluated in trial 2352, which compared FF/VI 100/25 to Advair 250/50 after 12 weeks of treatment. The same primary endpoint of change from baseline in trough FEV1 in 24-hour weighted mean FEV1 was specified. Similar to trial 3109, the FF/VI 100/25 change from baseline of 143 ml is numerically superior to Advair 250/50's 113 ml change from baseline, but per the sponsor's analysis this difference was not statistically significant (p = 0.267).

A total of 528 patients with COPD were evaluated in trial 3107 which compared F/VI 100/25 to Advair 500/50. The LS mean change from baseline FEV1 for FF/VI 100/25 is 130 ml and 107 ml for Advair 500/50. This provides for a difference of 22 ml in favor of FF/VI treatment; but this result is not statistically significant (p value =0.282).

Table 32: Efficacy data from COPD Advair Comparator Trials

	FF/VI 100/25	Advair 250/50	Advair 500/50
Trial 3107			
Change from baseline in 24 hour weighted mean FEV1, L	0.130		0.107
Day 84 LS mean Δ from FF/VI P value[1]			0.022 0.282
Trial 2352			
Change from baseline in 24 hour weighted mean FEV1, L	0.143	0.113	
Day 84 LS mean Δ from FF/VI P value[1]		0.029 0.267	
Trial 3109			
Change from baseline in 24 hour weighted mean FEV1, L	0.170	0.96	
Day 84 LS mean Δ from FF/VI P value[1]		0.8 P<0.001	

Source: CSRs 3107 2352 and 3109 Tables 12, 13

[1]Per sponsor's statistical analysis

The LS change from baseline over the 24 hour time period at the end of the study for trials 3109 and 2352 are seen in Figure 8 and Figure 9 below. In general, a consistent numeric increase for FF/VI treatment compared to Advair 250/50 is seen over the 24-hour time period providing support for the overall efficacy of the combination product. However, it is important to keep in mind that these data do not provide an assessment of whether the efficacy of the combination product is driven by both of the components or by VI.

Figure 8: LS Mean Change from baseline in FEV1 on Day 84: 3109

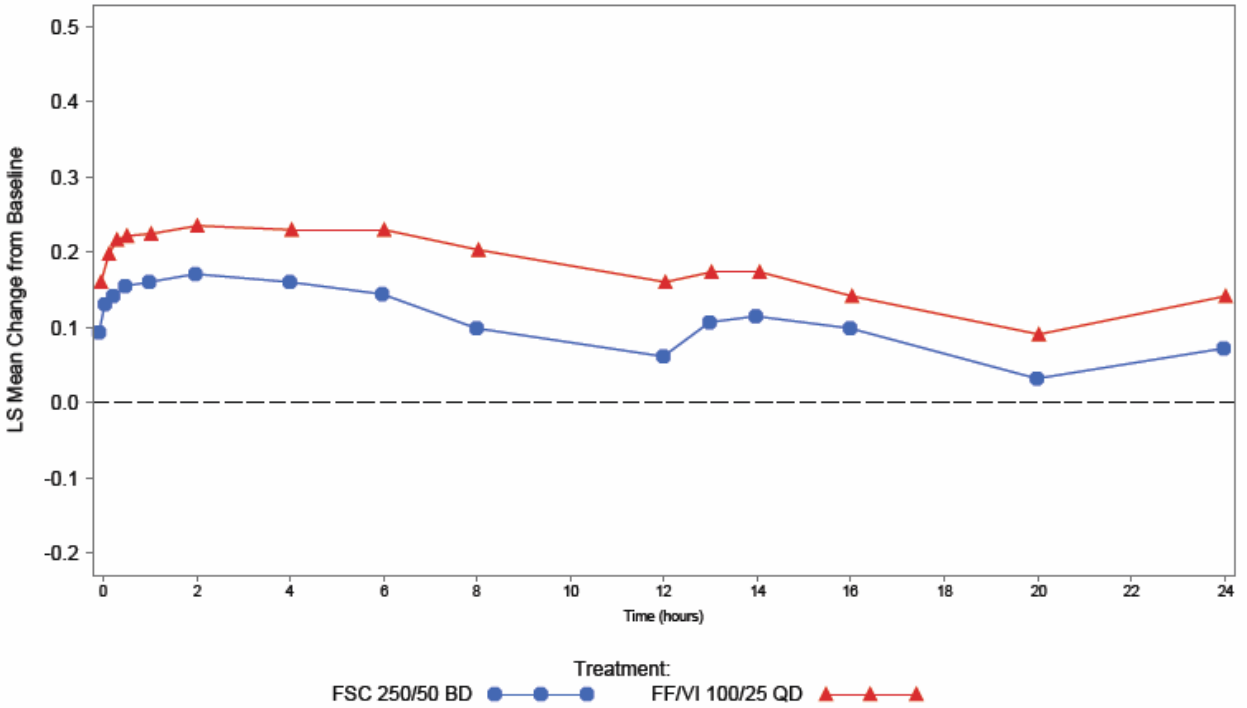
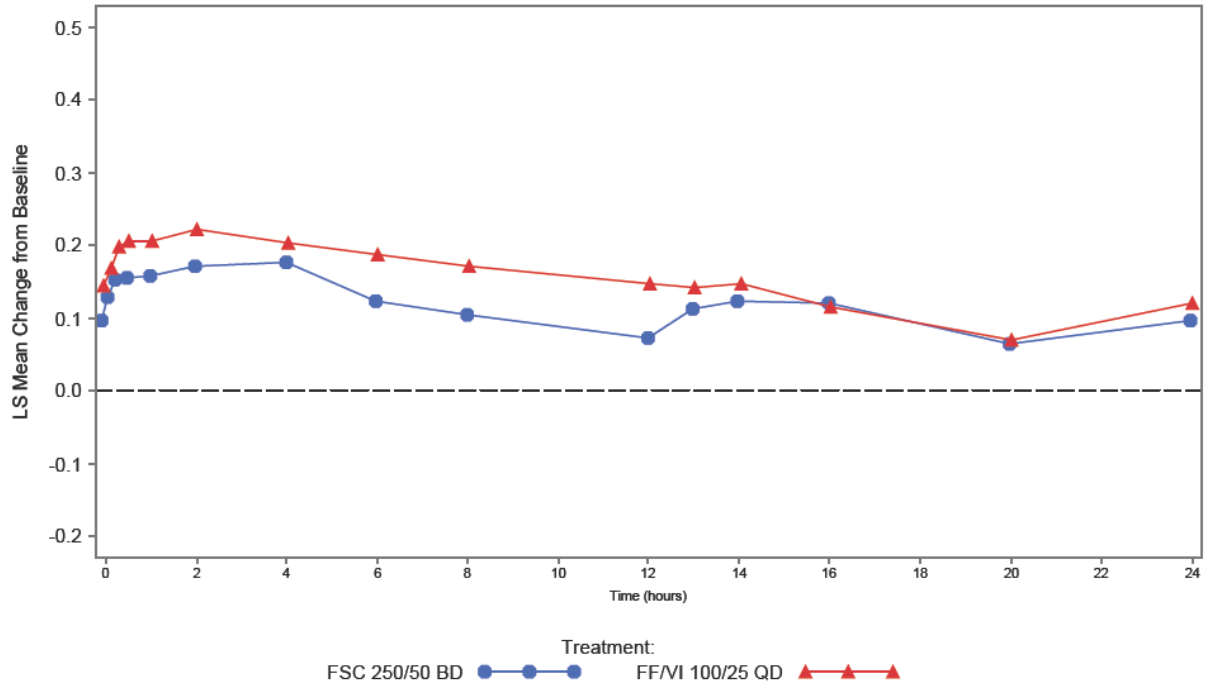
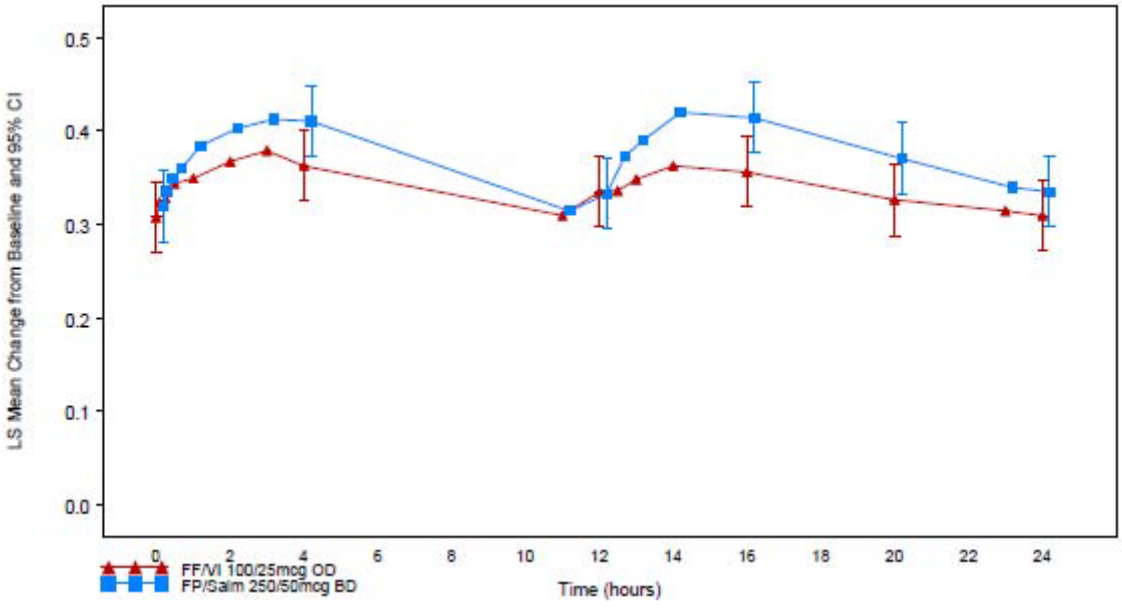


Figure 9: LS Mean Change from baseline in FEV1 on Day 84: 2352



In trial 3091, the single comparator trial conducted in asthma, FF/VI 100/25 was compared to Advair 250/50 in 806 adult and adolescent patients with asthma. In contrast to the COPD trials, Advair 250/50 was numerically superior to FF/VI 100/25 at most timepoints in the asthma comparator trial. The applicability of this finding to COPD is unclear.

Figure 10: Day 168 LS Mean Change from Baseline in FEV1 over Time: 3091



Source: CSR 3091 Figure 3

6.2 Reduction in COPD exacerbations

6.2.1 Methods

For the reduction in exacerbation indication, the sponsor has submitted data from two replicate, 52-week exacerbation trials (2871 and 2970). The efficacy data from these trials are reviewed below.

6.2.2 Demographics

Overall, the gender, age, and race distribution across the treatment groups are comparable in both trials. Similar to trials 2206 and 2207, an underrepresentation of patients of African heritage compared to the US population is evident. However, the demographics are similar to other ICS/LABA combination development programs for approved products.

The 52-week exacerbation trials enrolled a greater of number of patients with more severe disease (GOLD Stage 3: 46% and Stage 4: 15%) disease compared to the 24 week lung function trials (Stage 3: 44%; Stage 4: 9%). The majority of patients in the lung function trials had reversible disease, while those in the exacerbation trials did not. In addition, patients in the 52-week exacerbation trials were required by protocol to have had a recent COPD exacerbation.

Table 33: Demographic and Baseline Characteristics: 2871

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N = 1622
Age					
Mean Min - Max	63.6 40-87	63.6 40-88	63.6 41-88	63.8 41-90	63.6 40-90
Sex					
Female Male	170 (42) 239 (58)	163 (40) 245 (60)	172 (43) 231 (57)	153 (38) 249 (62)	658 (41) 964 (59)
Race					
White African Heritage Asian Other	331 (81) 9 (2) 39 (10) 29 (7)	334 (82) 8 (2) 37 (9) 29 (7)	332 (82) 6 (1) 37 (9) 28 (7)	324 (81) 9 (2) 41 (10) 27 (7)	1321 (82) 32 (2) 154 (10) 113 (7)
Duration of COPD					

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N = 1622
<1 year	20 (5)	27 (7)	23 (6)	18 (4)	88 (5)
≥1 to <5 years	136 (33)	167 (41)	134 (33)	156 (39)	593 (37)
≥5 to <10 years	134 (33)	120 (29)	123 (31)	132 (33)	509 (31)
≥10 to <15 years	68 (17)	50 (12)	62 (15)	54 (13)	234 (14)
≥15 to <20 years	24 (6)	20 (5)	36 (9)	24 (6)	104 (6)
≥20 to <25 years	20 (5)	13 (3)	14 (3)	12 (3)	59 (4)
≥25 years	7 (2)	11 (3)	11 (3)	6 (1)	35 (2)
Smoking Status at screening					
Current Smoker	174 (43)	171 (42)	174 (43)	166 (41)	685 (42)
Former Smoker	235 (57)	237 (58)	229 (57)	236 (59)	937 (58)
Baseline Lung Function					
Mean pre-bronchodilator FEV1 percent predicted	44.3	45.6	45.7	45.1	45.2
Reversibility[1]					
Reversible	125 (31)	116 (29)	121 (30)	106 (27)	468 (29)
Non-Reversible	282 (69)	287 (71)	279 (70)	290 (73)	1138 (71)
Concomitant Medications					
Short acting anticholinergics	102 (25)	117 (29)	101 (25)	112 (28)	432 (27)
Other respiratory medications	18 (4)	33 (8)	19 (5)	21 (5)	91 (6)

Source: CSR 2871 Tables 5.21, 5.26, 5.34, 6, 7, 9,
[1]Reversibility defined as: post-SABA increase in FEV1 ≥ 12% and ≥ 200 ml

Table 34: Demographic and Baseline Characteristics: 2970

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N = 1622
Age					
Mean	63.6	63.7	64	63.5	63.7
Min - Max	40-85	40-85	40-88	40-86	40-88
Sex					
Female	174 (43)	181 (44)	181 (45)	191 (47)	727 (45)
Male	235 (57)	231 (56)	222 (55)	218 (53)	906 (55)
Race					
White	360 (88)	359 (87)	353 (88)	359 (88)	1431 (88)
African Heritage	9 (2)	14 (3)	7 (2)	9 (2)	39 (2)
Asian	4 (<1)	3 (<1)	5 (1)	3 (<1)	15 (<1)
Other	36 (9)	36 (9)	38 (9)	38 (9)	148 (9)

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N = 1622
Duration of COPD					
<1 year	21 (5)	29 (7)	27 (7)	31 (8)	108 (7)
≥1 to <5 years	138 (34)	137 (33)	143 (35)	126 (31)	544 (33)
≥5 to <10 years	127 (31)	126 (31)	127 (32)	139 (34)	519 (32)
≥10 to <15 years	76 (19)	62 (15)	59 (15)	68 (17)	265 (16)
≥15 to <20 years	23 (6)	30 (7)	24 (6)	25 (6)	102 (6)
≥20 to <25 years	12 (3)	13 (3)	13 (3)	9 (2)	47 (3)
≥25 years	12 (3)	15 (4)	10 (2)	11 (3)	48 (3)
Smoking Status at screening					
Current Smoker	190 (46)	193 (47)	185 (46)	186 (45)	754 (46)
Former Smoker	219 (54)	219 (53)	218 (54)	223 (55)	879 (54)
Baseline Lung Function					
Mean pre-bronchodilator FEV1 percent predicated	46.1	45.2	46.4	45.3	45.7
Reversibility[1]					
Reversible	126 (31)	130 (32)	127 (32)	122 (30)	505 (31)
Non-Reversible	276 (69)	276 (68)	271 (68)	282 (70)	1105 (69)
Concomitant Medications					
Short acting anticholinergics	107(26)	125 (30)	112 (28)	107 (26)	451 (28)
Other respiratory medications	25 (6)	26 (6)	33 (8)	22 (5)	106 (6)

Source: CSR 2970 Tables 5.21, 5.26, 5.34, 6, 7, 9,
[1]Reversibility defined as: post-SABA increase in FEV1 ≥ 12% and ≥ 200 ml

6.2.3 Patient Disposition

A total of 1622 patients were randomized in trial 2871and 1633 in trial 2970. Overall, withdrawal rates are consistent with those expected for 52 week long trials. The most common reason for patient withdrawal was an adverse event. No consistent pattern is demonstrated across treatment arms. Protocol deviations occurred in 15-20% of patients, with use of a prohibited medication being the most common reason for the deviations in both trials (ranging from 11 to 13% in trial 2871 and 14 to 15% in trial 2970).

Table 35: Patient Disposition: 2871

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N = 1622
Completed	294 (72)	315 (77)	312 (77)	301 (75)	1222 (75)
Withdrawn	115 (28)	93 (23)	91 (23)	101 (25)	400 (25)
Primary reason for withdrawal					

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N = 1622
Adverse event	22 (5)	25 (6)	29 (7)	31 (8)	107 (7)
Lack of Efficacy	24 (6)	16 (4)	11 (3)	18 (4)	69 (4)
Exacerbation	15 (4)	10 (2)	4 (<1)	13 (3)	42 (3)
Lost to Follow-up	11 (3)	7 (2)	6 (1)	5 (1)	29 (2)
Protocol deviation					
Any Protocol deviation	64 (16)	68 (17)	72 (18)	65 (16)	269 (17)
Use of a prohibited medication	43 (11)	49 (12)	51 (13)	44 (11)	187 (12)
Source: CSR 2970 Table 4, 5.12					

Table 36: Patient Disposition: 2970

	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409	Total N = 1633
Completed	284 (69)	303 (74)	291 (72)	306 (75)	1184 (73)
Withdrawn	125 (31)	109 (26)	112 (28)	103 (25)	449 (27)
Primary reason for withdrawal					
Adverse event	25 (6)	32 (8)	35 (9)	30 (7)	122 (7)
Lack of Efficacy	35 (9)	14 (3)	16 (4)	14 (3)	79 (5)
Exacerbation	20 (5)	8 (2)	9 (2)	7 (2)	44 (3)
Lost to Follow-up	6 (1)	8 (2)	6 (1)	10 (2)	30 (2)
Protocol Deviation					
Any Protocol deviation	87 (21)	80 (19)	82 (20)	78 (19)	327 (20)
Use of a prohibited medication	62 (15)	57 (14)	55 (14)	57 (14)	231 (14)
Source: CSR 2970 Table 4, 5.12					

6.2.4 Analysis of Primary Endpoint(s)

Both exacerbation trials evaluated the annual rate of moderate and severe exacerbations as the primary endpoint with the primary comparison of interest between each dose of FF/VI and VI.

Numeric improvement, ranging from a 13% to 34% reduction in exacerbations over VI monotherapy, is seen in both trials for all tested dosage strengths of FF/VI. While this occurs in a dose responsive fashion for trial 2970, in trial 2871, the numeric improvement for the 200/25 mcg dose group (15%) is lower than that seen for the FF/VI 100/25 mcg group (34%).

While a numeric treatment benefit of FF/VI to VI is seen for all doses in both trials, the trials fail to provide replicate, statistically significant, improvement for the combination products compared to VI alone. Trial 2970 demonstrates statistically significant

improvement for all three strengths of FF/VI over VI alone, but trial 2871 fails to demonstrate an improvement of the highest tested dose (FF/VI 200/25) over VI alone. Due to the hierarchical statistical testing procedure, this means that further comparisons between the lower doses and VI are descriptive only.

Table 37: Annual Rate of Moderate and Severe Exacerbations: 2871 and 2970

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Trial 2871				
N	409	408	403	402
LS mean annual rate	1.05	0.92	0.70	0.90
Compared to VI 25				
Ratio		0.87	0.66	0.85
P value		0.181[1]	<0.001[1]	0.109
Percent Reduction		13	34	15
95% Confidence Intervals		(-6, 28) [1]	(19, 46)[1]	(-4, 30)
Trial 2970				
N	409	412	403	409
LS mean annual rate	1.14	0.92	0.9	0.79
Compared to VI 25				
Ratio		0.81	0.79	0.69
P value		0.04	0.024	<0.001
Percent Reduction		19	21	31
95% Confidence Intervals		(1, 34)	(3, 36)	(15, 44)

Source: CSR 2871 Table 13
[1] nominal p values only due to statistical hierarchal testing procedures

6.2.5 Analysis of Secondary Endpoints(s)

In addition to the trough FEV1 data previously discussed under Section 6.1.4 (See Table 19), the exacerbation protocols specified the following secondary endpoints. Of note, similar to the primary endpoint, the results of any statistical analysis for 2871 are descriptive only, due to failure of the statistical hierarchal testing procedures.

- Time to first moderate or severe exacerbation
- The annual rate of exacerbations requiring systemic/oral corticosteroids

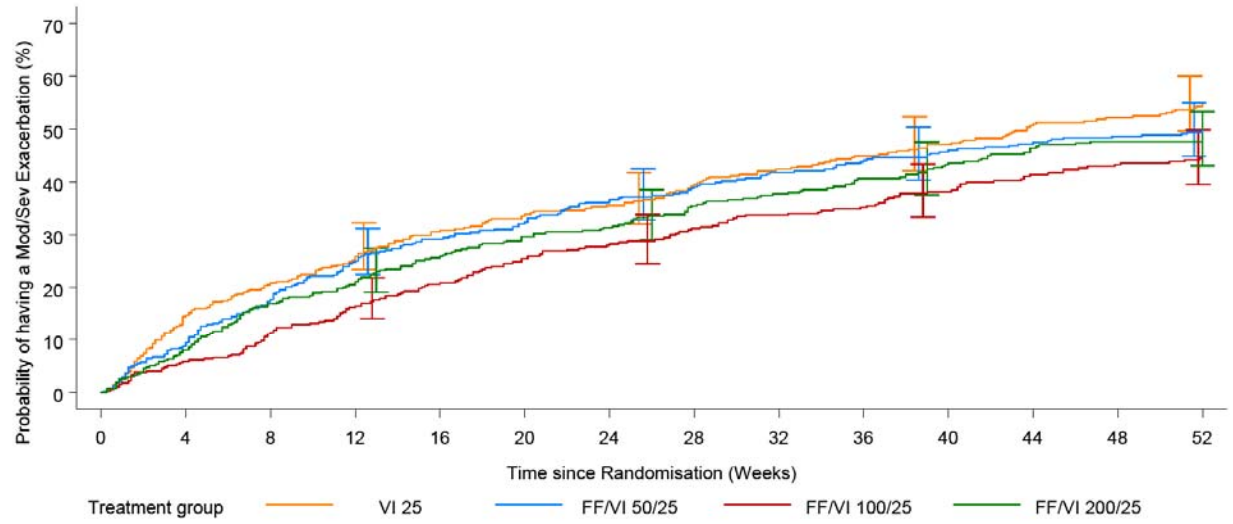
The data from these endpoints are supportive of the results from the primary efficacy endpoints. Numeric improvements compared to VI are seen for all dosage groups in both trials. This occurs in a dose-dependent manner for trial 2970, but not for 2871.

Time to First Moderate or Severe Exacerbation

Numeric improvements are consistently seen for the FF/VI treatment arms compared to VI monotherapy in the time to first moderate or severe exacerbation. Similar to the primary endpoint, a dose-dependent reduction is seen for 2970, but not for 2871.

These data are presented in the Kaplan-Meier Plots below.

Figure 11: Kaplan-Meier Plot: Time to First Moderate or Severe Exacerbation: 2871

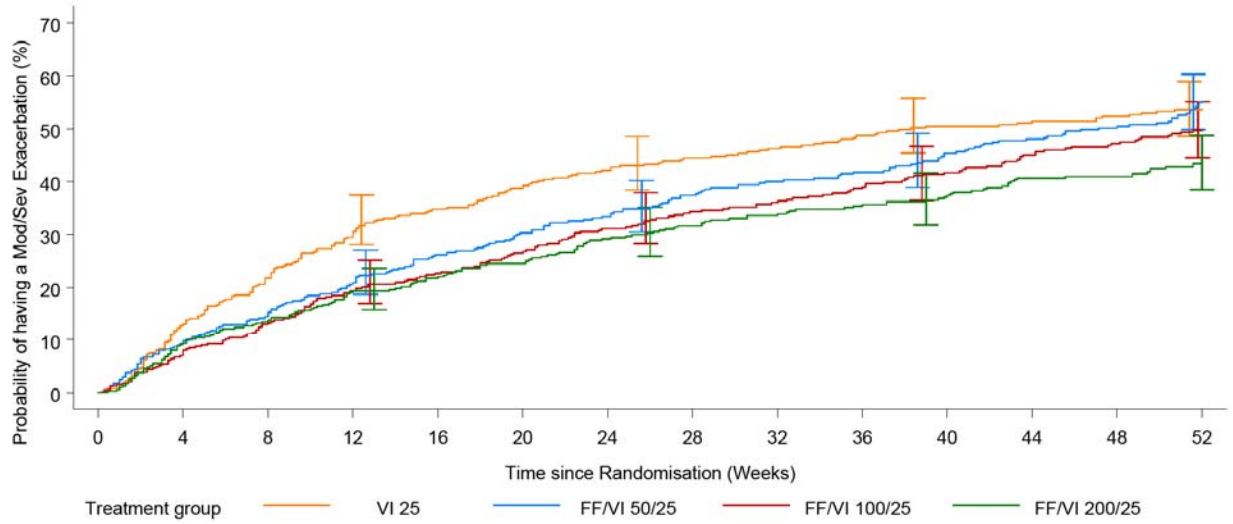


Number of Subjects at Risk:

Week	0	13	26	39	52
VI 25	409	268	224	176	0
FF/VI 50/25	408	281	232	195	0
FF/VI 100/25	403	299	249	209	0
FF/VI 200/25	402	287	241	196	0

Source: CSR 2871 Figure 6.03

Figure 12: Kaplan-Meier Plot: Time to First Moderate or Severe Exacerbation: 2970



Number of Subjects at Risk:

Week	0	13	26	39	52
VI 25	409	241	196	162	0
FF/VI 50/25	412	282	226	188	0
FF/VI 100/25	403	286	234	194	0
FF/VI 200/25	409	300	251	215	0

Source: CSR 2970 Figure 6.03

Annual Rate of Exacerbations requiring Systemic/Oral Corticosteroids
A similar pattern is seen for the results for the annual rate of exacerbation requiring systemic/oral corticosteroids. Numeric decreases for all treatment groups compared to VI are seen for all dosage groups compared to VI in both trials. This occurs in a dose-dependent fashion in trial 2970 but not in trial 2871.

Table 38 below summarizes these data.

Table 38: Annual Rate of Exacerbations Requiring Systemic/oral Corticsteroids: 2871 and 2970

	Trial 2871				Trial 2970			
	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
LS mean annual rate	0.84	0.71	0.52	0.68	0.86	0.72	0.66	0.56
Compared to VI								
Ratio P value		0.84 0.125	0.62 <0.001	0.81 0.064		0.84 0.154	0.77 0.041	0.65 <0.001
Percent reduction Confidence Interval		16 (-5,33)	38 (22.51)	19 (-1,36)		16 (-7,35)	23 (1,40)	35 (16,49)
Source: CSR 2871 and 2970: Table 17								

6.2.6 Other Endpoints

Each exacerbation trial evaluated the following additional endpoints:

- Annual rate of severe exacerbations
- Annual rate of all mild, moderate, severe exacerbations
- Time to onset of multiple moderate and severe exacerbations
- Change in Diary Symptoms

In addition to an analysis of the exacerbation rate, GSK provided an analysis of the imputed rates of exacerbation for these endpoints. This review focuses on the raw data as opposed to the imputed rates. Similar to the lung function data, the statistical results are not included below as these comparisons were not allowed per the statistical testing procedures.

In general, a similar pattern of results is seen from an analysis of these data as the primary endpoint.

Annual Rate of Severe Exacerbations
In trial 2871 all FF/VI groups demonstrate a numeric improvement over VI monotherapy with a 28%, 28%, and 21% reduction in annual rate of severe exacerbations for FF/VI 50/25, FF/VI 100/25, and FF/VI 200/25 respectively.

For trial 2970, GSK notes that “due to the sparseness of data…this analysis was not

possible"[5]. Instead a post-hoc analysis of time to first severe exacerbation was performed which demonstrates a 28% risk increase in the time to first severe exacerbation for the 100/25 FF/VI dose group and a 7% and 18% percent risk reduction for the 50/25 and 200/25 respectively.

Annual rate of all (mild, moderate and severe) exacerbations

In trial 2871, FF/VI 100/25 compared to VI demonstrates a 32% improvement, FF/VI 50/25 a 14% improvement compared to VI, and the 200/25 FF/VI dose group only a 1% reduction. All FF/VI dose groups in trial 2970 demonstrate a numeric improvement compared to VI monotherapy with a reduction in the annual rate of 15%, 19% and 31% for FF/VI 50/25, FF/VI 100/25, and FF/VI 200/25 respectively.

In addition to the annual rate of all exacerbations, the sponsor provided a breakdown of rates by severity as well as the mean duration of the exacerbation. In general, a review of these data is consistent with the primary endpoint (data not shown).

Table 39: Annual Rate of All Exacerbations: 2871 and 2970

	Trial 2871				Trial 2970			
	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
All exacerbations								
LS mean annual rate	1.37	1.17	0.92	1.35	1.55	1.31	1.25	1.06
Compared to VI								
Ratio		0.86	0.68	0.99		0.85	0.81	0.69
% Reduction		14	32	1		15	19	31
Source: CSRs 2871, 2970: Table 19								

Time to Onset of Multiple Moderate and Severe Exacerbations

A similar pattern in the time to each moderate and severe exacerbation is seen as the time to first moderate and severe exacerbation in each trial. These data are summarized in Table 40.

Table 40: Time to Each Moderate and Severe On-treatment Exacerbation: 2871 and 2970

	Trial 2871			Trial 2970		
	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
Compared to VI						
Hazard Ratio	0.87	0.68	0.86	0.82	0.8	0.72
Source: CSR 2871 and 2970 Table 20						

[5] CSR 2970 Section 6.5.1 "Annual Rate of Severe Exacerbation" page 74.

Change in Diary Symptoms

Patients completed daily dairies with information on night time awakenings due to COPD, use of rescue medication, symptoms of dyspnea, and sputum volume and purulence. In general, besides alterations in sputum, the changes in diary symptoms are suggestive of efficacy of FF/VI compared to VI. These data are summarized in the Table 41.

Number of night time awakenings

Both trials demonstrate a numeric decrease in the mean number of night time awakenings for the FF/VI groups compared to VI. The percentage of nights with no nighttime awakenings is higher for all FF/VI groups compared to VI in trial 2970; however similar results are not seen for all FF/VI treatment arms in trial 2871.

Rescue Medication Use

All FF/VI dose groups compared to VI in both trials demonstrate a decrease in the mean occasions of rescue medication uses in a 24 hour period. In addition, all FF/VI dose groups demonstrate an increase in the percentage of rescue-free 24 hour periods compared to VI.

Dyspnea

All FF/VI dose groups demonstrate a numeric decrease in dyspnea symptom scores compared to VI.

Sputum

The FF/VI treatment groups show a consistent decrease in the percentage of 24-hour periods with increased sputum in trial 2970; however this is not seen for trial 2871. Similar findings are seen for the percentage of 24-hour periods with discolored sputum.

Table 41: Diary Score: 2871 and 2970

	Trial 2871				Trial 2970			
	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
Night time awakenings/24 hours								
Compared to VI LS mean difference		-0.01	-0.07	-0.03		-0.1	-0.08	-0.12
% of nights with no awakenings	75.5	74.3	80.3	75.2	70.4	75.3	73.3	75.8
Use Rescue Medication/24 hours								
Compared to VI LS mean difference		-0.1	-0.17	-0.17		-0.3	-0.26	-0.33
% rescue free 24 hrs	37.8	38.7	39.2	39.4	34.2	34.4	39.3	38.5
Dyspnea								

	Trial 2871				Trial 2970			
	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
Compared to VI LS mean difference		-0.11	-0.08	-0.11		-0.05	-0.11	-0.12
Sputum								
% 24 hr periods with increased sputum	7.68	7.58	7.71	8.06	9.69	7.92	8.59	7.2
% 24 hr periods with increased yellow/green sputum	3.58	3.97	4.2	3.95	4.45	3.43	4.08	4.05
Source: CSRs 2871, 2970 Tables 22, 23, 24, 25, 26, 27, 28								

6.2.7 Subpopulations

The sponsor provided summary statistics for the following subgroup analyses for the primary analyses as well as for trough FEV1 on the pooled data from trial 2871 and 2970:

- age
- race
- gender
- smoking status
- geographical region
- reversibility
- percent predicted FEV1
- cardiovascular history and risk

In general where numeric differences are noted, consistency across the dose groups is not seen. Overall, a distinct conclusion for these subpopulation analyses that differs from the primary analysis can not be made.

6.2.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

No specific analysis for the persistence of efficacy or tolerance for the exacerbation data is presented in this NDA. However the Kaplan-Meier curves (see Figure 11) are not suggestive of a sudden loss of efficacy. A discussion of the persistence of efficacy for the airflow obstruction data is found in Section 6.1.9.

7 Review of Safety

Safety Summary

Over 7000 patients have received FF/VI in GSKs COPD development program. Of these, 1249 patients received at least one dose of the proposed FF/VI 100/25, and 1087 patients have received higher doses of FF/VI. Overall, the size of the safety database for FF/VI exceeds the size of the initial safety databases used for approval of other ICS/LABA COPD development programs.

The database is primarily comprised of data from two 24-week lung function trials and two 52-week exacerbation trials and is supplemented by data from other shorter trials in COPD. No unexpected safety signals are evident from a review of the database as the adverse event profiles are similar to those seen in other ICS/LABA COPD development programs. Three doses of FF were included in the pivotal phase 3 trials, including a lower dose (50 mcg) and higher dose (200 mcg) than the proposed 100 mcg FF dose. This allows for an exploration of dose dependency for ICS safety which is discussed throughout this review.

An increase in pneumonia is seen in the FF-containing treatment arms in the pooled 52-week exacerbation trials. Furthermore, an increase in pneumonia-related fatalities is also seen. However, all but one of the FF/VI fatalities occurred in the high dose FF/VI 200/25 mcg treatment arm; a dose that is not proposed for marketing. Of note, pneumonia is a known class effect of ICS use in COPD and current ICS/LABA product labeling contains warning language regarding this risk. However, this risk will need to be discussed in the context of the efficacy data for FF.

In addition, a fracture imbalance is seen in the FF-containing treatment groups in the pooled 52-week exacerbation trial data. This imbalance appears to be driven primarily by data from trial 2871, as a similar imbalance is not seen in trial 2970. Of note, the potential for bone loss with ICS use is already known, and class labeling warning for this potential effect is included in ICS/LABA prescribing information.

As the safety of earlier ICS/LABA products approved for COPD were supported by prior safety experience in asthma, a brief review of the available data from the ongoing asthma development program is provided. Specifically, data for the composite endpoint of asthma-related deaths, hospitalizations and intubations is presented in Section 7.4.5. No LABA-related safety signal is evident from this database. In addition, safety data from a one-month, VI-dose-ranging trial, which contained a higher VI dose (50 mcg) than the proposed 25 mcg, provides additional safety data.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Table 6 summarizes the main trials comprising the COPD safety database. As discussed above, the database is primarily comprised of data from the two 24-week lung function trials, and the two 52 week exacerbation trials.

The 120-day safety update, covering the reporting period of February 16, 2012 to August 31, 2012, was provided on November 9, 2012, and contains updates from the COPD and asthma development programs. This update contained data from three completed clinical trials, unblinded data from three concluded trials whose study reports were incomplete at the time of database lock, and blinded data from 13 ongoing studies. Of note, one of the concluded studies, FFA115283, is a retrospective pharmacogenetic study comprised of data from three completed asthma studies the data of which are included in the asthma ISS provided in the NDA application. The deaths and nonfatal SAEs and other data from the 120-day safety update are presented in the relevant subsections below; additional details from the safety update are provided in Section 7.7.

7.1.2 Categorization of Adverse Events

GSK's Integrated Summary of Safety (ISS) focuses on treatment-emergent adverse events (TEAEs). These are defined as events with an onset date the same or after the treatment start date but prior to or the same as the treatment stop date plus one day. A Serious Adverse Event (SAE) is defined according to the regulatory definition[6].
All adverse events in the ISS were coded or re-coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1.

For specific safety concerns associated with use of ICSs and LABAs, 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 Group: Subgroup, are presented below.

- Local steroid effects
- Pneumonia and Lower Respiratory Tract Infections: Excluding Pneumonia
- Pneumonia
- Cardiovascular Effects: Cardiac Arrhythmia
- Cardiovascular Effects: Hypertension
- Cardiovascular Effects: Cardiac Ischemia
- Cardiovascular Effects: Cardiac Failure
- Cardiovascular Effects: Acquired Long QT
- Effects on Glucose: Sudden Death
- Bone Disorders
- Ocular Effects

[6] 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.

- Effects on Potassium
- Tremor
- Systemic Steroid Effects
- Hypersensitivity

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

Three separate pooled safety datasets are included in GSK's application and are reviewed in this safety analysis. Depending on the safety issue of interest, the analysis of the most relevant or representative dataset is presented. The datasets are identified in this review as:

- the 24-week lung function trial data (2206 and 2207)
- the 52 week exacerbation trial data (2871 and 2970)
- Fully Integrated Dataset (2206, 2207, 2871, 2970, 1045, 1348, and 946)

Each dataset offers a different perspective on safety. The 24-week lung function trials include a placebo control and factorial treatment arms, but are of a shorter duration and contain a milder patient population than the 52-week exacerbation trials. In addition, patients were withdrawn if they developed of a COPD exacerbation, which did not occur in the 52-week exacerbation trials. The 52-week exacerbation trials do not contain placebo or FF monotherapy arms but have a longer duration of exposure and include a sicker population. GSK's Fully Integrated Dataset provides a larger pooled sample of patients. However, in general this dataset is not used in this review due the limitations of the data caused by differences in trial designs and the underlying patient severity. Instead, the individual pooled datasets are primarily used in this review. Given the replicate nature of the trial designs and reasonable number of patients enrolled, this allows for more straightforward comparisons without the need for caveats for interpretation of the data.

In addition to the COPD datasets, GSK provided an integrated summary of safety for its asthma development program. In particular, data for the asthma composite endpoint of asthma-related hospitalizations, deaths and intubations are presented in this review. For this endpoint, GSK had all serious adverse events (SAEs) from any asthma trial containing a VI or VI + ICS arm reviewed and categorized by an independent adjudication committee.

7.2 Adequacy of Safety Assessments

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

The size of the safety database for FF/VI exceeds the size of the initial safety databases used for approval of other ICS/LABA COPD development programs. However, unlike these other programs, the monocomponents are not already approved in orally inhaled formulations and FF/VI is not approved for use in asthma.

The two 24-week lung function trials enrolled a total of 2,254 patients with a mean exposure ranging from 138.7 days to 146.4 days for the FF/VI treatment arms. The 52-week exacerbation trials enrolled 3,255 patients with a mean exposure to FF/VI ranging from 306.2 days to 308.3 days. The tables below summarize the extent of exposure in the four pivotal phase 3 trials.

Overall the 52-week exacerbation trials enrolled a more severe patient population than the 24-week lung function trials. In the 52-week exacerbation trials, the majority of patients had GOLD Stage 3 (46%) and 4 (15%) disease compared to the 24 week lung function trials which enrolled a milder patient population (GOLD 2 46%; GOLD 3 44%; GOLD 4 9%). The majority of patients in the lung function trials had reversible disease, while those in the exacerbation trials did not. In addition, patients in the 52-week exacerbation trials were required by protocol to have had a recent COPD exacerbation.

Table 42: Extent of Exposure in 24-week Lung Function Trials: 2206 and 2207

	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
Exposure (Days)							
Mean	136.2	138.7	140.2	146.4	144.3	139.9	143.4
Range of Exposure, n (%)							
1 day-4 weeks	48 (12)	24 (12)	39 (10)	14 (7)	32 (8)	36 (9)	19 (9)
>4-8 weeks	14 (3)	2 (<1)	14 (3)	2 (<1)	15 (4)	15 (4)	7 (3)
>8-12 weeks	13 (3)	8 (4)	12 (3)	10 (5)	10 (2)	18 (4)	7 (3)
>12-16 weeks	28 (7)	14 (7)	27 (7)	10 (5)	18 (4)	25 (6)	6 (3)
>16-20 weeks	13 (3)	5 (2)	11 (3)	8 (4)	10 (2)	10 (2)	0
>20-24 weeks	153 (37)	74 (36)	172 (42)	81 (40)	175 (43)	174 (42)	78 (38)
>24-28 weeks	142 (34)	79 (38)	134 (33)	80 (39)	147 (36)	132 (32)	86 (42)
>28-36 weeks	1 (<1)	0	1 (<1)	0	1 (<1)	0	0
Source: ISS Table 3							

Table 43: Extent of Exposure in 52-week exacerbation Trials: 2871 and 2970

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF 200/25 N=811	VI 25 N=818
Exposure (Days)				
Mean	306.2	306.6	308.3	295.2
Range of Exposure, n (%)				
1 day – 4 weeks	46 (6)	43 (5)	42 (5)	45 (6)
>4 – 8 weeks	28 (3)	21 (3)	23 (3)	31 (4)
>8 – 12 weeks	20 (2)	24 (3)	19 (2)	38 (5)
>12 – 16 weeks	16 (2)	18 (2)	9 (1)	22 (3)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF 200/25 N=811	VI 25 N=818
>16 – 20 weeks	14 (2)	10 (1)	14 (2)	13 (2)
>20 – 24 weeks	11 (1)	16 (2)	15 (2)	13 (2)
>24 – 28 weeks	11 (1)	8 (<1)	10 (1)	13 (2)
>28 – 32 weeks	13 (2)	15 (2)	13 (2)	13 (2)
>31 – 36 weeks	5 (<1)	6 (<1)	19 (2)	8 (<1)
>36 – 40 weeks	10 (1)	12 (1)	15 (2)	14 (2)
>40 – 44 weeks	7 (<1)	8 (<1)	7 (<1)	8 (<1)
>44 – 48 weeks	6 (<1)	8 (<1)	8 (<1)	10 (1)
>48 – 52 weeks	404 (49)	395 (49)	382 (47)	381 (47)
>52 weeks	229 (28)	222 (28)	235 (29)	209 (26)
Source: ISS Table 4				

7.2.2 Explorations for Dose Response

The inclusion of three doses of FF (50, 100, 200 mcg) combined with a single VI dose (25 mcg) into the phase 3 trials allows for an exploration of dose dependency for ICS safety and is discussed throughout this review.

The one-month, VI dose-ranging trial in COPD (1045) allows for a review of shorter-term LABA related safety. The results of this trial, which included doses up to 50 mcg VI daily, are presented Table 55 and discussed in Section 7.3.4.

7.2.3 Routine Clinical Testing

Routine testing in this development program included serum chemistry, hematology, and 12-lead ECGs, in addition to 24-hour Holter data obtained in a subset of patients in the two 24-week lung function trials (2206 + 2207).

Serum chemistry evaluation 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. Additional laboratory analysis included hepatitis B surface antigen, Hepatitis C antibody, urine pregnancy tests, and fungal culture of oral mucosa if visual evidence of candidiasis is present

7.2.4 Metabolic, Clearance, and Interaction Workup

The drug development program for FF/VI includes three drug-drug interaction studies,

HZA105548, B2C112205 and DB113950, to evaluate the effects of co-administration of FF/VI with ketoconazole, VI with ketoconazole and VI with Verapamil respectively. The clinical impact of these studies is summarized in Section 7.5.5 and the results are discussed in further detail in the Clinical Pharmacology Summary Document.

7.2.5 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 and the results in Section 7.3.4 and under the laboratory and vital sign subheadings.

GSK provided an integrated summary of safety for its asthma program for this application. A review of the composite asthma endpoint for death, hospitalizations and intubations is presented in Section 7.4.5.

7.3 Major Safety Results

7.3.1 Deaths

Given a relatively older and chronically sick population, deaths are not unexpected in a COPD development program. As such, the rates of death across treatment arms in this program are not unexpected; however an imbalance in fatalities due to pneumonia is noted for the FF/VI treatment groups compared to VI-monotherapy arms in the 52-week exacerbation trials. Of note, these fatalities generally occurred in the high dose FF/VI treatment group (200/25) which is not being proposed for approval. Pneumonias are discussed in more detail in Section 7.3.4.

A total of 11 deaths were reported from the on- and post-treatment periods in the two 24-week lung function trials and 53 deaths for the two 52-week exacerbation trials. Eight deaths occurred during the on-treatment period in the lung function trials and 43 for the exacerbation trials. Table 44 summarizes the on-treatment and post-treatment deaths from GSK's two 24-week lung function trials and two 52-week exacerbation trials. The Preferred Terms for all of the deaths in the two 24-week lung function trials is

presented; all System Organ Class data and Preferred Terms occurring in > 1 patient is presented for the two 52-week exacerbation trials.

In addition to the deaths summarized in Table 44, a single death occurred in trial 1045; no other deaths occurred in GSK's supplemental one-month trials in COPD (1045, 1348 and 946). Three deaths occurred during the three FF/VI to Advair comparator trials. In trial 3107, a patient in the FF/VI 100/25 died of congestive heart failure during the post-treatment follow up; in 3109, a patient in the FP/salmeterol 500/50 group was found dead at home; and in 2352, a patient in the FF/VI 100/25 mcg group died due to myocardial infarction and cardiac failure.

One death was reported from trial 156 in the 120-day safety update. This trial was a 52-week COPD trial in Japanese patients evaluating FF/VI 200/25 and FF/VI 100/25. This death, due to multi-organ system failure in a patient with interstitial lung disease, occurred in the FF/VI 100/25mcg dose group. In addition, GSK reported 48 deaths from the ongoing trials in its 120-day safety update, 44 of which are from the ongoing 3-year mortality trial 113782 (SUMMIT trial). A review of the listed cause of death reveals the majority of these to be due to cardiovascular causes and one death due to pneumonia. Of note, GSK states that the patient population in this trial is enriched for patients with a history of cardiovascular disease. These data remain blinded so an assessment across treatment groups is not possible at this time.

Deaths in the asthma program are found in Section 7.4.5 of this review.

Table 44: On- and Post-Treatment Deaths in 24-week Lung Function Trials and 52-week Exacerbation Trials: 2206, 2207, 2871, and 2970

	Placebo	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
24-week Lung function Trials: 2206 and 2207							
N	412	206	410	205	408	410	203
Preferred Term, n (%)							
Any Event	2 (<1)	2 (<1)	2 (<1)	1 (<1)	3 (<1)	1 (<1)	0
Death	0	0	1 (<1)	0	0	0	0
Sudden cardiac death	0	0	0	0	1 (<1)	0	0
Sudden death	1 (<1)	0	0	0	0	0	0
Myocardial infarction	0	0	0	1 (<1)	0	0	0
Myocardial ischemia	1 (<1)	0	0	0	0	0	0
Accidental poisoning	0	0	0	0	1 (<1)	0	0
Alcohol poisoning	0	1 (<1) [1]	0	0	0	0	0
Cerebral hemorrhage	0	1 (<1)[1]	0	0	0	0	0
Thrombotic stroke	0	0	0	0	0	0	0
Gastrointestinal hemorrhage	0	1 (<1)	0	0	0	0	0
Anaphylactic reaction	0	0	0	0	1 (<1)[2]	0	0
Pulmonary embolism	0	0	0	0	0	1 (<1)	0
52-week Exacerbation Trials: 2871 and 2970							

	Placebo	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
N		820	806	811	818		
System Organ Class, n (%) Preferred Term[3], n (%)							
All Events		16 (2)	10 (1)	14 (2)	13 (2)		
Cardiac Disorders		5 (<1)	4 (<1)	3 (<1)	5 (<1)		
Myocardial infarction[4]		2 (<1)	1 (<1)	1 (<1)	1 (<1)		
Cardiac arrest		1 (<1)	2 (<1)	0	0		
Cardiopulmonary failure		1 (<1)	0	0	1 (<1)		
Respiratory, Thoracic, and Mediastinal Disorders		3 (<1)	3 (<1)	5 (<1)	3 (<1)		
COPD		3 (<1)	2 (<1)	4 (<1)	3 (<1)		
Acute respiratory failure		0	2 (<1)	0	0		
Infections and Infestations		1 (<1)	1 (<1)	6 (<1)	3 (<1)		
Pneumonia		0	1 (<1)	6 (<1)	1 (<1)		
Neoplasms, benign, malignant and unspecified		4 (<1)	1 (<1)	2 (<1)	1 (<1)		
Vascular Disorders		1 (<1)	1 (<1)	1 (<1)	1 (<1)		
Gastrointestinal Disorders		0	1 (<1)	0	1 (<1)		
General disorder & Admin. Site Conditions		1 (<1)	0	0	1 (<1)		
Nervous System d/o		2 (<1)	0	0	0		
Hepatobiliary d/o		0	1 (<1)	0	0		
Musculosk. & Connective Tissue disorder		1 (<1)	0	0	0		

Sources: ISS Tables 41, 42

[1] both events in same patient

[2] anaphylactic reaction to nuclear stress test injection

[3] Preferred Terms occurring in > 1 patient

[3] Similar Preferred Terms of Acute Coronary Syndrome, Acute Myocardial Infarction, Unstable angina, Coronary artery thrombosis occurred in 1 FF/VI 50/25 patient, 0 FF/VI 100/25 patients, 2 FF/VI 200/25 patients and 1 VI patient

7.3.2 Nonfatal Serious Adverse Events

The most common SAE reported in both the 24-week lung function trial data and the 52-week exacerbation trial data is COPD exacerbation followed by pneumonias.
These findings are not surprising given the underlying patient population and known risks associated with ICS/LABA use in COPD. Risks known to occur with both ICS and LABAs, including pneumonia, are discussed in more detail in Section 7.3.4 of this review. Of note, the data presented in Section 7.3.4 of the review uses a comprehensive list of Preferred Terms, while data is this section of the review does not.

Table 45 presents the SAE data as Preferred Terms occurring in > 1 patient across

treatment arms in the two 24-week lung function trials. Table 46 presents the Preferred Terms occurring in ≥ 3 patients in a treatment arm in the 52-week exacerbation trials. Both tables present the on-treatment SAE data; a review of the post-treatment SAE was unrevealing. In addition, the SAEs seen in the 120-day safety update are generally consistent with the SAEs presented below.

While the VI- monotherapy treatment arm has the largest overall rate of SAEs in the 24-week lung function trial trials, a consistent imbalance between VI-containing and non-VI containing treatments arm is not seen. In addition, no consistent imbalance in individual SAEs is demonstrated across treatment arms in this dataset.

As noted earlier, an imbalance in pneumonias between the FF-containing treatment arms and the VI-monotherapy arm is seen in the 52-week exacerbation trial data. These are discussed in more detail in Section 7.3.4. Interpretation of additional SAEs is limited by the rarity of occurrences.

Table 45: Serious Adverse Events in 24 week Lung Function Trials: 2206 and 2207

	PBO 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
System Organ Class, n (%) Preferred Term[1], n (%)							
Any Event	21 (5)	6(3)	23 (6)	15 (7)	31 (8)	22 (5)	10 (5)
Respir, thorac & mediast.	8 (2)	0	9 (2)	7 (3)	12 (3)	2 (<1)	2 (<1)
COPD	8 (2)	0	9 (2)	5 (2)	11 (3)	2 (<1)	2 (<1)
Pneumothorax	0	0	0	1 (<1)	1 (<1)	0	0
Infections and Infestations	2 (<1)	1 (<1)	3 (<1)	4 (2)	6 (1)	4 (<1)	3 (1)
Pneumonia	1 (<1)	1 (<1)	1 (<1)	3 (1)	5 (1)	2 (<1)	2 (<1)
Infective exacer. COPD	1 (<1)	0	0	0	1 (<1)	0	1 (<1)
Appendicitis	0	0	1 (<1)	1 (<1)	0	0	0
Sepsis	0	0	0	0	1 (<1)	1 (<1)	0
Cardiac Disorders	3 (<1)	1 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)	2 (<1)
Myocardial infarction	2 (<1)	0	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0
Supravent. extrasystole	0	1 (<1)	1 (<1)	0	0	0	0
Injury/poison/proc. complic[2]	3 (<1)	2 (<1)	3 (<1)	0	4 (<1)	1 (<1)	1 (<1)
Subdural hematoma	0	0	2 (<1)	0	0	0	0
Nervous System Disorders	0	2 (<1)	4 (<1)	1 (<1)	1 (<1)	4 (<1)	0
Carotid artery stenosis	0	0	0	0	0	2 (<1)	0
Ischemic stroke	0	0	2 (<1)	0	0	0	0
Syncope	0	0	0	0	0	0	2 (<1)
Neoplasms[3]	2 (<1)	0	1 (<1)	1 (<1)	3 (<1)	4 (<1)	0
Prostate cancer	1(<1)	0	1(<1)	0	0	1 (<1)	0
Gen. & admin. site cond.[4]	1 (<1)	0	0	1 (<1)	1 (<1)	1 (<1)	0
Chest discomfort	1 (<1)	0	0	0	0	1 (<1)	0

Source: ISS Table 45

[1] Preferred terms occurring > 1 patient across treatment arms presented

	PBO 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
[2] Injury poisoning and procedural complications [3] Neoplasms Benign, Malignant, and Unspecified [4] General Disorders and Administration Site Conditions							

Table 46: Serious Adverse Events in 52-week Exacerbation Trials: 2871 and 2970

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
System Organ Class, n (%) Preferred Term[1], n (%)				
Any event	136 (17)	123 (15)	124 (15)	126 (15)
Respir, thorac & mediast. d/o	59(7)	63(8)	59(7)	60(7)
COPD	53 (6)	55 (7)	53 (7)	53 (6)
Acute respiratory failure	3 (<1)	3 (<1)	2 (<1)	1 (<1)
Pneumothorax	2 (<1)	1 (<1)	3 (<1)	0
Respiratory failure	4 (<1)	0	2 (<1)	0
Pleural Effusion	1 (<1)	2(<1)	0	1 (<1)
Dyspnea	0	1 (<1)	1 (<1)	1 (<1)
Infections and Infestations	35 (4)	43 (5)	37 (5)	20 (2)
Pneumonia	22 (3)	21 (3)	21 (3)	8 (<1)
Infective exacerb. of COPD	2 (<1)	4 (<1)	3 (<1)	2 (<1)
Cellulitis	0	6 (<1)	1 (<1)	2 (<1)
Bronchitis	3 (<1)	1 (<1)	2 (<1)	2 (<1)
Lower respiratory tract infection	0	0	3 (<1)	1 (<1)
Cardiac Disorders	14 (2)	17 (2)	10 (1)	16 (2)
Myocardial infarction	3 (<1)	2 (<1)	3 (<1)	1 (<1)
Atrial fibrillation	2 (<1)	2 (<1)	0	2 (<1)
Acute myocardial infarction	2 (<1)	2 (<1)	0	1 (<1)
Angina pectoris	3 (<1)	0	0	2 (<1)
Nervous System Disorders	6 (<1)	6 (<1)	6 (<1)	8 (<1)
Cerebrovascular accident	1 (<1)	2 (<1)	3 (<1)	2 (<1)
Renal and Urinary Disorders	4 (<1)	1 (<1)	1 (<1)	3 (<1)
Renal Failure Acute	3(<1)	1(<1)	0	1 (<1)
Blood and Lymphatic Disorders	0	3 (<1)	1 (<1)	1 (<1)
Anemia	0	3(<1)	1(<1)	1 (<1)
Benign Prostatic Hyperplasia	0	0	0	3 (<1)
Source: ISS Table 47 [1]Preferred terms occurring in ≥ 3 patients in a treatment arm presented				

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 this COPD population or with use of ICS/LABA products.

In the 24-week lung function trials, the overall rate adverse events leading to study drug discontinuation is 9% in the placebo group compared to 9-11% in the active treatment groups. Discontinuation due to COPD exacerbation is most common reason (placebo: 2%; active treatment: <1%-2%). The decrease in discontinuations due to COPD in the active treatments groups is suggestive of efficacy compared to placebo.

Adverse events leading to drug discontinuation or withdrawal in the 52-week exacerbation trials are 6-8% in the FF/VI treatment groups compared to 6% in the VI-monotherapy treatment arm. Again the most common adverse event leading to discontinuation is COPD exacerbation [FF/VI: 12-15(1-2%); VI: 11(1%)]. This is followed by pneumonia, which occurs more frequently in the FF/VI groups in a FF dose-dependent manner [FF/VI 50/25: 3 (<1%); FF/VI 100/25: 5 (<1%); FF/VI 200/25: 8 (<1%); VI 3 (<1%)].

7.3.4 Submission Specific Primary Safety Concerns

As discussed in Section 7.1.2, GSK provided an Adverse Events of Special Interest analysis for FF/VI in COPD. These data are presented below and supplemented with individual preferred term data taken from the Adverse Event Page of the eCRF where relevant. Of note, discrepancies exist between data compiled from GSK's Adverse Events of Special Interest and the Preferred Term text taken from the Adverse Events Page. For example, there are inconsistencies in the number and types of fractures reported. GSK has clarified that the discrepancies are due to the collection of data in two different sections of the electronic case report form: the Adverse Events page and a specific Fracture Page. In some instances, the verbatim AE text mapped to Preferred Term Text different than the Term recorded on the Fracture Page. It is likely that similar situations occurred for the other Adverse Events of Special Interest. In general, the discrepancies that do occur are few in number and do not alter the general pattern of these events.

Pneumonia
As noted earlier, an imbalance in pneumonias between the FF-containing treatment arms and the VI monotherapy arm is evident from a review of the 52-week exacerbation trial data. Pneumonia is a known risk with ICS/LABA in COPD and is believed to be related to the ICS component. To help place the FF/VI data in perspective, a brief review of pneumonia data from the Advair and Symbicort COPD programs is presented at the end of this section. However, caution must be used when making any direct comparisons between the data given the inherit limitations of cross study comparisons.

This review focuses on the pneumonia data obtained from the 52-week exacerbation trials. The inclusion of three different strengths of FF/VI and the comparison to the VI comparator arm are helpful for characterizing the risk of pneumonia, since this risk is attributed to the ICS component of the combination product and not the LABA. In addition, the protocols for the 52-week exacerbation trials required x-ray evaluation of any case of suspected pneumonia or moderate/severe COPD exacerbation. X-rays were performed in 81-93% of the reported pneumonia adverse events.

To briefly summarize the 24-week lung function data, no consistent imbalance in pneumonia between FF-containing treatments and non-FF containing treatment arms is seen [placebo <1% (3), VI 2% (7) compared to FF/VI 50/25 3 (1%), FF/VI 100/25 6 (1%), FF/VI 200/25 4 (2%), FF 100 6 (1); FF 200 3 (1%). The lack of an imbalance may be related to the shorter trial duration and milder patient population enrolled in these trials.

In comparison, 54 to 65 pneumonia events are seen in the FF-containing treatment groups compared to 28 in the VI monotherapy treatment group in the 52-week exacerbation trial data. Similarly, an FF dose-dependent imbalance is also seen in the number of subjects with pneumonia in the FF/VI treatment groups [FF/VI 50/25: 48 (6); FF/VI 100/25 (51 (6); FF/VI 200/25 (55) (7)] compared to the VI monotherapy arm [VI: 27 (3)]. Furthermore, the Kaplan Meier curve for Time to First Pneumonia in the 52-week exacerbation trials also demonstrates a statistically significant difference between the FF-containing treatment groups and VI monotherapy arm and a FF dose-dependent effect is also seen.

While, no pneumonia-related fatalities occurred in the 24-week lung function trials, an imbalance in the number of fatal pneumonias is seen in the 52-week exacerbation trial data. Seven of events occurred in FF/VI 200/25 treatment group, a dose that is not being proposed for marketing. An additional pneumonia fatality was reported in FF/VI 100/25 and one in the post-treatment follow up period in the VI treatment arm. Four of fatal cases occurred at a single study site in the Philippines; the significance of this finding is unclear.

To further characterize this pneumonia risk, a Number Needed to Harm (NNTH) analysis on two 52-week exacerbation trial data was conducted by the Agency's biometrics reviewer. This analysis indicates that for every 39 patients in the FF/VI 50/25 group, 33 patients in the FF/VI 100/25 group or 29 patients in the FF/VI 200/25 dose group, 1 additional pneumonia will occur beyond that in the VI 25 mcg group.

Of note, the differences between all of the FF/VI dose groups and VI monotherapy for the Time to first pneumonia as well as the NNTH were both statistically significant.

Table 47: Pneumonia in 52-week Exacerbation trials[1]: 2871 and 2970

	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	58	65	28
Subjects with Pneumonia, n (%)	48 (6)	51 (6)	55 (7)	27 (3)
Absolute Risk Difference: FF/VI to VI Number needed to Harm (95% CI): FF/VI to VI	0.026 39 (22, 191)	0.03 33 (19,106)	0.035 29 (18, 73)	
Subjects with fatal Pneumonia, n (%)	0	1 (<1)	7 (<1) [2]	1 (<1) [3]
Time to first on treatment pneumonia Hazard Ratio: FF/VI to VI P value: FF/VI to VI	 1.7 0.025	 1.8 0.01	 2 0.003	

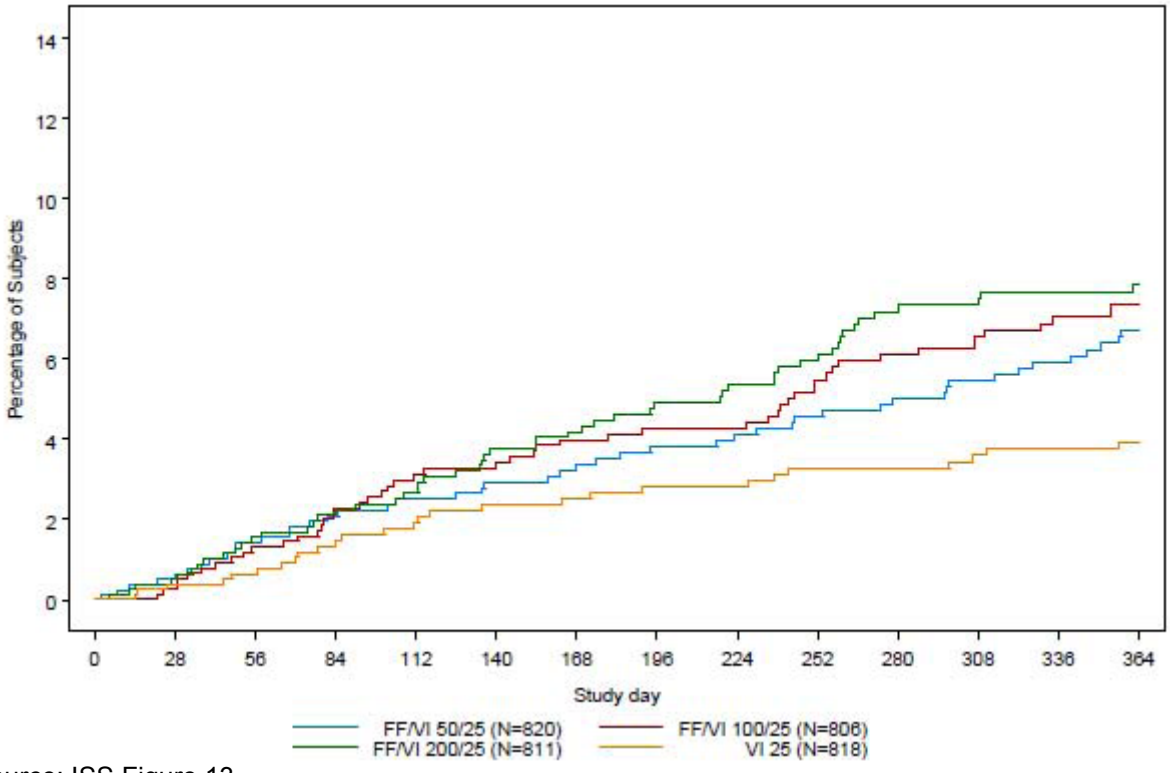
Source: ISS Tables 59, 69, 2.168

[1] No pneumonia related fatalities in the 24-week lung function trials

[2] Patient 111089 had fatal on-treatment SAE with PT of COPD but also had pneumonia eCRF completed for fatal pneumonia. This review includes this case in the pneumonia fatalities; this may result in different number from GSKs presentation.

[3] Patient 127070 in trial 2970: pneumonia fatality occurred in the post-treatment follow up phase

Figure 13: Kaplan Meier Plot: Time to First On Treatment Pneumonia for 52-week Exacerbation Trials: 2871 and 2970



Source: ISS Figure 13

To help place the FF/VI in context, the pneumonia data from other ICS/LABA COPD products is briefly summarized below. However, as noted above, when making a

comparison between the data, the limitations of cross-study comparisons must be kept in mind.

In two, replicate 52-week trials in 1,579 patients, Advair Diskus (fluticasone propionate/salmeterol; FP/S) 250/50 had a higher incidence of pneumonia reported in patients (7%) compared to salmeterol (3%)[7]. Similar imbalances were seen in the 3-year mortality study (TORCH trial) comparing FP/S 500/50 to FP, S, and placebo. A total of 248 (16%) and 224 (14%) of FP/S and FP patients had a pneumonia event compared to 162 (11%) and 139 (9%) of patients in the salmeterol and placebo arms.[8] In addition, a post-hoc analysis by Crim et al[9] determined that patients in FP/S and FP had a probability of developing pneumonia by 3 years of 19.6 and 18.3 compared to 13.3 and 12.3 for salmeterol and placebo. The analysis also determined that patients in ICS-containing treatment arms had a 1.5 fold higher risk of pneumonia than those in non-ICS arms (placebo + S). These data are summarized in the table below.

Table 48: Pneumonia Data From Previous FP/S Trials

	Placebo	Salm 50	FP 500	FP/Salm 500/50	FP/Salm 250/50
TORCH Trial[1]					
Patients, n	1544	1542	1552	1546	
Patients with PNA, n (%)	139 (9)	162 (11)	224 (14)	248 (16)	
Probability of PNA by 3 years	12.3	13.3	18.3	19.6	
Hazard Ratio compared to placebo 95% Confidence Interval P-value		1.09 (0.87, 1.37) 0.465	1.53 (1.24, 1.89) <0.001	1.64 (1.33,2.02) <0.001	
Advair Diskus: Two 52-week Exacerbation Trials[2]					
Pneumonia, % of patients		3			7

Sources:
[1] Crim et al[8]
[2] Advair Diskus Prescribing Information
S = salmeterol; FP = fluticasone propionate

The development program for Symbicort demonstrated a higher rate of lung infections in the 160/4.5 mcg treatment arm (7.6%) compared to the lower dose 80/4.5 mcg dose group (3.2%), formoterol (4.6%) and placebo (3.3%) in a six month trials. A similar pattern was seen in the 12-month trial (160/4.5: 8.1%; 80/4.5: 6.9%; formoterol 7.1%; placebo: 6.2%). This pattern was not seen when looking at specific rates of pneumonia[10]it is unclear if this is due to a difference in trial design.

[7] Advair Diskus; NDA 21-077; Prescribing Information
[8] Calverley et al; Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease; N Engl J Med 2007; 256:775-89.
[9] Crim et al; Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results; Eur Resp J 2009; 34:641-647.
[10] Symbicort®; NDA 021-929; Prescribing Information

Bone Disorders:
A consistent, numeric imbalance in the number of bone disorders, the majority of which are fractures, is evident between the FF-containing treatment arms (21-27 events; 3%) and the VI-monotherapy arm (9 events; 1%) in the pooled 52-week exacerbation trials. No imbalance is seen in the combined data from the shorter 24-week lung function trials (1 to 3 fracture events per treatment group). The difference between the 24-week lung function trial data and the 52-week exacerbation trial data may be due to the difference in trial duration and the ability to collect more data from the longer trials.

To further characterize this risk, a NNTH analysis was conducted by the Agency's biometrics reviewer for the fracture data from the two pooled 52-week exacerbation trial data. This analysis determined that one extra fracture beyond that in the VI group would occur for every 137 patients in the FF/VI 50/25, every 72 patients in the FF/VI 100/25 group and for every 134 patients in the FF/VI 200/25 dose group. In comparison to the NNTH analysis for the pneumonia data, the risk difference from VI is not statistically significant for all the FF/VI dose groups, only the difference for the 100/25 group is.

Table 49: On-treatment Bone Disorders and Fractures in 52-week Exacerbation Trials: 2871 and 2970

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Bone Disorders[1], n (%)	24 (3)	27 (3)	21 (3)	9 (1)
Absolute Risk Difference NNTH (95% CI)	0.018 55 (30, 216)	0.023 44 (26, 121)	0.015 67 (34, 597)	
Fractures[2]	14 (2)	19 (2)	14 (2)	8 (<1)
Absolute Risk Difference NNTH (95% CI)	0.007 137 (51, ∞)	0.014 72 (36, 857)	0.008 134 (50, ∞)	

Source:
[1] ISS Table 2.160
[3] Adverse Events assigned to Bone Disorders Special Interest Group excluding Preferred Terms of skeletal injury, osteoporosis, and osteopenia from Table 2.3 in Response to Information Request dated October 19, 2012

While an imbalance is evident from an analysis of the pooled 52-week exacerbation data, disparate findings are seen when looking at fracture data for the individual 52-week exacerbation trial results. An imbalance is seen between the FF-containing treatment groups and VI monotherapy arm in trial 2871; however this finding is not seen in the fracture data from trial 2970.

The bone disorder data, including fracture, fracture location, and bone biomarker data were analyzed by internal Agency consultants from the Division of Reproductive and Urology Products (DRUP). DRUP noted the lack of replication of the fracture imbalance between the two trials. In addition, the review noted that the osteocalcin measurements from trial 2871 are suggestive of a corticosteroid effect but the serum carboxy-terminal cross-linking telopeptide of collagen (sCTX) are not. Of note, bone biomarkers were not measured in trial 2970 and bone mineral density was not measured in either trial or at

any point in the FF/VI development program. Overall the DRUP reviewer determined that the fracture data in this development program do not appear to indicate a new risk beyond that already associated with ICS use. In addition, the DRUP reviewer concluded that a study to confirm the effect of FF on fracture would be hampered by logistical issues (e.g. retention, confounding from treatment with systemic corticosteroids, etc.) and would likely not provide definitive results.

Similar to the pneumonia data, it may be helpful to consider these data in the context of previous ICS/LABA COPD development programs. Bone disorder data was assessed in the 3-year COPD mortality trial (TORCH) evaluating Advair 500/50 versus salmeterol and placebo. Keeping in mind the limitations to cross-study comparisons, the Advair 500/50 arm had a rate of 22.4 fractures per 1000 treatment-years compared to 18.6 for placebo, 20.4 for Salmeterol and 20.3 for 500 mcg of fluticasone propionate[11].

Table 50: Bone Disorder Data from TORCH Trial

	Placebo N=1544	S 50 N=1542	FP 500 N=1552	FP/S 500/50 N=1546
SC030003 (TORCH: 3 year Advair mortality trial)				
All Fractures, n(%)	57(3.7)	61(4)	65(4.2)	78(5)
Fracture rate per 1000 treatment years*	18.6	20.4	20.3	22.4
Hazard Ratio to placebo (95% CI)		1.353 (0.77, 2.39)	0.696 (0.53, 1.79)	0.931 (0.51, 1.72)
Kaplan Meier estimate of probability for all fracture at 3 years	5.1	5.1	5.4	6.3
Source: Pages 109-110 and Table 57 briefing document for PADAC meeting May 1, 2007; sNDA 21-077 Salm = salmeterol; FP = fluticasone propionate; FP/S = fluticasone propionate/salmeterol				

Additional Corticosteroid Effects*:*
The development program for FF/VI also evaluated for other known effects of corticosterioid use in addition to pneumonia and bone loss. These included an analysis of local steroid effects (oral candidiasis and oropharyngeal discomfort), effects on glucose and the eye as well as systemic effects on the HPA axis. Evaluations of serum and urinary cortisol were also performed in a subset of patients. No unexpected findings are revealed from a review of these data which are presented below.

Local and Systemic Corticosteroid Effects:
An imbalance in local steroid effects is seen between the FF-containing arms and FF containing treatment arms. Theses events include PT text related to oral candidiasis and oropharyngeal discomfort. This imbalance is not surprising as these are known adverse effects associated with use of orally-inhaled ICS products. No imbalance or dose-response in systemic steroid effects, ocular effects, or on glucose is evident from

[11] Pulmonary and Allergy Advisory Committee FDA Clinical Briefing Document for sNDA 21-077; May 1, 2007

these data.

Table 51: ICS-related AEs[1] in 24-week Lung Function Trials: 2206 and 2207

	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
Adverse Event of Special Interest related to ICS use, n (%)							
Local Steroid Effects	15(4)	24(12)	27(7)	13(6)	14(3)	18(4)	17(8)
Systemic Steroid Effects	2(<1)	2(<1)	1(<1)	0	1(<1)	0	0
Effects on Glucose	3(<1)	3(1)	7(2)	3(1)	6(1)	5(1)	3(1)
Ocular Effects	1(<1)	1(<1)	1(<1)	0	1(<1)	3(<1)	0

Source: ISS Table 57
[1] Excluding pneumonia and bone disorders

Table 52: ICS-related AEs[1] in 52-week Exacerbation Trials: 2871 and 2970

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Adverse Events of Special Interest related to ICS use, n (%)				
Local steroid effects	142 (17)	121 (15)	140(17)	96(12)
Systemic Steroid Effects	0	0	0	0
Effects on Glucose	18(2)	15(2)	22(3)	14(2)
Ocular Effects	7(<1)	12(1)	7(<1)	9(1)

Source: ISS Table 59
[1] Excluding pneumonia and bone disorders

Cortisol

Twenty-four hour urinary cortisol excretion was assessed in a subset of patients in both 24-week lung function trials (2206 and 2207). No significant imbalances between FF-containing and non-FF-containing treatment groups in the median change from baseline is seen (placebo: 0.98; FF/VI 100/25: 1.12; FF/VI: 100/25; FF/VI 200/25 0.95; VI: 0.95; FF 100: 0.92; FF 200: 0.93). In addition, an outlier analysis, defined as a decrease from baseline more than 25% minus 1.5 times the interquartile range, was also performed. A total of 10 patients had outlier results: 3 patients in placebo group, 1 in VI 25 group, 3 in FF 100, 1 in FF/VI 50/25, and 2 in FF/VI 200/25.

Twenty-four hour serum cortisol was collected on Day 28 of each treatment period in trial 946. Samples were collected pre-dose and a 2, 4, 8, 12, 16, and 24 hours post-dose. The geometric mean for 0-24h weighted mean serum cortisol for the FF/VI 50/25 (181.2 nmol/L) and 100/25 FF/VI (185.9 nmol/L) are similar to placebo (189.1 nmol/L). The geometric mean for FF/VI 200/25 is lower at 168.8 nmol/L.

Overall, these results are supportive of the results from GSK's dedicated HPA axis trial, which has been reviewed in detail by the Clinical Pharmacology team (see Clinical Pharmacology Briefing document). The team's overall conclusion was that a dose-dependent corticosteroid effect is seen on the HPA axis, but not at therapeutic FF doses.

A dose-related effect on the HPA axis is known corticosteroid effect, and current product labeling already contains warning language regarding a potential effect on the HPA axis at supratherapeutic doses and in susceptible individuals.

Beta Adrenergic Effects:

The effects of beta adrenergic stimulation are well understood and include effects on the cardiovascular system, alterations in laboratory values and vital signs and increased tremor. No unexpected increase in adrenergic effects is seen in the data. A detailed analysis follows below.

Cardiovascular Effects and Tremor:

No consistent effect on cardiovascular system or in tremor is seen between the VI-containing treatment arms and the non-VI-containing treatment arms from an analysis of cardiac events from the pooled 24-week lung function trials or the 52-week exacerbation trials. In addition, the AE profile for VI 25 is similar to lower doses of VI in the smaller, one-month VI dose-ranging trial in COPD (trial 1045). These data provide additional support for the safety of VI 25 in terms of LABA-related AEs.

Table 53: Cardiac data in 24-week Lung Function Trials: 2206 and 2207

	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
Adverse Event of Special Interest, n(%)							
Cardiac Arrhythmia	27 (7)	8 (4)	21 (5)	8 (4)	19 (5)	20 (5)	14 (7)
Hypertension	10 (2)	5 (2)	4 (<1)	1 (<1)	3 (<1)	8 (2)	7 (3)
Cardiac Ischemia	9 (2)	3 (1)	5 (1)	2 (<1)	2 (<1)	8 (2)	2 (<1)
Cardiac Failure	3 (<1)	1 (<1)	3 (<1)	4 (2)	3 (<1)	2 (<1)	0
Acquired Long QT	0	0	1 (<1)	0	0	0	0
Sudden Death	0	0	0	0	1 (<1)	0	0
Tremor	1(<1)	0	1 (<1)	0	0	1 (<1)	0
Special MedDRA Query (SMQ), n(%)							
Cardiac Arrhythmia	30 (7)	11 (5)	22 (5)	10 (5)	20 (5)	23 (6)	16(8)
Ischemic Heart Disease	4 (<1)	3 (1)	4 (<1)	1 (<1)	3 (<1)	4 (<1)	2(<1)
Cardiac Failure	3 (<1)	1 (<1)	3 (<1)	4 (2)	3 (<1)	4 (<1)	0
Source: ISS Table 57 and 58							

Table 54: On-treatment Cardiac Data in 52-week exacerbation trials: 2871 and 2970

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Adverse Event of Special Interest, n(%)				
Cardiac Arrhythmia	30(4)	27(3)	22(3)	31(4)
Hypertension	32(4)	36(4)	36(4)	25(3)
Cardiac Ischemia	30(4)	19(2)	21(3)	26(3)

Cardiac Failure	22(3)	26(3)	13(2)	33(4)
Acquired Long QT	0	1(<1)	0	0
Sudden Death	0	0	0	0
Tremor	1(<1)	2(<1)	2(<1)	3(<1)
Special MedDRA Query (SMQ), n(%)				
Cardiac Arrhythmia	32(4)	33(4)	24(3)	31(4)
Cardiac Failure	30(4)	29(4)	17(2)	39(5)
Ischemic Heart Disease	26(3)	13(2)	20(2)	22(3)
Tremor	1(<1)	2(<1)	2(<1)	3(<1)
Source: ISS Table 59, Table 60				

Table 55: LABA related Adverse Events in COPD VI Dose-Ranging Trial: 1045

	Placebo N=101	VI 3 N=99	VI 6.25 N=101	VI 12.5 N=101	VI 25 mcg N=101	VI 50 mcg N=99
Adverse Events of Special Interest, n, (%)						
Ventricular extrasystoles	2 (2)	0	1 (<1)	0	0	3 (3)
Sinus tachycardia	0	0	0	0	0	1 (1)
Supraventricular extrasystoles	0	0	1 (<1)	0	0	0
Hypertension	0	0	0	1 (<1)	2 (2)	1 (1)
Blood pressure increased	1 (<1)	0	0	1 (<1)	0	0
Atrial fibrillation	0	0	0	2 (2)	0	0
Palpitations	1 (<1)	0	1 (<1)	0	0	0
Hypokalemia	1 (<1)	1 (1)	0	0	0	0
Blood potassium decreased	0	0	0	0	0	1 (1)
Tremor	0	1 (1)	1 (<1)	0	0	0
Blood glucose increased	3(3)	0	1(<1)	3(3)	1(<1)	0
Hyperglycemia	1(<1)	0	0	0	0	0
Source: ISS Table 63 Analysis conducted post hoc, as AE of special interest were not pre-specified in protocol,						

Effects on Potassium

Hypokalemia due to beta-adrenergic stimulation is a well described phenomenon. To assess for this in its development program, GSK collected 30 minute post-dose values in the 24-week lung function trials and trough values in both the 24-week lung function and 52-week exacerbation trials. The analysis of these data focuses on measures of central tendency and shifts from normal to abnormal. In addition, effects on potassium were designated as an Adverse Event of Special Interest in the pivotal phase 3 trials.

Overall, no unexpected effect on potassium is evident from the data. In addition to the pivotal phase 3 data, no dose-related increase is seen in the one-month VI dose-ranging trial (see Table 55 above) providing additional evidence that the selected VI dose does not have a clinically significant effect on impact potassium. Data from trials 2206 and 2207, which include data from non-VI containing treatment arms for comparison, are summarized in Table 56 below.

Table 56: Potassium Effects in 24-week Lung Function Trials: 2206 and 2207

	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
Trough (mmol/L)							
Day 84 trough, median	-0.1	-0.1	-0.1	-0.05	-0.1	-0.1	-0.1
Day168 trough, median	-0.1	-0.1	-0.1	-0.1	0	-0.1	-0.1
30-minute post dose (mmol/L)							
Day 84, median	0	0	-0.1	0.1	0	-0.1	-0.1
Day 168 median	-0.1	0	-0.1	0.1	0	0	-0.1
Anytime shift to high							
Anytime post baseline n (%)	30 (9)	6 (4)	22 (7)	15 (8)	24 (7)	16 (5)	11 (7)
Adverse Event of Special Interest:							
Effect on Potassium n, (%)	1 (<1)	0	0	1 (<1)	0	1 (<1)	0
Source: ISS Table 3.01, 3.02, 3.03, 3.04, 3.05, 3.06							

Effects on Glucose

An increase in blood glucose is a known class-related effect for both ICS and LABAs. These effects were evaluated in a similar fashion to potassium in GSK's development program. Again, the analysis of these data focuses on measures of central tendency and shifts from normal to abnormal, as well as on GSKs Adverse Events of Special Interest analysis. Review of these data does not indicate a clinically meaningful effect of FF/VI on either of these parameters at the timepoints tested.

Table 57: Glucose Effects in 24-week Lung Function Trials: 2206 and 2207

	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
Trough (mmol/L)							
Day 84, median	-0.1	-0.2	-0.1	-0.2	-0.2	-0.15	-0.1
Day 168, median	-0.1	-0.1	-0.1	-0.1	0	-0.1	-0.1
30 min post-dose							
Day 84, median (mmol/L)	-0.1	-0.3	-0.1	-0.2	-0.2	-0.2	-0.2
Day 168 median (mmol/L)	-0.1	-0.1	0	-0.1	-0.1	-0.1	0
Anytime Shift to High							
Anytime post baseline, n (%)	53 (16)	33 (20)	57 (17)	24 (14)	49 (14)	52 (16)	27 (16)
Adverse Event of Special Interest							
Effects on Glucose, n (%)	3 (<1)	3 (1)	7 (2)	3 (1)	6 (1)	5 (1)	3 (1)
Source: ISS Table 3.01, 3.02, 3.03, 3.04, 3.05, 3.06							

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. The following tables summarize the most common on-treatment adverse events in the pivotal phase 3 trials. Similar events are seen in the completed trials from the 120-day safety update.

In the tables below, common adverse events are defined as preferred terms occurring in > 3% patients in the FF/VI treatment group. Of note, any adverse event that occurs more commonly in placebo is not included in Table 58. Specific adverse events of interest are discussed in detail in Section 7.3.4.

Table 58: Most Common Adverse Events (≥ 3%) in 24-week Lung Function Trials 2206 and 2207

	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
Preferred Term, n %							
Nasopharyngitis	31 (8)	14 (7)	35 (9)	13 (6)	41 (10)	32 (8)	20 (10)
Headache	20 (5)	12 (6)	29 (7)	15 (7)	36 (9)	30 (7)	11 (5)
Upper respiratory tract infection	13 (3)	16 (8)	29 (7)	7 (3)	20 (5)	16 (4)	5 (2)
Oral/Oropharyngeal candidiasis[1]	9 (2)	20 (10)	22 (5)	9 (4)	9 (2)	13 (3)	13 (6)
Back pain	10 (2)	7 (3)	10 (2)	2 (<1)	10 (2)	6 (1)	2 (<1)
Chronic obstructive pulmonary disease	8 (2)	0	9 (2)	5 (2)	11 (3)	2 (<1)	2 (<1)
Hypertension	7 (2)	3 (1)	3 (<1)	1 (<1)	1 (<1)	7 (2)	7 (3)
Lower respiratory tract infection	11 (3)	3 (1)	2 (<1)	1 (<1)	7 (2)	3 (<1)	2 (<1)

Source: ISS Table 21
[1] includes the following preferred terms: oral candidiasis, oropharyngeal candidiasis, candidiasis, oropharyngitis fungal

Table 59: Most common Adverse Events (≥3%) in 52 week Exacerbation Trials: 2871 and 2970

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Preferred Term, n(%)				
Nasopharyngitis	112 (14)	128 (16)	158 (19)	112 (14)
Oral/Oropharyngeal candidiasis	110 (13)	87 (11)	88 (11)	55 (7)
Upper respiratory tract infection	84 (10)	90 (11)	75 (9)	78 (10)
Headache	61 (7)	57 (7)	67 (8)	60 (7)
Chronic obstructive pulmonary disease	53 (6)	56 (7)	53 (7)	53 (6)
Back pain	40 (5)	54 (7)	37 (5)	53 (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)
Cough	35 (4)	31 (4)	35 (4)	34 (4)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Oropharyngeal pain	30 (4)	31 (4)	39 (5)	31 (4)
Influenza	28 (3)	27 (3)	31 (4)	27 (3)
Arthralgia	19 (2)	36 (4)	26 (3)	30 (4)
Hypertension	27 (3)	30 (4)	28 (3)	22 (3)
Pharyngitis	18 (2)	24 (3)	29 (4)	26 (3)
Diarrhea	22 (3)	22 (3)	30 (4)	19 (2)
Urinary tract infection	24 (3)	20 (2)	29 (4)	15 (2)
Dyspnea	25 (3)	20 (2)	15 (2)	27 (3)
Nausea	24 (3)	18 (2)	19 (2)	21 (3)
Rhinitis	23 (3)	15 (2)	25 (3)	18 (2)
Edema peripheral	21 (3)	22 (3)	12 (1)	25 (3)
Pyrexia	21 (3)	22 (3)	20 (2)	10 (1)
Pain in extremity	15 (2)	18 (2)	17 (2)	22 (3)
Dizziness	22 (3)	12 (1)	14 (2)	20 (2)
Lower respiratory tract infection	12 (1)	14 (2)	11 (1)	21 (3)

Source: ISS Table 22

[1] includes the following preferred terms: oral candidiasis, oropharyngeal candidiasis, candidiasis esophageal candidasis,

7.4.2 Laboratory Findings

No clinically meaningful effects on hematologic or chemistry parameters are noted from the FF/VI development program. Representative data of the laboratory findings from the 24-week lung function trials are presented below. In general, no consistent imbalances between treatment groups are noted. Specific effects on potassium, glucose and urinary cortisol are discussed in Section 7.3.4.

Table 60: Shift Table of Hematology Parameters[1] in 24-week Lung Function Trials: 2206 and 2207

	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
WBC, n (%)							
N	396	196	388	198	383	392	193
To low	10 (3)	3 (2)	3 (<1)	2 (1)	9 (2)	7(2)	3 (2)
To high	30 (8)	9 (5)	32 (8)	20(10)	28 (7)	29 (7)	19 (10)
Lymphocyte, n (%)							
N	396	196	388	198	387	392	193
To low	32 (8)	16 (8)	34 (9)	19 (10)	32 (8)	34 (9)	20 (10)
To high	14 (4)	9 (5)	9 (2)	7 (4)	18 (5)	16 (4)	7 (4)
Neutrophil, n (%)							
N	396	196	388	198	383	192	193

	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
To low To high	14 (4) 27 (7)	4 (2) 11 (6)	7 (2) 29 (7)	2 (1) 17 (9)	9 (2) 22 (6)	13 (13) 28 (7)	6 (3) 17 (9)
Eosinophil, n (%)							
N To high	396 21 (5)	196 6 (3)	388 2 (6)	198 5 (3)	383 21 (5)	392 16 (4)	193 9 (5)
Platelets, n (%)							
N To low To high	387 5 (1) 4 (1)	196 4 (2) 4 (2)	383 9 (2) 6 (2)	197 3 (2) 6 (3)	383 9 (2) 2 (<1)	388 6 (2) 7 (2)	192 5 (3) 3 (2)
Hemoglobin, n (%)							
N To low	396 26 (7)	197 5 (3)	388 21(5)	199 9(5)	385 12(3)	393 25(6)	194 14(17)
Platelets, n (%)							
N To low To high	387 5 (1) 4 (1)	196 4 (2) 4 (2)	383 9(2) 6(2)	197 3(2) 6(3)	383 9(2) 2(<1)	388 6(2) 7(2)	192 5(3) 3(2)

Source: ISS Table 3.16
[1]includes labs performed at scheduled, unscheduled and early withdrawal visits

Table 61: Shift table of Chemistry Parameters[1] in 24-week Lung Function Trials: 2206 and 2207

	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
Alkaline phosphatase, n (%)							
N To high	397 7 (2)	198 5(3)	388 6(2)	200 2(1)	296 9(2)	296 8(2)	192 3(2)
Aspartate aminotransferase, n (%)							
	320 13 (3)	165 8(4)	321 13(3)	162 10(5)	333 9(2)	324 12(3)	160 4(2)
Calcium, n (%)							
N To low To high	397 13 (3) 9 (2)	197 4(2) 6(3)	388 8(2) 8(2)	199 5(3) 9(5)	395 16(4) 13(3)	396 17(4) 9(2)	192 8(4) 4(2)
Bicarbonate, n (%)							
N To low To high	397 38 (10) 1 (<1)	198 21(11) 0	388 50(13) 0	199 21(11) 0	395 43(11) 0	396 36(9) 0	192 23(12) 0
Creatinine Kinase, n (%)							
N To high	397 19 (5)	198 16 (8)	388 23 (6)	200 12 (6)	396 26 (7)	395 22 (6)	192 8(4)

	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
Total Bilirubin, n (%)							
N	397	197	388	200	396	396	192
To high	5 (1)	2 (1)	2 (<1)	1 (<1)	6 (2)	5 (1)	3 (2)
Direct Bilirubin , n (%)							
N	397	198	388	200	396	396	192
To high	3 (<1)	0	2 (<1)	1 (<1)	0	0	2
GGT, n (%)							
N	397	198	398	200	296	396	192
To high	17 (4)	16 (8)	21 (5)	4 (2)	21 (5)	14 (4)	7 (4)
Phosphorus, n (%)							
N	397	197	388	200	396	396	192
To high	16 (4)	3 (2)	9 (2)	9 (5)	24 (6)	12 (3)	8 (4)
Sodium, n (%)							
N	397	198	388	200	396	396	192
To low	8 (2)	5(3)	9 (2)	6 (3)	8 (2)	6 (2)	4 (2)
To high	4 (1)	1 (<1)	1 (<1)	1 (<1)	2 (<1)	6 (2)	3 (2)
Albumin, n (%)							
N	397	198	388	200	396	396	192
To low	0	0	1 (1)	0	1 (<1)	3 (<1)	1 (<1)
To high	7 (2)	1 (<1)	2 (<1)	9 (5)	6 (2)	3 (<1)	2 (1)
Creatinine, n (%)							
N	397	198	388	200	396	395	192
To low	34 (9)	16 (8)	29 (7)	14 (7)	34 (9)	29 (7)	12 (7)
To high	7 (2)	7(4)	4 (1)	2 (1)	4 (1)	3 (<1)	2 (1)
Total Protein, n (%)							
N	397	198	388	200	396	396	192
To low	4 (1)	5 (3)	6 (2)	2 (1)	7 (2)	5 (1)	3 (2)
To high	3 (<1)	3 (2)	3 (<1)	0	3 (<1)	5 (1)	1 (<1)
Urea/BUN, n (%)							
N	397	198	388	200	396	396	192
To low	7 (2)	3 (2)	3 (<1)	1 (<1)	5 (1)	5 (1)	4 (2)
To high	11 (3)	7 (4)	11 (3)	8 (4)	11 (3)	12 (2)	5 (3)
Uric Acid, n (%)							
N	397	197	387	199	396	396	192
To low	15 (4)	3 (2)	8 (2)	3 (2)	16 (4)	4(1)	1 (<1)
To high	23 (6)	6 (4)	17 (4)	6 (3)	20 (5)	12(3)	8 (4)

Source: ISS Table 3.16
[1]includes labs performed at scheduled, unscheduled and early withdrawal visits

7.4.3 Vital Signs

A review of the vital sign data from the pooled analyses of the 24-week lung function trials and the 52-week exacerbations trials does not reveal any clinically meaningful differences among treatment groups. Of note, specific adverse events of cardiac arrhythmias (including tachycardia) and hypertension are discussed in Section 7.3.4. Below is a table of data from the 24-week lung function trials. No significant difference is noted from a review of the 52-week exacerbation trial data.

Table 62: Vital Sign Data in 24-week Lung Function Trials: 2206 and 2207

	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
Systolic Blood Pressure (mmHg)							
Baseline							
Median	130	130	130	130	130	130	130
Min	87	93	100	90	94	90	95
Max	172	180	180	167	185	170	169
Day 1 10 min post dose							
Median	130	130	130	130	130	130	130
Min	90	85	92	90	90	80	88
Max	172	172	180	160	170	168	170
Day 84 10 min post dose							
Median	129	126	126	130	130	129	130
Min	90	94	97	90	80	96	81
Max	178	175	175	162	170	170	176
Diastolic Blood Pressure (mmHg)							
Baseline							
Median	83	80	80	80	80	80	80
Min	43	48	54	60	47	46	57
Max	114	107	104	100	110	105	110
Day 1 10 minute post dose							
Median	80	80	80	80	79	80	80
Min	52	50	48	51	50	40	55
Max	104	122	106	100	110	100	110
Day 84 10 minute post dose							
Median	80	78	78	80	78	79	80
Min	54	50	50	57	50	54	55
Max	104	102	140	106	100	105	100
Pulse (beats/minute)							
Baseline							
Median	74	75	74	76	76	75	75
Min	45	45	49	51	49	50	50
Max	125	109	112	106	119	122	106

	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
Day 1 10 min post dose							
Median	72	74	75	74	73	73	74
Min	48	45	47	51	50	47	50
Max	113	108	109	101	112	123	109
Day 84 10 min post dose							
Median	72	73	74	72	74	72	72
Min	48	51	29	50	48	46	48
Max	114	101	114	112	108	102	110
Source: ISS Table 4.01							

7.4.4 Electrocardiograms (ECGs)

To further evaluate for possible cardiac effects of FF/VI, 12-lead ECGs were conducted in all patients at Screening, Day 1, Day 84 and Day 168 in the two 24-week lung function trials and at Screening, Day 1, Day 84, Day 196, and Day 364 in the two 52-week exacerbation trials. GSK identified potentially clinically significant changes in ECG parameters using a team of central cardiologists who over-read the ECGs.

In general, changes in ECGs parameters from baseline are small and similar across treatment groups. In addition, the percentages of subjects with abnormalities of potential clinical importance are also balanced across treatment groups. The table below summarizes the ECGs parameters from the two 24-week lung function trials. These data are representative of data from the development program.

Table 63: ECG and 24 hour Holter Data: 2206 and 2207

	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
Heart Rate, beats per minute							
N	286	147	297	159	306	301	162
Baseline, mean (SD)	73.6	74.4	73.2	74.4	74.4	73	75.1
Day168 LS mean change from baseline	-0.8	-2.9	-1.8	-1.9	-1.5	-1.2	-0.5
QTcF, msec							
N	286	147	297	159	306	301	162
Baseline, mean	405.2	408.2	406.4	406.4	406.4	405.6	405.5
Day168 LS mean change from baseline	1.4	0.4	-0.1	0.9	1	0.9	0.3
Abnormality of potential clinical importance at any time post baseline[12]							
N (%)	57(14)	28(14)	50(12)	34(17)	49(12)	44(11)	28(14)

Source: ISS Table 85, 88, 90
[1] per central cardiologists read of the ECG
[2] any time post baseline

Twenty-four hour Holter monitoring was obtained in a subset of patients (half of each treatment arm) in the lung function trials (2206 and 2207) Similar to the ECGs over-reads, all Holter monitoring was read by cardiologists and categorized as normal, abnormal but not clinically significant, abnormal and clinically significant or unable to evaluate.

A total of 17 (10%) of patients in the placebo group; 13 (13%) in FF/VI 50/25, 27 (15%) in FF/VI 100/25, 12(13%) in FF/VI 200/25, 21 (11%) in VI 25, 25(14%) in FF 100 and 5 (6%) in FF 200 demonstrated abnormalities of potential clinical importance at any time post baseline. No imbalance is seen between the VI and non-VI containing treatment groups.

In addition to ECG monitoring and 24 hour Holter monitoring during the Phase 3 trials, QTc prolongation for FF/VI was evaluated in a dedicated study, HZA102936. The Agency's clinical pharmacology IRT team reviewed these results and noted that the largest upper bounds of the 2-sided 90% CI for the mean difference between FF/VI 200/25 mcg and placebo are below 10 msecs in this trial. However, the largest upper bounds of the 2-sided 90% CI for the mean difference between FF/VI 800/100 and placebo is above 12.2 msecs. Overall, the team concluded that while FF/VI 800/100 causes effects of concern, the dosage levels are higher than the predicted worst case scenario for FF (drug interaction with ketoconazole) and VI (hepatic impairment study).

7.4.5 Special Safety Studies/Clinical Trials

As there are risks associated with LABA use in asthma, the composite asthma endpoint data of asthma-related hospitalizations, intubations and deaths from GSK's asthma development program for FF/VI is summarized in this section of the review. This

development program includes data from 68 phase 1, 2, and 3 clinical trials in 10,000 patients with asthma. Over 2,500 of these patients received treatment with orally inhaled FF/VI.

To generate this data, GSK had the SAE narratives for all asthma studies containing a VI or VI+ ICS treatment arm adjudicated by an independent, blinded committee. These SAEs were initially classified as a death, hospitalization, and/or intubation, then as respiratory-related or non-respiratory related. These respiratory related SAEs were then classified as asthma-related, COPD-related, pneumonia-related or other respiratory-related. In general, a review of these narratives by this reviewer concurs with the adjudication results of the independent committee.

Overall, these data do not indicate an increased risk of asthma-related adverse events..

The database contains a total of 93 patients with SAEs; 35 of which are labeled as respiratory-related. Three of the SAEs are deaths, two of which were adjudicated as respiratory-related (1 each in FF/VI 100/25 and placebo+ ICS groups) and one as pneumonia-related (FF 100 treatment group). Of note, the only death in a VI-containing treatment group occurred in an individual who fell off a bar stool while intoxicated and sustained a cerebral hemorrhage. Given the circumstances, this death is unlikely related to study drug.

The database contains three intubations, two of which are labeled as respiratory-related. The database also contains 87 hospitalizations with 34 adjudicated as respiratory-related. The greatest number of hospitalizations (n=42, 3%) and asthma-related hospitalizations (n=11; 1%) are seen in the proposed FF/VI 100/25 dose group. However, this finding is not maintained in the higher FF/VI 200/25 dose group and importantly, the overall rate of hospitalizations appears low for all treatment groups. These findings are summarized in Table 64.

Table 64: Asthma Composite Endpoint: Pooled Asthma Safety Database

	PBO N=307	FF/VI 100/25 N=1509	FF/VI 200/25 N=455	FF 100 N=1239	FF 200 N=194	PBO+ OCS N=15	FP 1000 N=295	PBO +ICS N=218	VI 25+ICS N=231	Salm + ICS N=116
Death										
Total	0	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0	0
Respiratory	0	0	0	1 (<1)	0	0	0	0	0	0
Asthma	0	0	0	0	0	0	0	0	0	0
PNA	0	0	0	1 (<1)	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0	0	0
Non-respiratory	0	1 (<1)	0	0	0	0	0	1 (<1)	0	0
Hospitalization										
Total	0	42 (3)	7 (2)	29 (2)	1 (<1)	0	7 (2)	0	1 (<1)	0
Respiratory	0	16 (1)	1 (<1)	12 (<1)	1 (<1)	0	3 (1)	0	1 (<1)	0
Asthma	0	11 (<1)	0	7 (<1)	1 (<1)	0	2 (<1)	0	1 (<1)	0

	PBO N=307	FF/VI 100/25 N=1509	FF/VI 200/25 N=455	FF 100 N=1239	FF 200 N=194	PBO+ OCS N=15	FP 1000 N=295	PBO +ICS N=218	VI 25+ICS N=231	Salm + ICS N=116
PNA	0	4 (<1)	1 (<1)	5 (<1)	0	0	1 (<1)	0	0	0
Other	0	1 (<1)	0	1 (<1)	0	0	4 (1)	0	0	0
Non-respiratory	0	27 (2)	6 (1)	17 (1)	0	0	0	0	0	0
Intubations										
Total	0	0	0	3 (<1)	0	0	0	0	0	0
Respiratory	0	0	0	2 (<1)	0	0	0	0	0	0
Asthma	0	0	0	0	0	0	0	0	0	0
PNA	0	0	0	1 (<1)	0	0	0	0	0	0
Other	0	0	0	1 (<1)	0	0	0	0	0	0
Non-respiratory	0	0	0	1 (<1)	0	0	0	0	0	0
Source: ISS Asthma Table 68										

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

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

7.5.2 Time Dependency for Adverse Events

GSK provided summary tables for adverse events with an onset during the first 6 months of studies and with onset greater than 6 months after randomization for the 52-week exacerbation trials. An analysis of both reveals no difference in the most common adverse events.

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. However, in general, females reported these same adverse events more frequently than males. This same pattern occurred in both the pooled safety analysis for the 24-week lung

function trials as well as the 52-week exacerbation trials. A review of AE incidence in the ≤ 64 and > 65 years of age groups reveals no consistent pattern due to 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 24-week lung function and 52-week exacerbation trial databases.

7.5.4 Drug-Disease Interactions

The application includes an analysis of adverse events based on COPD severity, renal and hepatic impairment and history of cardiovascular risk factors.

A review of the SAE data by GOLD classification reveals a higher frequency of SAEs in patients with more severe disease; however these appear balanced across treatment groups. This finding is unsurprising as one might expect more SAEs in a sicker patient population.

The effect of renal impairment and hepatic impairment on the pharmacokinetics of FF and VI following repeat administrations of FF/VI 200/25 mcg was assessed in trials HZA113970 and HZA111789 respectively. These results were reviewed by the Clinical Pharmacology team (see Clinical Pharmacology Summary Document for details). Overall, the results indicate no effect on FF or VI exposure in renal impairment, but hepatic impairment appears to increase FF exposure. The Clinical Pharmacology team recommends no dosage adjustments for use in renal or hepatic impairment.

7.5.5 Drug-Drug Interactions

The drug development program for FF/VI included multiple drug-drug interaction studies. Trial HZA105548 evaluated the effects of co-administration with ketoconazole and DB113950 evaluated the effects of co-administration of VI with verapamil. Both of these trials were reviewed by the Clinical Pharmacology team (see Clinical Pharmacology Summary document). The team recommends no dose adjustments for co-administration with either ketoconazole or verapamil.

7.6 Additional Safety Evaluations

7.6.1 Human Reproduction and Pregnancy Data

No pregnancies occurred during the COPD development program.

A total of 36 pregnancies are reported in the Integrated Summary of Safety for the Asthma program. Of these, 29 had known outcomes at the time of the report. The report

contains details of 16 live births (one set of twins), nine spontaneous abortions, two stillbirths, and two elective terminations. There is no consistent imbalance noted in the reports of spontaneous abortion (placebo: 1; FF/VI 100/25: 2; FF/VI 200/25: 0; FF 100: 2; FF 200: 2; FF other doses: 3; FP all doses: 0; FP/salmeterol: 1) and stillbirths (one each in the FF 100 and FP 100). There is one report of a congenital abnormality, a patent ductus arteriosus and ventricular septal defect that occurred in the FF/VI 100/25 mcg dose group. Also, the neonate of one patient was delivered prematurely and died 5 days after delivery from respiratory distress syndrome (FF/VI 100/25 mcg group).

Information for two additional pregnancies in the asthma development program is contained in the 120-day safety update. A miscarriage was reported occurring prior to study drug being administered. The report of the second pregnancy is from an on-going trial. No outcome data was provided as the estimated due date (October 2012) exceeded the data lock for the safety update (August 31, 2012).

Given the background frequency of events expected in pregnancy it is not possible to establish a causal relationship between the reported pregnancy outcomes and FF/VI, FF, or VI in the asthma program.

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 for this combination drug product. Additionally, the mode of administration and low systemic bioavailability make abuse less likely. However, theoretically, abrupt stoppage of excessive dosages of FF/VI 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

GSK submitted its 120-day safety update on November 9, 2012 which includes all new clinical safety data from the COPD and asthma programs from February 16, 2012 through August 31, 2012. In general, the data from this safety update are similar to those seen within the initial NDA application. The studies included in the safety update are summarized in Table 65. Specific details from this safety update are included in relevant Sections above.

Table 65: Studies from 120-day safety update

Trial	Design	Duration	Population	Treatment Arms	N
HZA112777 Completed	R, DB, 2 per XO	2 14 day tx periods	Pediatric asthma (5-11)	FF/VI 100/25 FF 100	12 11
HZC114156 Completed	R, DB, PG	12 months	COPD (Japanese): FEV1<80%	FF/VI 100/25 FF/VI 200/25	60 127

HZA113989 completed	R, OL, PG	12 months	Asthma (Japanese)	FF/VI 100/25 FF/VI 200/25 FF 100	60 93 90
FFA115440 concluded	R, OL, 6-way XO,	Single dose	Healthy subjects	FF/VI 400/50 FF 400 single strip FF 400 dual strip	30
FFA115283 concluded	R, DB, PC, PG	12 week	Asthma	FF 50 Placebo	110 110
FFA115354* concluded	Retrospective pharmacogenentic study			FFA109684 FFA109685 FFA109687	622 615 598
Source: Source: 120-day Safety Update Appendix 7.1 submitted November 11, 2012 *results of the individual studies already included in the original NDA application in the asthma ISS					

8 Postmarket Experience

Breo Ellipta is not available for marketing in any country.

Statistical Review for the Pulmonary-Allergy Drug Advisory Committee Meeting

March 7, 2013

Fluticasone Furoate/Vilanterol Inhalation Powder
NDA 204275

Dose: Fluticasone Furoate 100 mg and Vilanterol 25 mg

Proposed indication: chronic obstructive pulmonary disease

Reviewer: Kiya Hamilton, PhD
Team Leader: Joan Buenconsejo, PhD
Division Director: Thomas Permutt, PhD

Department of Health & Human Services

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

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

GlaxoSmithKline (GSK) proposes fluticasone furoate/vilanterol (FF/VI) inhalation powder, administered once daily for the long-term 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. GSK is requesting approval for dosage strength of fluticasone furoate 100 mg (FF) and vilanterol 25 mg (VI). Neither of the components is approved for treatment of COPD.

The clinical program for FF/VI includes multiple dose-ranging and dose-interval studies for the FF and VI monocomponents and for the FF/VI combination, four key efficacy and safety studies, as well as four additional active comparator studies. The focus of the statistics review is on the four efficacy and safety studies. All four studies were designed to demonstrate the efficacy of FF/VI and its components in terms of improvement in airflow obstruction and symptomatic endpoints, including reduction in the annual rate of moderate and severe COPD exacerbations (studies HZC102871 and HZC102970 only).

Lung function endpoints (weighted mean FEV_1 (0–4 h) and change from baseline in trough FEV_1) were the primary endpoints in studies HZC112206 and HZC112207 and the primary endpoint in studies HZC102970 and HZC102871 was annual rate of moderate and severe exacerbations. Of note, within each of the four primary studies, in order to account for multiplicity across treatment comparisons and key endpoints, a specific step-down testing procedure was applied, whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for the previous tests in the hierarchy.

Compared to placebo, both VI 25 and all dosage strengths of FF/VI showed efficacy with respect to the weighted mean FEV_1 (0–4 h) and change from baseline in trough FEV_1 (studies HZC112206 and HZC112207). These studies also demonstrated the contribution of VI to the FF/VI combination at all dosage strengths, based on the difference in weighted mean FEV_1 (0–4 h). However, neither study demonstrated the contribution of FF to the FF/VI combination at all dosage strengths based on trough FEV_1. Change from baseline in trough FEV_1 for VI 25 was 100 mL compared to 150 mL for FF/VI 100/25 and about 140 mL for FF/VI 200/25. Therefore, for the proposed dose of FF/VI 100/25, the difference when compared to VI 25 was about 50 mL (95% CI -6, 102). Since the confidence interval includes zero, this implies that the direction of the difference, if any, is not known with much confidence.

In both studies, the higher dose FF/VI combination did not have a larger effect on the primary endpoints (weighted mean FEV_1 or trough FEV_1) compared to the lower dose FF/VI combination.

Only one of the two exacerbation studies showed a statistically significant improvement for all FF/VI doses over VI 25 for annual rate of moderate and severe exacerbations. In study HCZ102970, the mean rate of moderate and severe exacerbation in the VI 25 group is about one

exacerbation per year. For the proposed dose of FF/VI 100/25, the rate of moderate and severe exacerbation is reduced by about a quarter of an event in one year.

2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

GlaxoSmithKline (GSK) proposes fluticasone furoate/vilanterol inhalation powder (hereafter referred to as FF/VI), administered once daily for the long-term 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. It contains fluticasone furoate, an inhaled corticosteroid (ICS), hereafter referred to as FF, and vilanterol tridentate, a long acting beta$_2$-agonist (LABA), hereafter referred to as VI. GSK is requesting approval for dosage strength of fluticasone furoate 100 mg and vilanterol 25 mg. As neither of the components is approved for treatment of COPD, the clinical development program aimed to demonstrate the efficacy of FF and VI individually, their contribution to the combination, and the efficacy of the FF/VI combination.

2.1.2 History of Drug Development

GSK had several interactions with the Division of Pulmonary, Allergy, and Rheumatology Products regarding their FF/VI clinical development program for COPD (under IND 77,855). They also met with the Division to discuss their clinical development program for asthma, as well as their development program for each of the individual components (under IND 74,696 for the VI program and under IND 70,297 for the FF program). Pertinent parts of the statistical portion of the communications and interactions for the FF/VI COPD program are summarized herein.

The design and analysis of the phase 3 studies (Table 1) as well as the results from the Phase 2 dose-ranging and dose-interval studies were discussed at the End-of-Phase 2 meeting held on June 17, 2009. In this meeting the applicant discussed the primary endpoint, the annual rate of COPD moderate/severe exacerbations, for the two 52-week studies (HCZ102871 and HCZ102970, hereafter referred to as 2871 and 2970, respectively). The applicant stated that the rate would be calculated as the total number of moderate and/or severe exacerbations experienced by the patient during the treatment period and analyzed using a generalized linear model, assuming the Negative Binomial distribution, with the logarithm of time on treatment as an offset variable. While the Division informally agreed to the applicant's proposed primary analysis, we recommended that the applicant also analyze the exacerbation rates by Poisson regression as a sensitivity analysis. The applicant also discussed the primary endpoints, namely the trough FEV_1 for comparisons pertaining to the evaluation of the FF and VI components and weighted mean (based on the AUC) FEV_1 over 0–4 hours for comparisons pertaining to the evaluation of the VI component, for the two 6-month studies (HCZ112206 and HZC112207, hereafter referred to as 2206 and 2207, respectively). The applicant stated that for each of these endpoints, change from baseline would be analyzed using mixed models repeated measures (MMRM), with an unstructured variance-covariance matrix. Visit would be fitted as a categorical variable and a treatment by visit interaction term would be fitted to allow estimates of

treatment effect at each visit separately. While the Division informally agreed to the applicant's proposed approach, we also recommended that the applicant conduct sensitivity analyses using other missing data imputation methods and other covariance matrix structures. The applicant also proposed a hierarchy of statistical tests across the primary and pre-defined secondary endpoints in order to control for multiplicity. The Division at that time responded

> When there are multiple studies available and each study has multiple doses, the efficacy evidence will be evaluated collectively from the multiple studies and multiple doses. The error rate of approving an ineffective drug will be controlled if the dose- response relationship is reasonable and results across studies are consistent. The proposed hierarchical testing procedure protects against type I error in a rigid way and may lead to irrational conclusion when the dose- response was guessed incorrectly. In addition, this procedure does not add any value in the selection of the optimal doses, as the optimal doses should be selected based on the effect size, safety concerns, and risk/benefit ratio.

In the discussion that followed, the applicant agreed that the closed testing procedure protects Type I error in a rigid way and may lead to an irrational conclusion. However, the applicant still would like to use the procedure. The Division agreed the procedure was acceptable and recommended that the applicant not include the comparison between FF versus placebo in the testing procedure and to include the comparison between the FF/VI versus VI for trough FEV_1 in order to evaluate the contribution of FF. While the evidence of efficacy is evaluated collectively from the multiple studies, we agree with the applicant that a strong control of type 1 error should be in place for each individual studies.

A Type B pre-NDA meeting was held on July 13, 2011, to discuss the applicant's data to support the use of the FF/VI inhalation powder in the treatment of COPD and Asthma. The Division raised concerns regarding the lack of robust results to support the proposed bronchodilation indication and satisfy the Combination Rule for COPD population. Based on the preliminary review of the data from studies 2206 and 2207 at that time, only the lowest combination dose FF/VI 50/25 mcg showed a statistically significant benefit in terms of trough FEV_1 over VI 25 and there does not appear to be a replicated comparison of FF/VI 50/25 to placebo in the clinical program. Furthermore, trough FEV_1 data for FF/VI 100/25 and FF/VI 200/25 compared to VI were not supportive. The Division noted that the COPD exacerbation studies (2871 and 2970) may provide efficacy support for the addition of FF to VI, but positive exacerbation results may be problematic in the context of the negative lung function results. There was also a discussion of the proposed statistical methodology for examining subgroups as outlined in the summary Document Analysis Plans for the ISE (submitted on March 11, 2011 with serial No. 0291) and for the ISS (submitted on March 24, 2011 with serial No. 0296) for COPD in IND 77,855. The Division informally agreed that their approach was reasonable and noted that generally the results from individual studies to support any claims in the label are used.

> Pooled analyses are not usually very helpful in this regard with the exception of required analyses by age, sex and race. Additional analyses may be performed using pooled data; however, little weight will be given to the results from these analyses.

2.1.3 Specific Studies Reviewed

The clinical program for FF/VI includes multiple studies for the FF and VI monocomponents and for the FF/VI combination. The applicant submitted data from 12 dose-ranging and dose-interval studies for the FF and VI monocomponents and for the FF/VI combination, data from four key efficacy and safety studies, as well as data from four additional active comparator studies.

The focus of the statistics review is on the four key efficacy and safety studies (Table **1**). All four studies were phase 3, randomized, double-blind, parallel-group, multi-center studies in male and female patients at least 40 years of age at screening. The review will also include results from the active-comparator studies, except for study 3107 where the dose of the active comparator is not approved in the US for COPD (Table 2). Review of the dose-ranging and dose-interval studies can be found in the Clinical Review.

Table 1: Study Design for the Four Efficacy Studies

	Phase and Design	Length of the Study	Treatment Arms	Number of Patients per Arm	Study Population	Primary Efficacy Endpoints	% in US Sites
HZC112206	Phase 3, randomized, double-blind, parallel-group, multi-center	RI: 2 weeks TP: 24 weeks FU: 1 week	FF/VI 50/25 mcg FF/VI 100/25 mcg FF/VI 100 mcg VI 25 mcg Placebo	206 206 206 205 207	Moderate/severe COPD	Weighted mean Clinic Visit FEV_1 0–4 hours on Day 168 Change from baseline in Clinic Visit trough FEV_1 on Day 169	39%
HZC112207	Phase 3, randomized, double-blind, parallel-group, multi-center	RI: 2 weeks TP: 24 weeks FU: 1 week	FF/VI 100/25 mcg FF/VI 200/25 mcg FF 100 mcg FF 200 mcg VI 25 mcg Placebo	204 205 204 204 204 205	Moderate/severe COPD	Weighted mean Clinic Visit FEV_1 0–4 hours on Day 168 Change from baseline in Clinic Visit trough FEV_1 on Day 169	25%
HZC102871	Phase 3, randomized, double-blind, parallel-group, multi-center	RI: 4 weeks TP: 52 weeks FU: 1 week	FF/VI 50/25 mcg FF/VI 100/25 mcg FF/VI 200/25 mcg VI 25 mcg	408 403 402 406	Moderate/severe COPD	Annual rate of moderate and severe exacerbations	33%
HZC102970	Phase 3, randomized, double-blind, parallel-group, multi-center	RI: 4 weeks TP: 52 weeks FU: 1 week	FF/VI 50/25 mcg FF/VI 100/25 mcg FF/VI 200/25 mcg VI 25 mcg	412 403 409 409	Moderate/severe COPD	Annual rate of moderate and severe exacerbations	36%

- RI: Run-in period, TP: Treatment period, FU: Follow-up

Table 2 Study Design for the Active Comparator Studies

	Phase and Design	Length of the Study	Treatment Arms	Number of Patients per Arm	Study Population	Primary Efficacy Endpoints	% in US Sites
HZC112352	Phase 3b, randomized, double-blind, double-dummy, parallel-group, multi-center	RI: 2 weeks TP: 12 weeks FU: 1 week	FF/VI 100/25 mcg FP/salmeterol 250/50 mcg	259 252	COPD	Change from baseline trough in 24–hour weighted mean serial FEV_1 on Day 84	29%
HZC113109	Phase 3b, randomized, double-blind, double-dummy, parallel-group, multi-center	RI: 2 weeks TP: 12 weeks FU: 1 week	FF/VI 100/25 mcg FP/salmeterol 250/50 mcg	261 260	COPD	Change from baseline trough in 24–hour weighted mean serial FEV_1 on Day 84	28%
HZC113107	Phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center	RI: 2 weeks TP: 12 weeks FU: 1 week	FF/VI 100/25 mcg FP/salmeterol 500/50 mcg	266 262	COPD	Change from baseline trough in 24–hour weighted mean serial FEV_1 on Day 84	0%
HZA113091	Phase 3, randomized, double-blind, double-dummy, parallel-group, multi-center	RI: 4 weeks TP: 24 weeks FU: 1 week	FF/VI 100/25 mcg FP/salmeterol 250/50 mcg	403 403	Persistent bronchial asthma	Weighted mean for 24–hour serial FEV1 at the end of the 24–week treatment period	30%

- RI: Run-in period, TP: Treatment period, FU: Follow-up

2.2 Data Sources

NDA 204-275 was submitted on July 12, 2012. The study reports including protocols, statistical analysis plan, and all referenced literature were submitted by the Applicant to the Agency.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data are acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary efficacy endpoint analyses for each clinical study submitted. I was able to verify the randomization of the treatment assignments.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The summary of the study designs and endpoints for the four key efficacy studies are given in Table **1**. All four studies were Phase 3, randomized, double-blind, parallel-group, multi-center studies in male and female patients at least 40 years of age at screening (Visit 1). The design and efficacy endpoints are explained in detail in the following paragraphs.

Studies 2206 and 2207 were designed similarly. Both studies consisted of 24 weeks of treatment and were designed to assess the efficacy and safety of FF/VI when administered once daily via the novel dry powder inhaler in patients with COPD. Study 2206 studied the dosage strengths of FF/VI 50/25 mcg and 100/25 mcg, FF 100 mcg, VI 25 mcg and placebo. Study 2207 studied the dosage strengths FF/VI 100/25 mcg, 200/25 mcg, FF 100 mcg, FF 200 mcg, VI 25 mcg and placebo. Studies 2871 and 2970 were designed similarly. These two studies were designed to evaluate the effects of once daily dosing in the morning with dosage strengths FF/VI (50/25, 100/25 and 200/25 mcg) versus one dosage strength of VI (25 mcg) in patients with COPD. For each of the four studies, following the run-in period, patients were randomized into treatment arms with stratification on smoking status (current smoker or previous smoker).

The primary endpoints for both studies 2206 and 2207 were weighted mean clinic visit FEV_1 0–4 hours post-dose on treatment day 168 (Visit 11) and change from baseline in clinic visit trough (pre-bronchodilator and pre-dose) FEV_1, on treatment day 169 (Visit 12). Trough FEV_1 on treatment day 169 was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on treatment day 168, measured at visit 12. If one of the two paired assessments was missing then trough FEV_1 was defined as the single 23 or 24 hour assessment. For inclusion in the calculation the 23- and 24-hour values must have been pre- the next day's dose.

Baseline FEV_1 was defined as the mean of the two assessments made 30 and 5 minutes pre-dose on Treatment Day 1. The -30 and 0 minutes pre-dose measurements must have had time of assessments less than or equal to the time of Day 1 dosing to be included in the baseline

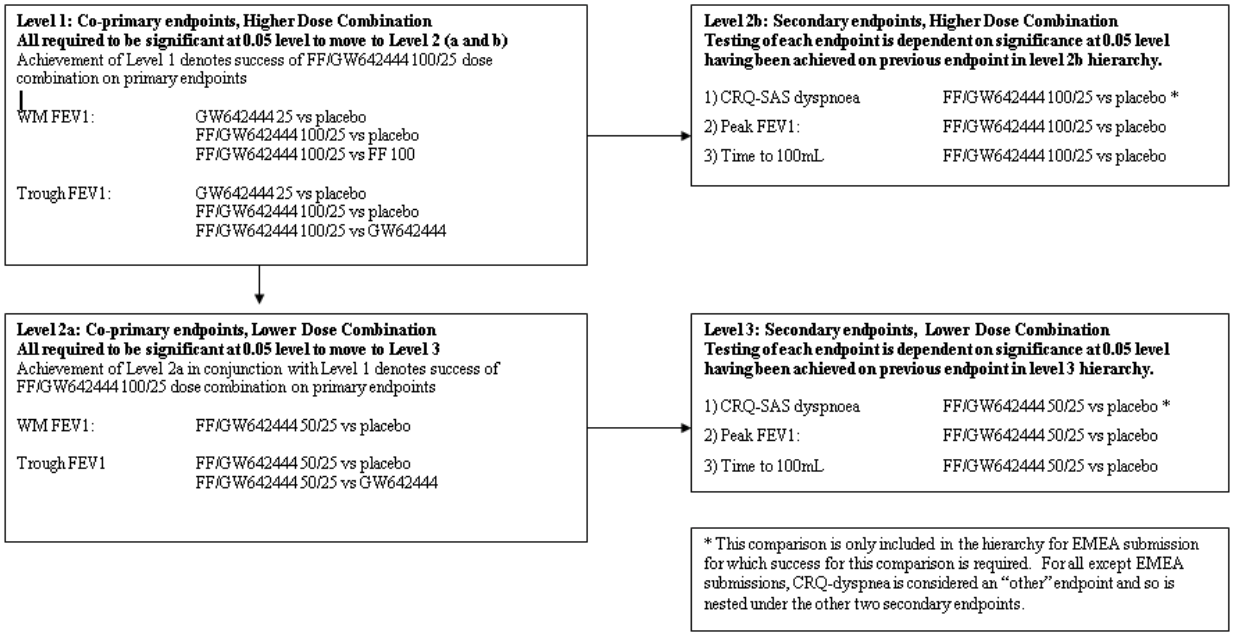
calculation; measurements after the time of Day 1 dosing were set to missing. If one of these two assessments was missing then baseline was defined as the single pre-dose FEV_1 value on Day 1. If both were missing then baseline was missing.

The weighted mean clinic FEV_1 was used to evaluate the contribution of VI and the trough FEV_1 was used to evaluate the contribution of FF in the intent-to-treat (ITT) population. The ITT population was defined as all patients who were randomized to and received at least one dose of randomized double-blind study medication in the treatment period. The secondary endpoints for studies 2206 and 2207 were peak FEV_1 on treatment day 1 and time to onset (increase of 100 mL above baseline in FEV_1) on treatment day 1 in the ITT population.

The primary endpoint in both studies 2871 and 2970 was the annual rate of moderate and severe exacerbations. The secondary endpoints for both studies were time to first moderate and severe exacerbation, annual rate of exacerbations requiring systemic/oral corticosteroids, and change from baseline in trough FEV_1 at visit 11. COPD exacerbation was defined as an acute worsening symptom of COPD requiring the use of any treatment other than study medication or rescue albuterol/salbutamol. A moderate exacerbation was defined as worsening symptoms of COPD that required treatment with oral corticosteroids and/or antibiotics. A severe exacerbation was defined as worsening symptoms of COPD that required treatment with in-patient hospitalization. Albuterol/salbutamol was used as rescue medication.

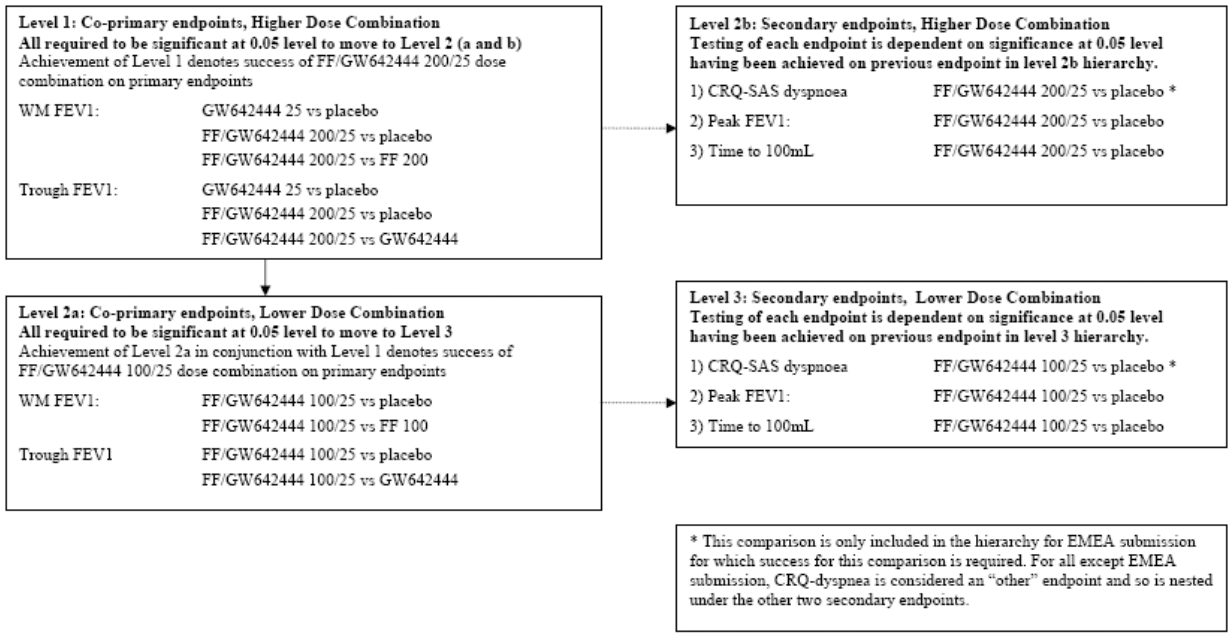
There was a strong control of the Type 1 error for the primary endpoints. Studies 2206 and 2207 used a step-down procedure to account for multiplicity across treatment comparisons and key endpoints (Figure 1 and Figure 2).

Figure 1: Statistical Testing Strategy Study 2206



Source: Clinical Study Report-Protocol Number HZC112206 Attachment 2, page 2043

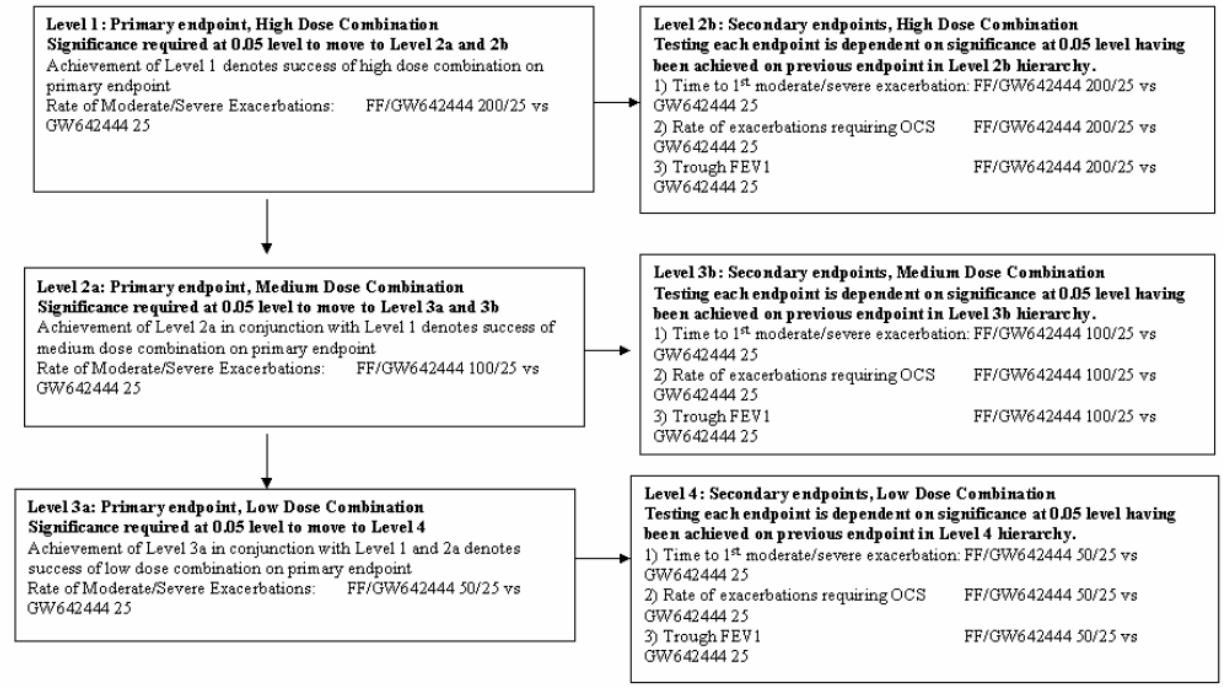
Figure 2: Statistical Testing Strategy Study 2207



Source: Clinical Study Report-Protocol Number HZC112207 Attachment 1, page 2029

A step-down testing approach (Figure 3) was used to account for multiplicity across treatment comparisons and key endpoints in both studies 2871 and 2970. Using this approach the inference for the primary efficacy endpoint for the FF/VI 100/25 combination dose versus VI 25 was dependent upon statistical significance at the 5% level having first been achieved for the primary efficacy endpoints for the FF/VI 200/25 versus VI 25. For a given FF/VI combination dose, the secondary endpoints were nested under the primary endpoint.

Figure 3: Statistical Testing Strategy Studies 2871 and 2970



Source: Protocol Amendment Protocol-Protocol Number HZC102871 Figure 1, page 64 and Clinical Protocol-Protocol Number HZC102970 Figure 1, page 63

The summary of the study designs and endpoints for the four active-comparator studies are given in Table 2. Studies 2352, 3109 and 3107 were designed similarly. All three studies consisted of 12 weeks of treatment and were designed to assess the efficacy and safety of FF/VI inhalation powder administered once daily in the morning versus FP/salmeterol inhalation powder administered twice daily on lung function in subjects with COPD. Studies 2352 and 3109 studied the dosage strengths of FF/VI 100/25 mcg and FP/salmeterol 250/50 mcg. Study 3107 studied the dosage strengthens FF/VI 100/25 mcg and FP/salmeterol 500/50 mcg. Because the dose of the active comparator FP/salmeterol 500/50 mcg is unapproved, the results from this study are not included in the review. Study 3091 was designed to evaluate the efficacy and safety of once daily in the evening treatment with FF/VI 100/25 mcg compared with twice daily FP/salmeterol 250/50 mcg (morning and evening) on lung function in subjects with persistent bronchial asthma over a 24-week treatment period. For each of the COPD studies (2352, 3107 and 3109), following the run-in period, patients were randomized into treatment arms with stratification on the subject's reversibility (reversible or non-reversible) to albuterol (salbutamol).

The primary endpoint for studies 2352, 3107 and 3109 was change from baseline trough in 24–hour weighted mean serial FEV_1 on Day 84. The weighted mean was calculated from the pre-dose FEV_1 and post-dose FEV_1 measurements at 5, 15, 30 and 60 minutes and 2, 4, 6, 8, 12, 13, 14, 16, 20 and 24 hours on treatment Day 84. Baseline trough FEV_1 was the mean of the two assessments made 30 and 5 minutes pre-dose on treatment Day 1. The primary endpoint for study 3091 was weighted mean for 24 hour serial FEV_1, calculated from serial spirometry over 0–24 hours at the end of 168-day double-blind treatment period. The 24 hour serial FEV_1 included a pre-dose assessment within 5 minutes prior to dosing and post-dose assessments after 5, 15 and 30 minutes and 1, 2, 3, 4, 11, 12, 12.5, 13, 14, 16, 20, 23 and 24 hours.

3.2.2 Statistical Methodologies

For studies 2206 and 2207 the primary analyses for the primary endpoints, 0–4 hours post-dose weighted mean FEV_1 and trough FEV_1, were analyzed using mixed model repeated measures (MMRM) in the ITT population. The model covariates were baseline FEV_1, smoking status (stratum), Day (1, 14, 56, 84 and 168), center grouping, treatment, Day by baseline interaction and Day by treatment interaction. Additional analyses assessed whether the effect of the active treatment groups were modified by smoking status at screening, center grouping or baseline FEV_1. This was achieved by fitting separate repeated measures models identical to the primary analysis model but also including additional terms for the treatment by smoking status interaction, treatment by center grouping and treatment by baseline FEV_1 interaction, respectively. An assessment of whether the effect of the active treatment groups were modified by reversibility, percent predicted GOLD categories, and cardiovascular (CV) history/risk factors were also conducted by fitting separate repeated measures models, identical to the primary analysis model but also included additional terms for reversibility and the reversibility by treatment interaction, percent predicted and the percent predicted by treatment interaction, cardiovascular history/risk factors and the cardiovascular history/risk factors by treatment interaction respectively. If the interactions from any of these analyses were significant at the 10% level, further investigation and characterization of the interactions was undertaken. The applicant defined reversibility as an increase in FEV_1 of ≥12% and ≥200 mL following administration of albuterol/salbutamol. The applicant defined percent predicted GOLD categories as:

I: $FEV_1 \geq 80$ % predicted
II: 50 % ≤ $FEV_1 < 80$ % predicted
III: 30 % ≤ $FEV_1 < 50$ % predicted
IV: $FEV_1 <30$ % predicted

The CV history/risk factors were defined as any patient with at least one of the following current or past medical conditions at screening:

- Coronary Artery Disease
- Myocardial Infarction
- Arrhythmia

- Congestive Heart Failure
- Hypertension
- Cerebrovascular Accident
- Diabetes Mellitus
- Hypercholesterolemia.

The secondary endpoint, peak FEV_1 on treatment day1, for studies 2206 and 2207 was analyzed using an Analysis of Covariance (ANCOVA) model. The covariates included in this model were baseline FEV_1, smoking status, center grouping and treatment. The secondary endpoint, time to ≥100 mL increase from baseline in FEV_1, was analyzed using the log-rank test, stratified for smoking status for each of the treatment comparisons. Actual times of FEV_1 results were used. A Kaplan-Meier plot showing the survival curves for all treatment groups was produced. Median time to ≥100 mL increase from baseline in FEV_1 (taken from the Kaplan-Meier analysis) was also presented.

For studies 2871 and 2970 the primary endpoint, annual rate of moderate and severe exacerbations, was analyzed using a general linear model assuming the negative binomial distribution in the ITT population. The response variable was the number of recorded, on-treatment, moderate and severe exacerbations experienced per patient. The explanatory variables consisted of treatment group, smoking status at screening (stratification variable), baseline disease severity (as percent predicted FEV_1) and center grouping. The model also included the logarithm of time on treatment per patient (derived from exposure start and stop) as an offset variable. The same model was also used assuming a Poisson regression model on the ITT population. Subgroup analyses were conducted to explore the effect of treatment by covariate interactions. There were three models fitted for both the Negative Binomial and the Poisson regression models in the ITT population: (i) with the addition of an interaction term for treatment by smoking status; (ii) with the addition of an interaction term for treatment by center grouping; and (iii) with the addition of an interaction term for treatment by percent predicted FEV_1. Two additional models were fitted to investigate the effect of treatment by covariate interactions: (iv) with the addition of a covariate of CV history/risk factors and an interaction term for treatment by CV history/risk factors, and (v) with the addition of a covariate of reversibility (yes/no) and an interaction term for treatment by reversibility.

The secondary endpoint, time to first moderate or severe exacerbation, in studies 2871 and 2970 was analyzed using a Cox proportional hazard model, with the exact method for handling ties in times of first exacerbation in the ITT population. The covariates included in the model were treatment group, smoking status at screening, baseline disease severity (percent predicted FEV_1) and center grouping. Annual rate of exacerbations requiring systemic/oral corticosteroids was analyzed using a generalized linear model assuming a negative binomial distribution. The response variable was the annual rate of exacerbations requiring systemic/oral corticosteroids for each patient. The explanatory variables were treatment group, smoking status at screening, baseline disease severity and center grouping. The model also included the logarithm of time on treatment per patient (derived from exposure start and stop) as an offset variable. The secondary endpoint, trough FEV_1 at visit 11 (week 52), was analyzed using mixed–models repeated–measures with a repeated effect of visit within each patient and an unstructured covariance matrix. The response variable was change from baseline in trough FEV_1 at visits 3 to 11 with

explanatory variables: treatment group, smoking status at screening (stratum variable), visit by baseline and visit by treatment interaction. Similar to the primary efficacy endpoint, additional models were fitted which explored the effect of treatment by covariate interactions: (i) with the addition of an interaction term for treatment by smoking status; (ii) with the addition of an interaction term for treatment by center grouping; and (iii) with the addition of an interaction term for treatment by baseline FEV_1.

In studies 2206 and 2207, the applicant pre-specified four additional analyses to explore missing data for the primary endpoints in the ITT population. One of the sensitivity analyses conducted by the applicant was the last observation carried forward (LOCF) for both primary endpoints. If the data was missing for the endpoint then the last non-missing post-baseline value was imputed. The LOCF analysis was performed using an ANCOVA model with covariates baseline FEV_1, smoking status, center grouping, and treatment. The Division generally does not accept LOCF as an imputation strategy because this implies patients who discontinue treatment will have the same outcome over time. This may lead to a biased standard error estimates since we are ignoring inherent uncertainty in the imputed values. In addition, this approach may not be conservative in terms of the patient's imputed outcome. For example, if a patient discontinued due to adverse events but had a good FEV_1, we will then be imputing a good score when in fact this patient was not successfully treated.

The applicant also applied two multiple imputation approaches, which they referred to as missing at random (MAR) and copy differences from control (CDC), to show how different assumptions influence the results obtained in the primary analysis. The multiple imputation methods allowed post-discontinuation missing observations to be imputed by fitting a Bayesian multivariate normal model for the data (including the same covariates as for the primary MMRM analysis) within each treatment using a Markov Chain Monte Carlo approach and quasi-independent samples drawn from the posterior distributions for the parameters of the multivariate normal distribution for each arm. Joint distribution of the pre- and post-withdrawal data was constructed based on the applicant's pre-specified assumptions concerning the post-withdrawal data (i.e., MAR and CDC). Conditional distribution of post-withdrawal given pre-withdrawal data and also covariates values for the individual subjects was then constructed using the joint distribution. This approach allowed the creation of completed datasets.

The MAR approach is based on the means and variance-covariances structures using patients in the same treatment group as the withdrawn patient. The main difference is that this approach uses separate covariance parameter estimation for each arm and also separate regression parameters using baseline covariates within each arm. Since the MAR approach assumes missing at random mechanism, this is concerning given that we are assuming that the behavior of the post-withdrawal data can be predicted from the observed variables. Like LOCF, this approach may not be conservative given that patients who discontinued from treatment may have the worse post-withdrawal outcome (e.g., they may be the more severe population) than patients who continued treatment.

An alternative method is the CDC approach. This is based on the assumption that patients who withdrew from the treated group would have followed the same trend over time (difference in

mean value between time points) as those in the placebo group. According to the article provided by the applicant[1], a patient's mean profile in the treated group following withdrawal tracks that of the mean profile in the placebo group, but starting from the benefit already obtained. Post-withdrawal data in the placebo group are imputed under the MAR approach. Therefore, the placebo patients who withdrew are handled the same way as those who continued treatment. While this approach provided a specific assumption about the treated patients who withdrew from the study, it is unclear whether the assumption is suitable given that placebo patients who completed the trial may be more likely to be doing better than those placebo patients who discontinued. Furthermore, this approach may not account for patients who may have worse post-withdrawal outcomes (e.g. they may be the more severe population) that potentially decline over time compared to those who continued treatment.

To shed light on the nature and pattern of missing data, data for the 0–4 hours weighted mean FEV_1 and the trough FEV_1 endpoints were examined through cohorts of patients where the cohorts are defined based on the scheduled visits that were completed by each patient. The cohorts helped to show if there were any differences between the treatment groups in the mean values at each visit within and across cohorts. Such comparisons may be of use in speculating whether or not the MAR assumption is reasonable and whether the pre-specified primary and sensitivity analyses are adequate to address the missing data problem.

In studies 2871 and 2970, the exacerbation data was summarized in terms of recorded (i.e., not imputed) on-treatment exacerbations only and imputed year rates and counts of moderate and severe exacerbations. Supplementary analyses used imputed yearly rates and counts of moderate and severe exacerbations using a linear equation that accounted for the number of recorded on-treatment exacerbations and which quarter the exacerbation fell into (Table 3). The calculation of imputed exacerbation rates was based on treatment period intervals in order to avoid obtaining high imputed rates if a subject withdrew very early from the study after experiencing an exacerbation. Since treatment courses for moderate/severe exacerbations were to be ≤4 weeks when possible, imputed numbers of exacerbations for subjects who withdrew from the study were based on 4-week intervals of the treatment period.

Table 3: Exacerbation Quarters

Period	Period Start	Period End
Quarter 1	day 1	day 91
Quarter 2	day 92	day 182
Quarter 3	day 183	day 273
Quarter 4	day 274	day 364
N/A	day 365	N/A

Like the primary analysis, this approach assumes that there is no relationship between the response and the missing outcome i.e., the method assumes that the event rate after withdrawal from trial is the same as the event rate on study treatment. This is often not the case, particularly when the reason for missing data is treatment-related.

[1] Carpenter, Roger and Kenward. Analysis of Longitudinal Trials with Protocol Deviation: A Framework for Relevant, Accessible Assumptions, and Inference via Multiple Imputation

For studies 2352 and 3109 the primary analysis for the primary endpoint, change from baseline trough in 24–hour weighted mean serial FEV_1 on Day 84, was analyzed using an ANCOVA model with covariates baseline FEV_1, reversibility stratum, smoking status (at screening), country and treatment. For study 3091 the primary analysis for the primary endpoint, weighted mean serial FEV_1 over 0–24 hour post-dose at the end of the 24-week treatment (Day 168), was analyzed using an ANCOVA model with covariates baseline FEV_1, region, sex, age, and treatment group. All analyses were conducted on the ITT population.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

The summary of the patient disposition in studies 2206 and 2207 is given in Table 4 and Table 5 respectively and studies 2871 and 2970 are shown in Table 5. Study 2206 had about 30% of the patients withdraw from the study. Study 2207 had about 25% of the patients withdraw from the study. Note that the applicant assumed that approximately 27% of patients would withdraw before the end of the treatment period in studies 2206 and 2207. The primary reasons for discontinuation were adverse advent (AE) with 7% to 9% in the FF/VI groups and 7% to 12% in the VI group and lack of efficacy with 3% to 6% in the FF/VI groups, 6% to 10% in the placebo group, 5% to 7% in the VI groups and 2% to 9% in the FF group. For both studies, lack of efficacy was higher in the placebo groups compared to the other treatment groups. Protocol violations accounted for 1% to 3% overall for the discontinuations.

About 25% of the patients withdrew in study 2871 and about 27% of the patients withdrew in study 2970 (Table 6). The primary reasons for discontinuation was AE (7% overall in both studies) and withdrawal of consent (6% overall in both studies). Lack of efficacy accounted for 5% to 6% of the discontinuation. Lack of efficacy due to exacerbations accounted for 3% in both studies.

Table 4: Study 2206 Summary of Patient Disposition

	Number (%) of Patients				
	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25	Placebo
Randomized	206	205	206	206	207
Completed	145 (70)	142 (69)	147 (71)	151 (73)	138 (67)
ITT	206	205	206	206	207
PP	204	191	195	197	196
Discontinued	61 (30)	63 (31)	59 (29)	55 (27)	69 (33)
Adverse Event	23 (11)	24 (12)	17 (8)	14 (7)	15 (7)
Lack of Efficacy	18 (9)	15 (7)	12 (6)	12 (6)	20 (10)
Exacerbation	16 (8)	13 (6)	9 (4)	12 (6)	17 (8)
Protocol Deviation	4 (2)	2 (<1)	1 (<1)	4 (2)	3 (1)
Patient Reached Protocol-defined Stopping Criteria	5 (2)	8 (4)	13 (6)	9 (4)	11 (5)
Study closed/terminated	0	0	0	0	0
Lost to Follow-up	0	2 (<1)	1 (<1)	3 (1)	4 (2)
Investigator discretion	2 (<1)	5 (2)	5 (2)	4 (2)	5 (2)
Patient Withdrew Consent	9 (4)	7 (3)	10 (5)	9 (4)	11 (5)

Source: Clinical Study Report-Protocol Number HZC112206 Table 6, page 72

Table 5: Study 2207 Summary of Patient Disposition

	Number (%) of Patients					
	FF 100	FF 200	VI 25	FF/VI 100/25	FF/VI 200/25	Placebo
Randomized	204	204	204	204	205	205
Completed	155 (76)	160 (79)	161 (79)	144 (71)	158 (77)	146 (71)
ITT	204	203	203	204	205	205
PP	193	190	191	193	194	198
Discontinued	49 (24)	43 (21)	42 (21)	60 (29)	47 (23)	59 (29)
Adverse Event	12 (6)	15 (7)	15 (7)	17 (8)	19 (9)	18 (9)
Lack of Efficacy	5 (2)	6 (3)	11 (5)	8 (4)	7 (3)	12 (6)
Exacerbation	2 (<1)	5 (2)	11 (5)	7 (3)	7 (3)	12 (6)
Protocol Deviation	7 (3)	2 (<1)	3 (1)	8 (4)	4 (2)	7(3)
Patient Reached Protocol-defined Stopping Criteria	12 (6)	7 (3)	7 (3)	15 (7)	12 (6)	7 (3)
Study closed/terminated	1 (<1)	0	0	0	1 (<1)	0
Lost to Follow-up	2 (<1)	0	0	2 (<1)	1 (<1)	3 (1)
Investigator discretion	1 (<1)	6 (3)	3 (1)	1 (<1)	1 (<1)	4 (2)
Patient Withdrew Consent	9 (4)	7 (3)	3 (1)	9 (4)	2 (<1)	8 (4)

Source: Clinical Study Report-Protocol Number HZC112207 Table 6, page 71

Table 6: Summary Patient Disposition Study 2871 and Study 2970

	Number (%) of Patients			
	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Study 2871				
Randomized	409	408	403	402
Completed	294 (72)	315 (77)	312 (77)	301 (75)
ITT	409	408	403	402
PP	390	393	381	381
Discontinued	115 (28)	93 (23)	91 (23)	101 (25)
Adverse Event	22 (5)	25 (6)	29 (7)	31 (8)
Withdrew Consent	34 (8)	18 (4)	17 (4)	22 (5)
Lack of Efficacy	24 (6)	16 (4)	11 (3)	18 (4)
Exacerbation	15 (4)	10 (2)	4 (<1)	13 (3)
Protocol Deviation	8 (2)	7 (2)	8 (2)	7 (2)
Patient Reached Protocol-defined Stopping Criteria	10 (2)	14 (3)	13 (3)	10 (2)
Study closed/terminated	2 (<1)	0	1 (<1)	0
Lost to Follow-up	11 (3)	7 (2)	6 (1)	5 (1)
Investigator discretion	4 (<1)	6 (1)	6 (1)	8 (2)
Study 2970				
Randomized	409	412	403	409
Completed	284 (69)	303 (74)	291 (72)	306 (75)
ITT	409	412	403	409
PP	382	391	379	386
Discontinued	125 (31)	109 (26)	112 (28)	103 (25)
Adverse Event	25 (6)	32 (8)	35 (9)	30 (7)
Withdrew Consent	30 (7)	22 (5)	25 (6)	25 (6)
Lack of Efficacy	35 (9)	14 (3)	16 (4)	14 (3)
Exacerbation	20 (5)	8 (2)	9 (2)	7 (2)
Protocol Deviation	7 (2)	11 (3)	9 (2)	8 (2)
Patient Reached Protocol-defined Stopping Criteria	11 (3)	13 (3)	12 (3)	9 (2)
Study closed/terminated	1 (<1)	1 (<1)	0	0
Lost to Follow-up	6 (1)	8 (2)	6 (1)	10 (2)
Investigator discretion	10 (2)	8 (2)	9 (2)	7 (2)

Source: Clinical Study Report-Protocol Number HZC102871 Table 4, page 55 and HZC10290 Table 4, page 54

The demographics and baseline characteristics in studies 2206 and 2207 are summarized in Table 18 and Table 19, respectively for the ITT population (see appendix). The patients' mean age was about 62 to 63 years in the two studies. Most of the patients were White (72% ~ 94%) and male (67% ~ 72%) in these two studies. The mean body mass index (BMI) of the patients was 26.1 kg/m^2 to 26.5 kg/m^2 which indicated that the patients were slightly overweight in both studies.

The demographics and baseline characteristics in studies 2871 and 2970 are summarized in Table 20 and Table 21, respectively for the ITT population (see appendix). The patients' mean age was about 63.6 to 63.7 years in these two studies. Most of the patients were White (82% ~ 88%) and male (59% ~ 55%) in these two studies. The BMI of the patients was 26.69 kg/m^2 to 27.05 kg/m^2 which indicated that the patients were slightly overweight in both studies.

Less than 11% of patients withdrew from the three active-comparator studies (7% in study 2352, 9% in 3109, and 11% in 3091). The reasons for discontinuation varies from withdraw of consent, protocol deviation, lack of efficacy, and adverse events, but generally they were well-balanced across treatment groups. For studies 2352 and 3109 the patients' mean age was about 61 to 63 years. Majority of the patients were White (81% ~ 97%) and male (64% ~ 82%) in these three studies. The BMI of the patients was 25.9 kg/m^2 to 27.5 kg/m^2 which indicated that the patients were slightly overweight in these studies. In the asthma study, study 3091, the patients are younger with a mean age of 43 years. Most of the patients were White (59%) and female (61%). The median height was 163 cm and the median weight was 70.5 kg.

3.2.4 Results and Conclusions

3.2.4.1 Lung Function Studies (Studies 2206 and 2207)

In both studies, the VI 25 treatment group showed a statistically significant improvement in the weighted mean FEV_1 compared to the placebo group, with a 103 mL improvement in study 2206 (Table 7) and a 185 mL improvement in study 2207 (Table 8).

In study 2206, the FF/VI 100/25 treatment group showed a statistically significant improvement over the placebo group (with a 173 mL improvement), as well as over the FF 100 treatment group (with a 120 mL improvement). This statistically significant improvement supports the demonstration of the benefit of FF/VI 100/25 over FF 100 on lung function in study 2206. In study 2207, the FF/VI 200/25 treatment group showed a statistically significant improvement over the placebo group with a 209 mL improvement, as well as over the FF 200 treatment group with a 168 mL improvement. This statistically significant improvement supports the demonstration of the benefit of FF/VI 200/25 over FF 200 to lung function, similar to study 2206 but in a different dosage. In both studies, the higher dose FF/VI combination did not have a larger effect on the weighted mean FEV_1 compared to the lower dose FF/VI combination.

In both studies, the results for trough FEV_1 also showed a statistically significant improvement for the VI 25 treatment group compared to the placebo group, with a 67 mL improvement in study 2206 and a 100 mL improvement in study 2207.

In study 2206, the FF/VI 100/25 treatment group showed a statistically significant improvement in trough FEV_1 over the placebo group but failed to show statistically significant improvement over the VI 25 group. The same was observed in study 2207 where FF/VI 200/25 treatment group also failed to show statistical significant improvement over VI 25. In both studies, a numerical improvement was observed comparing FF/VI to VI 25 (48 mL in study 2206 and 32 mL in study 2207). In both studies, the higher dose FF/VI combination did not have a larger effect on the trough FEV_1 compared to the lower dose FF/VI combination.

Because multiple endpoints and multiple arms were being evaluated in both studies, hierarchical order for testing the null hypotheses was pre-specified by the applicant (Figures 1 and 2) with the high dose combination tested first (level 1) before the low dose combination (level 2a) or the secondary endpoints (level 2b and level 3). In both studies, achievement of level 1 in the hierarchical step-down approach at the 5% significance level was not met since the FF/VI treatment group did not achieve statistical significance over the VI 25 treatment group for the primary endpoint trough FEV_1 at day 169. In the strictest sense of alpha spending, all the alpha has been spent at level 1. Therefore, the p-values reported by the applicant from their analyses of the lower dosages are nominal p-values (Tables 7 and 8).

Table 7: Study 2206 Primary Efficacy Results (ITT Population)

	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Placebo N=207
0–4 hrs Weighted Mean FEV_1 (L) at Day 168					
n[1]	206	205	205	206	207
LS Mean	1.29	1.34	1.43	1.41	1.24
LS Mean Δ	0.08	0.13	0.22	0.20	0.03
Drug vs Placebo					
Difference	0.053	0.103	0.192	0.173	
95% CI	0.003,0.104	0.052, 0.153	0.141,0.243	0.123, 0.224	
p-value	0.040*	<0.001	<0.001*	<0.001	
Drug vs FF 100					
Difference				0.120	
95% CI				0.07, 0.17	
p-value				<0.001	
Drug vs VI 25					
Difference			0.090	0.071	
95% CI			0.039,0.140	0.021,0.121	
p-value			<0.001*	0.006*	
Trough FEV_1 (L) at Day 169					
n[1]	202	202	204	206	205
LS Mean	1.28	1.32	1.38	1.36	1.25
LS Mean Δ	0.07	0.10	0.17	0.15	0.04
Drug vs Placebo					
Difference	0.033	0.067	0.129	0.115	
95% CI	-0.022,0.088	0.012,0.121	0.074,0.184	0.06,0.17	
p-value	0.241*	0.017	<0.001*	<0.001	
Drug vs FF 100					
Difference				0.082	
95% CI				0.028,0.136	
p-value				0.003*	
Drug vs VI 25					
Difference			0.062	0.048	
95% CI			0.008,0.117	-0.006,0.102	
p-value			0.025*	**0.082**	

Source: Clinical Study Report-Protocol Number HZC112206 Table 19, page 91 and Table 21, page 96.
1 Number of patients with analyzable data for 1 or more time points
* Nominal p-values
Black font = Level 1 of the testing hierarchy, Red font = Level 2a of the testing hierarchy, Blue font = additional analyses

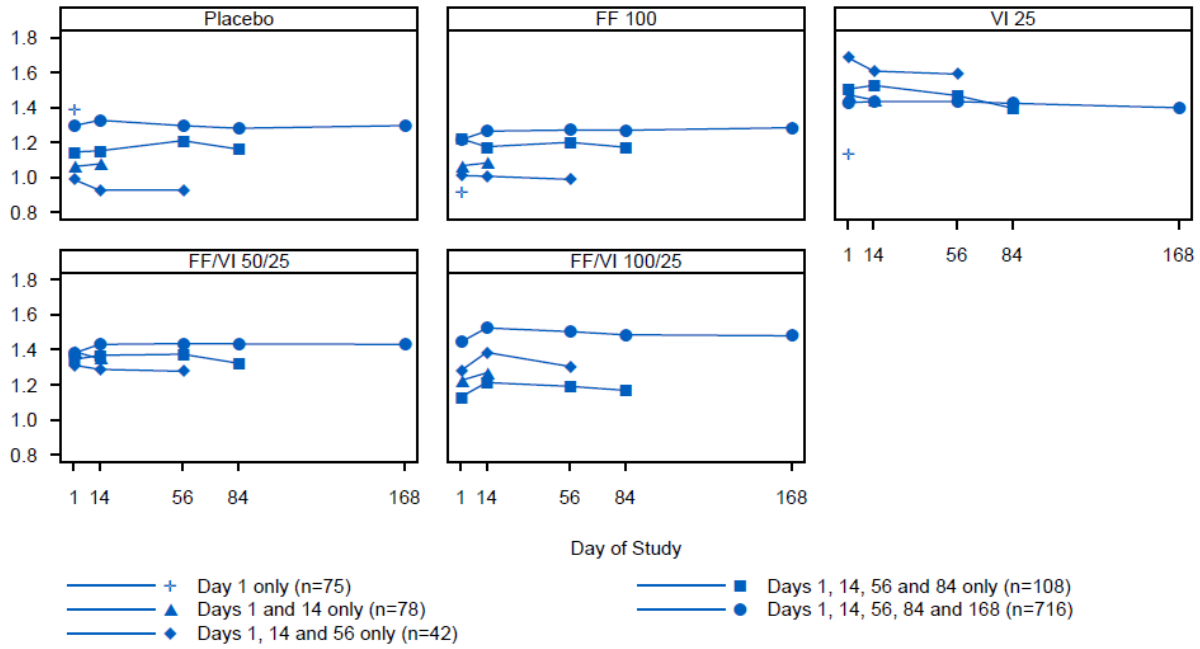
Table 8: Study 2207 Primary Efficacy Results (ITT Population)

	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N=205	Placebo N=205
0–4 hrs Weighted Mean FEV_1 (L) at Day 168						
n[1]	203	203	202	203	205	205
LS Mean	1.38	1.37	1.52	1.55	1.54	1.33
LS Mean Δ	0.03	0.03	0.17	0.20	0.20	-0.01
Drug vs Placebo						
Difference	0.046	0.041	0.185	0.214	0.209	
95% CI	-0.006,0.098	-0.011,0.093	0.133, 0.237	0.161,0.266	0.157, 0.261	
p-value	0.085*	0.123*	<0.001	<0.001	<0.001	
Drug vs FF 100						
Difference				0.168		
95% CI				0.116, 0.220		
p-value				<0.001		
Drug vs FF 200						
Difference					0.168	
95% CI					0.117, 0.219	
p-value					<0.001	
Drug vs VI 25						
Difference				0.029	0.024	
95% CI				-0.023,0.081	-0.027,0.075	
p-value				0.274*	0.357*	
Trough FEV_1 (L) at Day 169						
n[1]	202	202	202	200	204	202
LS Mean	1.39	1.36	1.45	1.49	1.48	1.35
LS Mean Δ	0.05	0.01	0.10	0.15	0.14	0.004
Drug vs Placebo						
Difference	0.044	0.008	0.100	0.144	0.131	
95% CI	-0.008,0.097	-0.044,0.060	0.048,0.151	0.091,0.197	0.08,0.18	
p-value	0.095*	0.756*	<0.001	<0.001*	<0.001	
Drug vs FF 100						
Difference				0.100		
95% CI				0.047,0.152		
p-value				<0.001*		
Drug vs FF 200						
Difference					0.123	
95% CI					0.072,0.174	
p-value					<0.001*	
Drug vs VI 25						
Difference				0.045	0.032	
95% CI				-0.008,0.097	-0.019,0.083	
p-value				**0.093***	**0.224**	

Source: Clinical Study Report-Protocol Number HZC112207 Table 19, page 89 and Table 21, page 95.
1. Number of patients with analyzable data for 1 or more time points
* Nominal p-values
Black font = Level 1 of the testing hierarchy, Red font = Level 2a of the testing hierarchy, Blue font = additional analyses

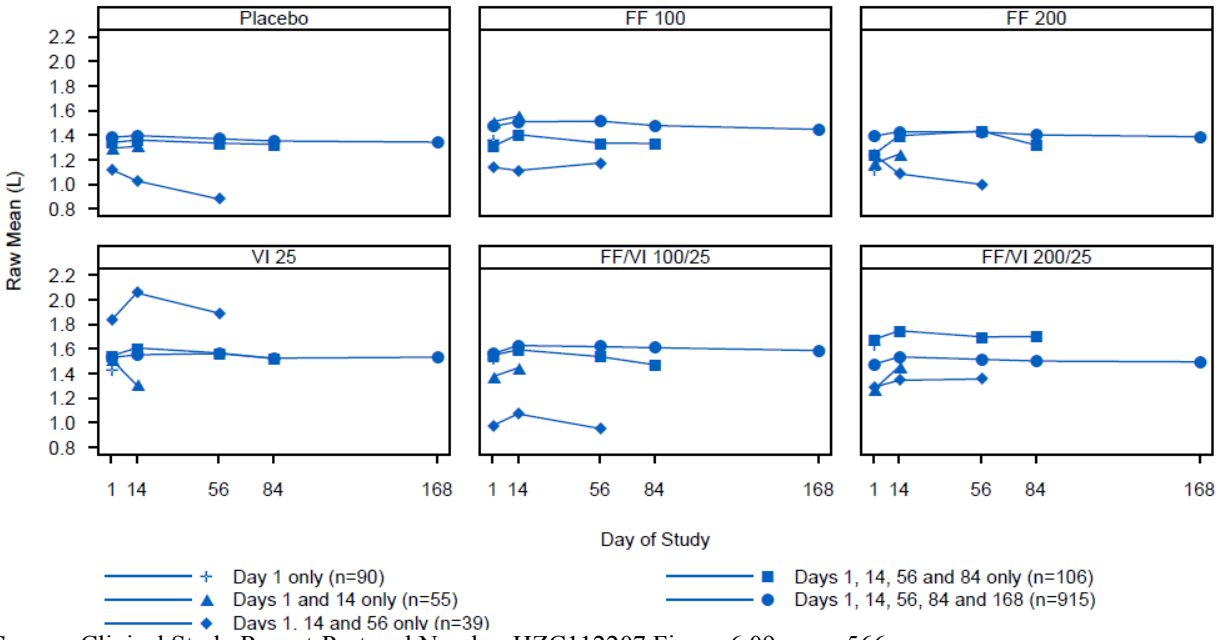
A large percentage of patients withdrew from studies 2206 (30%) and 2207 (25%). The primary reasons for the discontinuations were adverse events and lack of efficacy. The observed FEV_1 scores (0–4 hours weighted mean, Figure 4 and Figure 5, or trough, Figure 6 and Figure 7) for patients in the active arm appeared to be better than those in the placebo arm. Although cohorts who discontinued early appeared to have worse observed scores than those who discontinued later or those who completed the study, this is not as concerning because this happened in almost all treatment arms. The pre-specified primary analysis method and the sensitivity analyses have limitations since these approaches do not account for patients who may get worst post-withdrawal. Nonetheless, it is reassuring that the results of the LOCF, MAR and the CDC multiple imputations analyses (applying various missing data assumptions) conducted by the applicant were all consistent in magnitude and direction to the primary analysis (MMRM) and that the dropout rates and the reasons for discontinuations were well-balanced across the active treatment arms.

Figure 4: Study 2206- Raw Mean 0–4 hours Weighted Mean FEV_1 (L) at Each Visit by Cohort



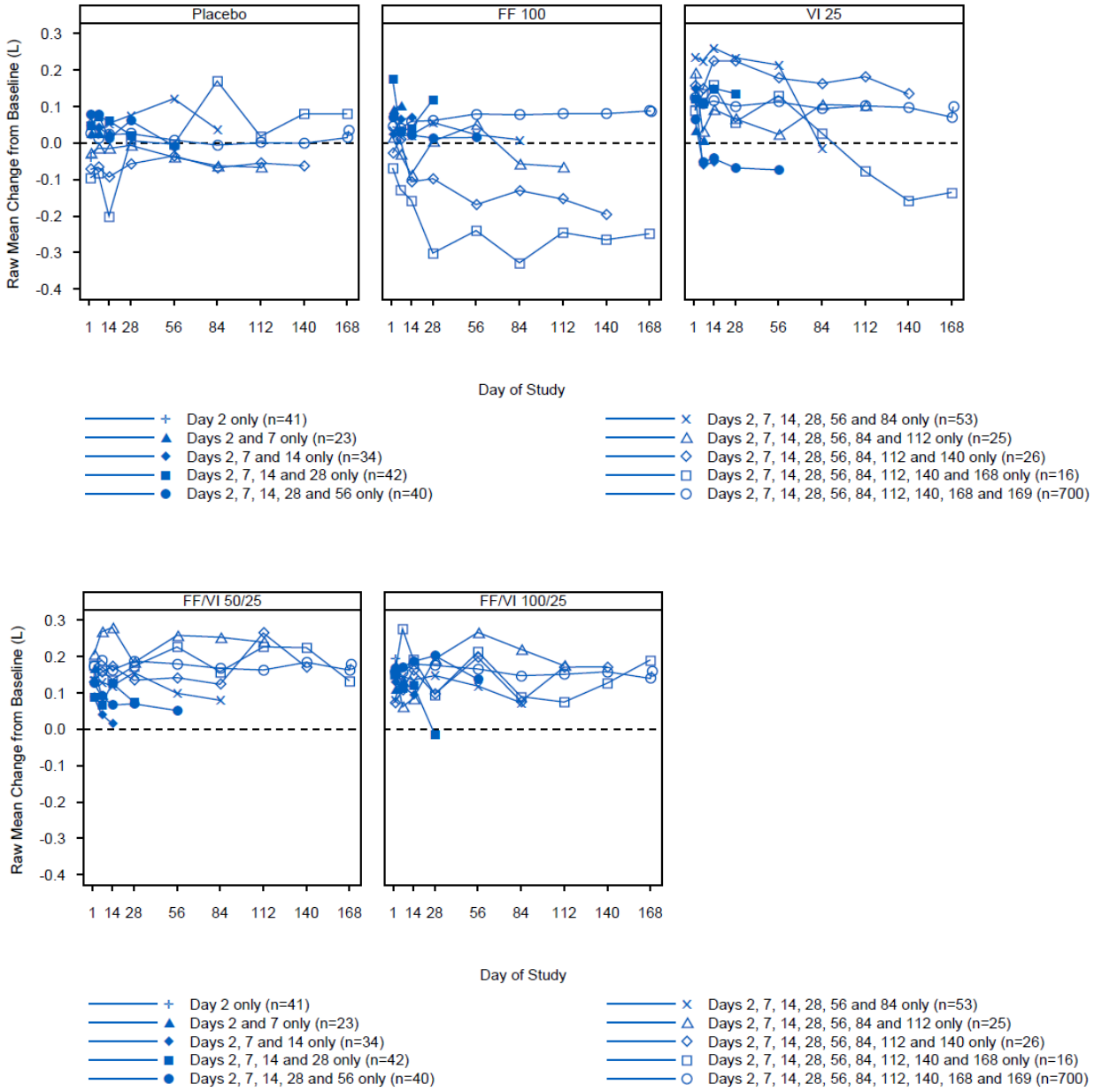
Source: Clinical Study Report-Protocol Number HZC112206 Figure 6.09, page 640

Figure 5: Study 2207- Raw Mean 0–4 hours Weighted Mean FEV_1 (L) at Each Visit by Cohort



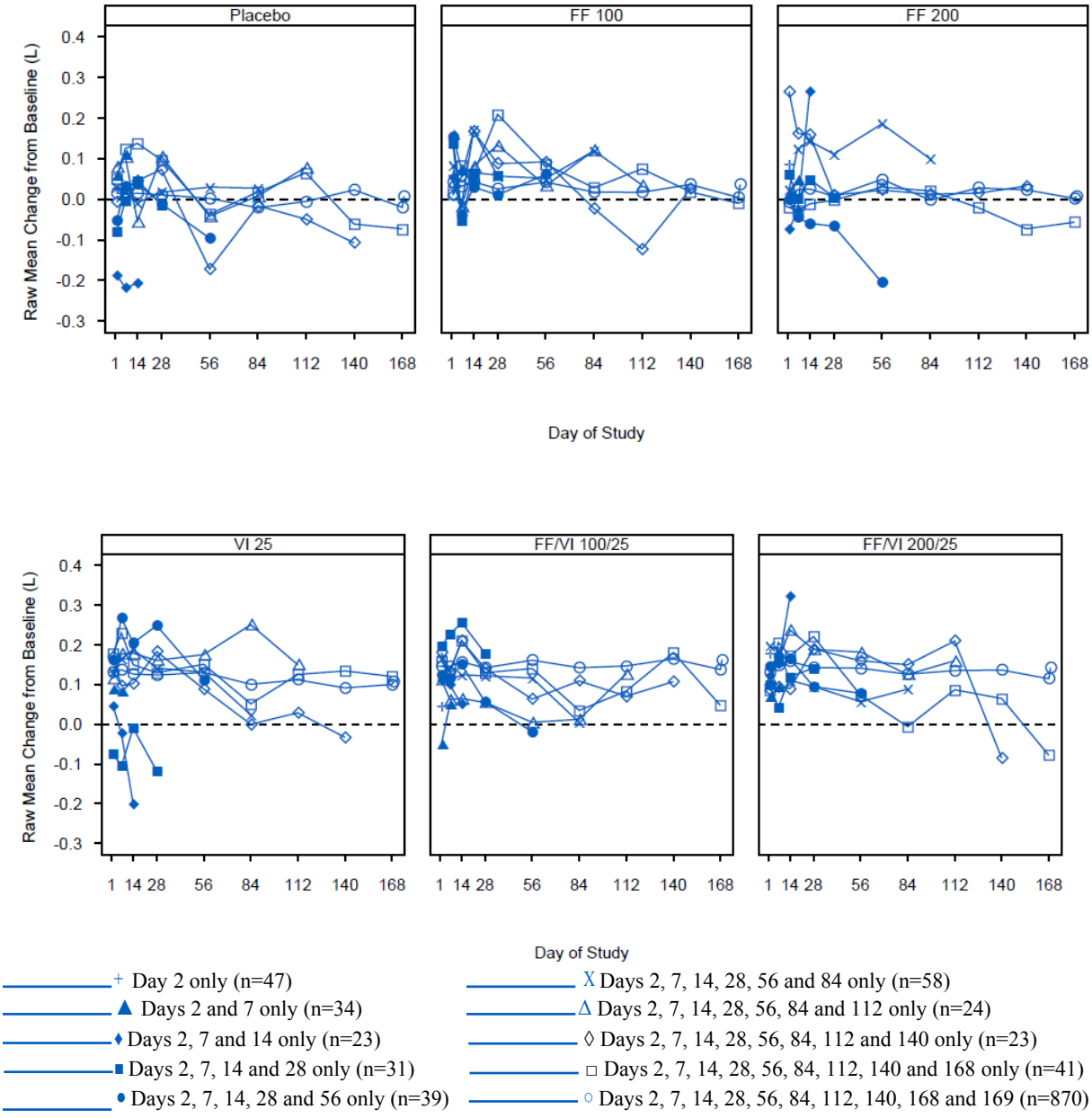
Source: Clinical Study Report-Protocol Number HZC112207 Figure 6.09, page 566

Figure 6: Study 2206-Raw Mean Change from Baseline in Trough FEV_1 (L) at Each Visit by Cohort



Source: Clinical Study Report-Protocol Number HZC112206 Figure 6.19, page 651

Figure 7: Study 2207-Raw Mean Change from Baseline in Trough FEV_1 (L) at Each Visit by Cohort



Source: Clinical Study Report-Protocol Number HZC112207 Figure 6.19, page 577

To complete the review, the results for the secondary endpoint, peak FEV_1, are shown in Table 9 and

Table 10 for studies 2206 and 2207, respectively. These results are described for descriptive purposes only and the p-values reported are nominal p-values. The results from both studies were consistent in that FF/VI combination with at least a 140 mL improvement from placebo in peak FEV_1.

Table 9: Study 2206 Peak FEV_1 at Day 1-ITT Population

	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25	Placebo
Randomized[1]	206	205	205	206	207
LS Mean	1.33	1.46	1.47	1.46	1.32
LS Mean Δ	0.12	0.25	0.25	0.25	0.11
Drug vs Placebo					
Difference	0.012	0.142	0.148	0.139	
95% CI	-0.015,0.039	0.114,0.169	0.120,0.175	0.112,0.166	
p-value*	0.393	<0.001	<0.001	<0.001	
Drug vs FF 100					
Difference				0.127	
95% CI				0.100,0.154	
p-value*				<0.001	
Drug vs VI 25					
Difference			0.006	-0.003	
95% CI			-0.022,0.033	-0.030,0.025	
p-value*			0.672	0.844	

Source: Clinical Study Report-Protocol Number HZC112207 Table 19, page 89.
* p-values are nominal

Table 10: Study 2207 Peak FEV_1 at Day 1-ITT Population

	FF 100 N=204	FF 200 N=203	VI 25 N=203	FF/VI 100/25 N=204	FF/VI 200/25 N=205	Placebo N=205
N[1]	203	202	201	203	205	204
LS Mean	1.49	1.47	1.61	1.61	1.60	1.46
LS Mean Δ	0.14	0.13	0.27	0.27	0.26	0.12
Drug vs Placebo						
Difference	0.024	0.007	0.147	0.152	0.141	
95% CI	-0.006,0.055	-0.023,0.037	0.117,0.177	0.122,0.182	0.111,0.171	
p-value*	0.111	0.635	<0.001	<0.001	<0.001	
Drug vs FF 100						
Difference				0.128		
95% CI				0.100,0.158		
p-value*				<0.001		
Drug vs FF 200						
Difference					0.134	
95% CI					0.104,0.164	
p-value*					<0.001	
Drug vs VI 25						
Difference				0.005	-0.006	
95% CI				-0.025,0.036	-0.036,0.024	
p-value*				0.725	0.699	

Source: Clinical Study Report-Protocol Number HZC112207 Table 25, page 103.
* all p-values are nominal

3.2.4.2 Exacerbation Studies (Studies 2871 and 2970)

Neither study 2871 nor study 2970 included a placebo group since it was not appropriate to include a placebo control arm for the duration of one year in patients with a history of exacerbations. Treatment with FF/VI at all strengths provided a statistically significant improvement over the VI 25 group in study 2970, but FF/VI 200/25 failed to show a statistically significant improvement over the VI 25 group in study 2871 (Table 11). In study 2871, there was a numeric improvement with FF/VI at all strengths with 13%, 34%, and 15% reduction in the annual rate of moderate and severe exacerbations for FF/VI 50/25, FF/VI 100/25 and FF/VI 200/25, respectively. For the FF/VI 100/25 group in both studies, the rate of moderate and severe exacerbation is reduced by about a quarter to a third of an event in one year. The results from the Poisson analysis were consistent in magnitude and direction with the Negative Binomial results in the ITT population.

Achievement of level 1 in the hierarchical step-down approach at the 5% significance level was not met in study 2871 since the FF/VI 200/25 treatment group did not achieve statistical significance over the VI 25 treatment group for the primary endpoint, annual rate of moderate and severe exacerbations (Figure 3). Therefore, the p-values reported by the applicant from their analyses of the lower dosages in study 2871 are nominal p-values (Table 11).

Table 11: Study 2871 and Study 2970 analysis of Moderate and Severe Exacerbations Negative Binomial Model-ITT Population

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Study 2871				
N	409	408	403	402
n	407	404	401	398
LS Mean Annual Rate	1.05	0.92	0.70	0.90
Column vs. VI 25				
Ratio		0.87	0.66	0.85
95% CI		0.72, 1.06	0.54, 0.81	0.70, 1.04
p-value		0.181*	<0.001*	0.109
Percent Reduction		13	34	15
95% CI		-6, 28	19, 46	-4, 30
Study 2970				
N	409	412	403	409
n	402	411	401	407
LS Mean Annual Rate	1.14	0.92	0.90	0.79
Column vs. VI 25				
Ratio		0.81	0.79	0.69
95% CI		0.66, 0.99	0.64, 0.97	0.56, 0.85
p-value		0.040	0.024	<0.001
Percent Reduction		19	21	31
95% CI		1, 34	3, 36	15, 44

Source: Clinical Study Report-Protocol Number HZC102871 Table 13, page 67 and Protocol Number HZC102970 Table 13, page 66.
* nominal p-values

Like the lung function studies, a large proportion of patients withdrew from studies 2871 (25%) and 2970 (28%). The dropout rate was slightly higher in the VI 25 group but the reasons for discontinuation were generally well-balanced. The applicant attempted to address the missing data problem by imputing the annual rates and counts of moderate and severe exacerbations using a linear equation that accounted for the number of recorded on-treatment exacerbations and which quarter the exacerbation occurred. Like the primary analysis, this approach assumes that there is no relationship between the response and the missing outcome i.e., the method assumes that the event rate after withdrawal from trial is the same as the event rate on study treatment. This is often not the case particularly when the reason for missing data is treatment-related. In fact, it is difficult to predict the number of exacerbations one may have post-withdrawal except to collect the actual exacerbation data after patient withdraws from the study. Therefore, the applicant's reported rates are crude estimates based on the assumption that the same event rates occur between pre- and post-withdrawal.

Examining the exacerbation data in other ways can be informative. One such analysis is the time to first moderate or severe exacerbation. Compared to the primary endpoint (i.e., annual rate of moderate and severe exacerbation), the number of missing data can be smaller since many patients may have had their first exacerbation prior to withdrawal. In study 2871, of the 25% of patients who withdrew from the study or treatment, about 54% had missing exacerbation data.

Therefore, only 14% of the ITT population had missing exacerbation data. In study 2970, of the 27% of patients who withdrew from study or treatment, about 59% had missing exacerbation data. Therefore, only 16% of the ITT population had missing exacerbation data. Assigning patients with missing data as having an exacerbation at the time of withdrawal, the results were consistent with the Applicant's findings (Table 12).

Table 12: Study 2871 and Study 2970 Analysis of Time to First Moderate or Severe On-treatment Exacerbations ITT Population

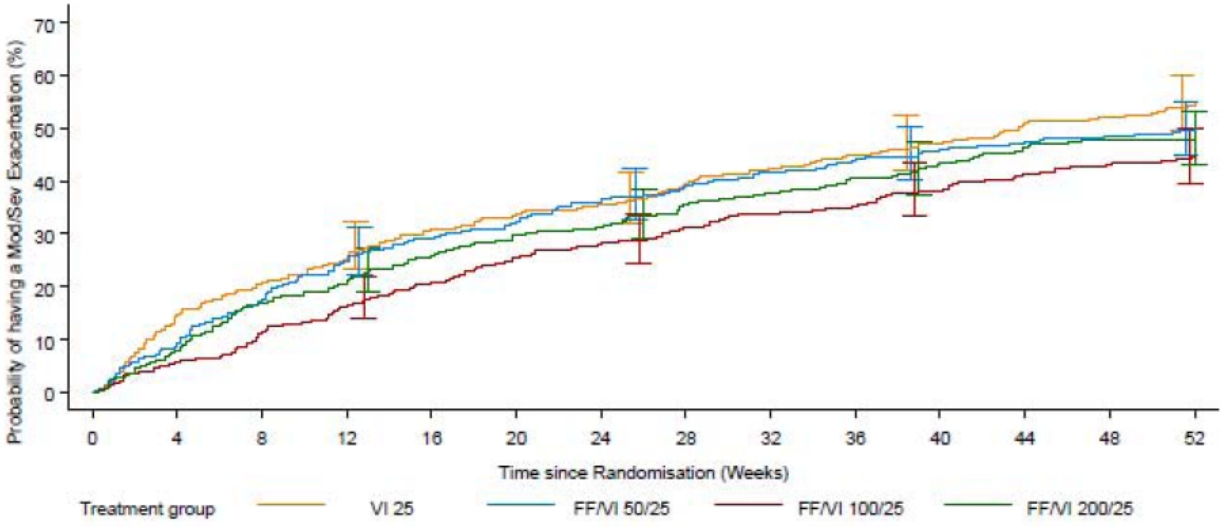
	Study 2871				Study 2970			
	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Applicant's Results								
N	409	408	403	402	409	408	403	409
n	407	404	401	398	402	411	401	407
Column vs. VI 25								
Hazard Ratio		0.92	0.72	0.85		0.87	0.80	0.66
95% CI		0.76, 1.13	0.59, 0.89	0.69, 1.04		0.71, 1.06	0.66, 0.99	0.54, 0.82
Reviewer's Results								
Column vs. VI 25								
Hazard Ratio		0.88	0.78	0.84		0.89	0.83	0.71
95% CI		0.73, 1.04	0.65, 0.93	0.7, 1.00		0.75, 1.05	0.69, 0.98	0.59, 0.84

Source: Clinical Study Report-Protocol Number HZC102871 Table 16, page 72 and Protocol Number HZC102970 Table 16, page 70.

The time to first moderate or severe exacerbation showed a numerical treatment benefit for FF/VI 100/25 over VI 25 alone in both trials (

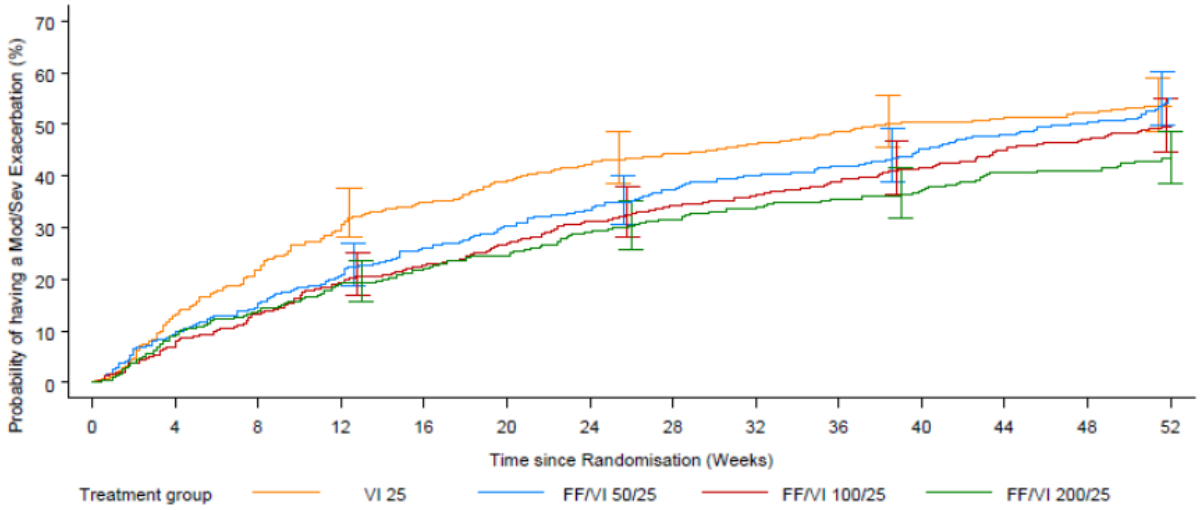
Figure 8 and Figure 9).The findings are the same (figures not shown) for imputed data.

Figure 8: Kaplan-Meier Plot of Time to First Moderate or Severe Exacerbation – Study 2871



Source: Clinical Study Report-Protocol Number HZC102871 Figure 4, page 73

Figure 9: Kaplan-Meier Plot of Time to First Moderate or Severe Exacerbation – Study 2970



Source: Clinical Study Report-Protocol Number HZC102970 Figure 4, page 71

At the Pre-NDA meeting held last July 13, 2011, the Agency raised concerns regarding the lack of robust results to support the proposed bronchodilation indication from the two lung function studies (studies 2206 and 2207). The applicant proposed that the contribution of FF be demonstrated in these exacerbation studies by the difference in exacerbation rates. Since these studies also measured trough FEV_1, they could further define the contribution of FF to changes in lung function. As noted in Section 2.1.2, the Division noted that the COPD exacerbation studies (2871 and 2970) may provide efficacy support for the addition of FF to VI, but positive

exacerbation results may be problematic in the context of the negative lung function results observed in Studies 2206 and 2207.

Because FF/VI 200/25 failed to show a statistically significant improvement over the VI 25 group in study 2871 for the primary endpoint, the pre-specified multiplicity plan does not allow the test of hypotheses at the lower dosages or secondary endpoint. Nonetheless, in study 2871, all three FF/VI dosage strengths showed numerical improvement compared to VI 25 for trough FEV_1 (Table 13); both FF/VI 200/25 and 100/25 had about 60 mL improvement over VI 25 and FF/VI 50/25 had a 41 mL improvement over VI 25.

On the other hand, in the positive exacerbation study 2970, there was no statistically significant improvement over VI 25 for dosages FF/VI 200/25 or FF/VI 100/25 for trough FEV_1. All three dosage strengths showed numerical improvement of about 20 to 30 mL over VI 25.

Table 13: Studies 2871 and 2970 Trough FEV_1 (L) at Week 52/Visit 11-ITT Population

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
Study 2871				
N	409	408	403	402
N	392	395	388	387
LS Mean (SE)	1.18 (0.0114)	1.22 (0.0112)	1.24 (0.0112)	1.24 (0.0114)
Column vs. VI 25				
Difference		0.041	0.058	0.064
95% CI		0.009, 0.072	0.027, 0.090	0.033, 0.096
p-value		0.011*	<0.001*	<0.001*
Study 2970				
N	409	412	403	409
N	387	387	381	391
LS Mean (SE)	1.22 (0.0116)	1.25 (0.0113)	1.24 (0.0115)	1.24 (0.0113)
Column vs. VI 25				
Difference		0.034	0.024	0.026
95% CI		0.003, 0.066	-0.008, 0.056	-0.006, 0.057
p-value		0.034	0.143	0.115

Source: Clinical Study Report-Protocol Number HZC102871 Table 18, page 75 and Protocol Number HZC102970 Table 18, page 73.
* nominal p-values

In summary, only one of the two exacerbation studies showed a significant improvement for all FF/VI doses over VI 25 for annual rate of moderate and severe exacerbations. In both studies, the mean rate of moderate and severe exacerbation in the VI 25 group is about 1 exacerbation per year. For the proposed dose of FF/VI 100/25, the rate of moderate and severe exacerbation is reduced by about a quarter to a third of an event in one year.

3.2.4.3 Active Comparator Studies (Studies 2532, 3109 and 3091)

In study 2532, 7% of patients discontinued from the study; however, there were an additional 8% of patients without Day 84 primary endpoint data. Similarly, in study 3109, only 9% of patients discontinued from the study, but an additional 6% (4% in FF/VI group and 8% in FP/Salmeterol group) of patients had missing Day 84 primary endpoint data. Therefore, the results presented (Table 14) by the applicant included only about 85% of the ITT population (i.e., observed case analysis). Using only observed cases in the analysis will likely introduce bias. In many cases, the use of observed cases only may not preserve the baseline comparability between treatment groups achieved by randomization. In addition, excluding patients who dropped out that are related to outcome may introduce bias and influence the results. To examine the effect of missing data, a zero change from baseline was assigned to the missing data (i.e., baseline imputation). This assumed that patients who dropped out from treatment or study did not improve and reverted back to their original baseline score. The results were consistent with the Applicant's results (Table 15). In study 3109, there was a significant improvement in weighted mean FEV_1 in the FF/VI 100/25 OD treatment group compared to FP/Salmeterol 250/50 mcg BID. Although the difference did not reach statistical significance in study 2532, there was a numeric improvement of about 25 mL in favor of FF/VI 100/25 treatment group.

Table 14: Applicant's Analysis of Weighted-Mean FEV_1 (L) up to 24 Hours on Day 84 (Completer's)

	Study 2352		Study 3109	
	FF/VI 100/25 OD PM N=259	FP/salmeterol 250/50 mcg BID N=252	FF/VI 100/25 OD PM N=260	FP/salmeterol 250/50 mcg BID N=259
N	219	217	228	213
LS Mean	1.475	1.447	1.513 (0.015)	1.433 (0.016)
LS Mean Change	0.142 (0.018)	0.114 (0.018)	0.174 (0.015)	0.094 (0.016)
FF/VI 100/25 mcg vs. FP/salmeterol 250/50 mcg	0.029		0.08	
95% CI	(-0.022, 0.080)		(0.037, 0.124)	
p-value	0.267		<0.001	

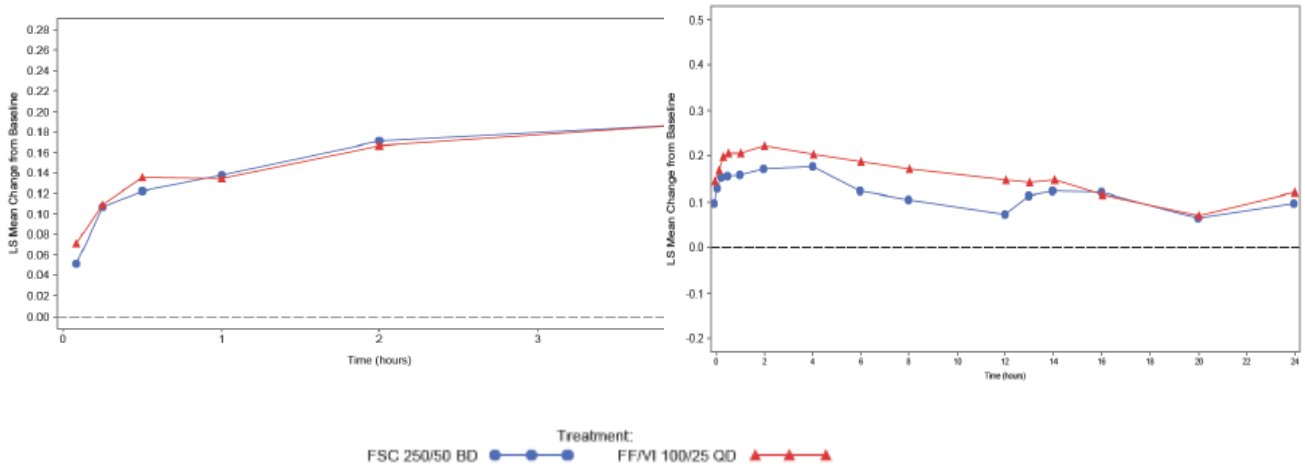
Source: Clinical Study Report HCZ112352, Table 13 page 51; Clinical Study Report HCZ113109, Table 13 page 53

Table 15: Reviewer's Analysis of Weighted-Mean FEV_1 (L) up to 24 Hours on Day 84 (ITT Population)

	Study 2352		Study 3109	
	FF/VI 100/25 OD PM N=259	FP/salmeterol 250/50 mcg BID N=252	FF/VI 100/25 OD PM N=260	FP/salmeterol 250/50 mcg BID N=259
n	259	251	260	259
LS Mean	1.48	1.45	1.52	1.44
LS Mean Change	0.13	0.11	0.20	0.12
FF/VI 100/25 mcg vs. FP/salmeterol 250/50 mcg	0.025		0.08	
95% CI	(-0.020, 0.069)		(0.04, 0.12)	
p-value	0.278		<0.001	

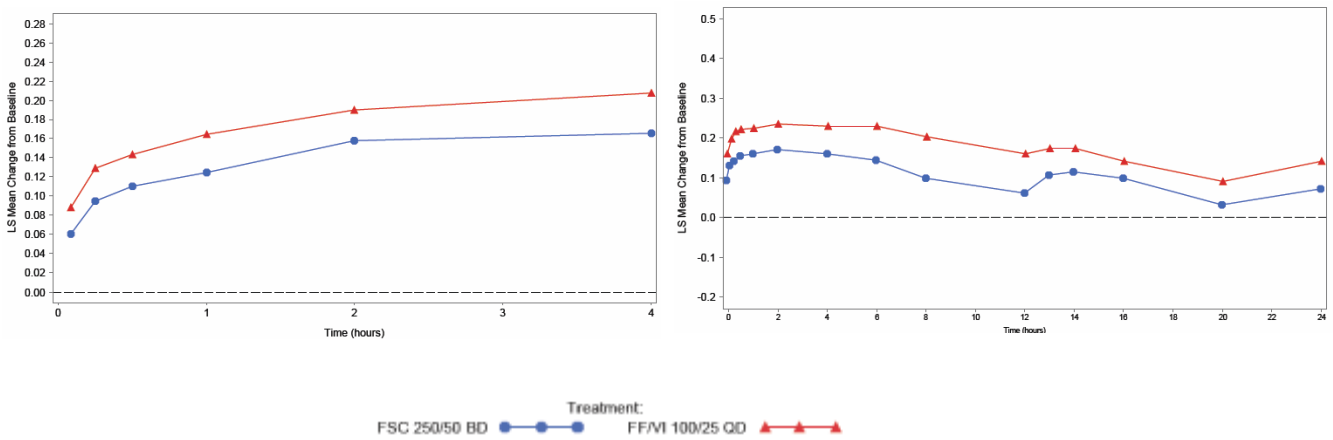
Serial FEV_1 at Day 1 and at Day 84 were also examined by the applicant. Twenty-four FEV_1 measurements were recorded at Day 84 and 4 hour measurements were recorded at Day 1. The applicant's results from applying repeated measures model at Day 1 and Day 84 are presented in Figure 10 and Figure 11. The model includes the same covariates as the primary endpoint, and missing data were not implicitly imputed in the analysis. The results were consistent with the primary analysis, in that, there is a clear separation of the curves favoring FF/VI in Study 3109 as early as Day 1 and Day 84. In Study 2352, there was a small separation during the first 12 hours on Day 84 favoring FF/VI (a once a day dosing) compared to FP/Salmeterol (a twice a day dosing), but none was observed on Day 1. The findings are the same (figures not shown) for the observed data.

Figure 10: LS Mean Change from baseline in FEV_1 (L) on Day 1 and Day 84 (ITT Population) – Study 2352



Source: Clinical Study Report HCZ112352, Figure 2 page 52 and Figure 4 page 55
Note: Scale in the y-axis is slightly different between the two figures.

Figure 11: LS Mean Change from baseline in FEV_1 (L) on Day 1 and Day 84 (ITT Population) – Study 3109



Source: Clinical Study Report HCZ112352, Figure 2 page 53 and Figure 4 page 57
Note: Scale in the y-axis is slightly different.

In the asthma study, study 3091, there were 11% of patients who discontinued treatment or from study. Unlike the COPD studies where 6% to 8% additional patients have missing Day 84 data, in this study only 2% additional patients have missing Day 168 data. Assigning a zero change from baseline to the missing data, the results were still consistent with the applicant's findings (Table 16). There was no significant difference observed in weighted mean FEV_1 between the FF/VI 100/25 group and FP/Salmeterol 250/50 group. There was a numeric improvement of about 22 to 37 mL in favor of FP/salmeterol treatment group in this patient population.

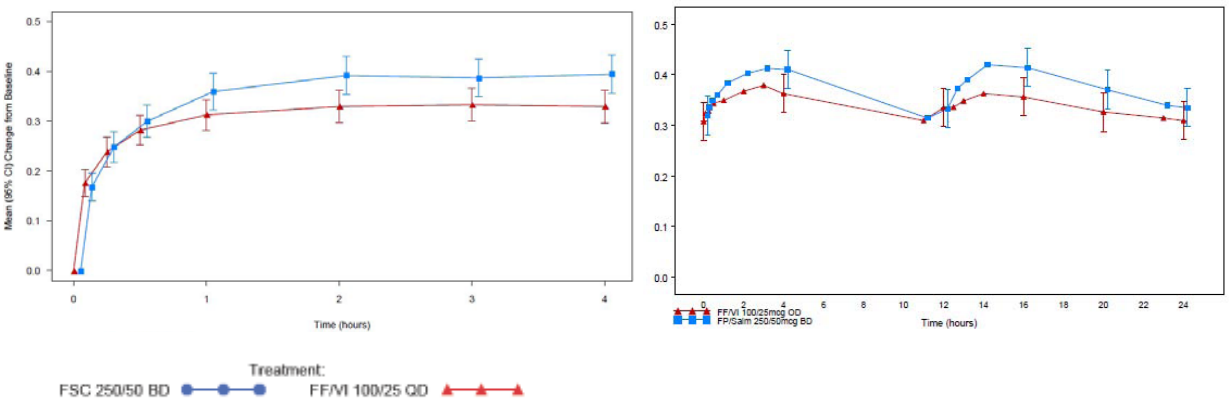
Table 16: Analysis of Weighted-Mean FEV_1 (L) up to 24 Hours on Day 84 (ITT Population) – Study 3091

	Applicant's		Reviewer's	
	FF/VI 100/25 OD PM N=403	FP/salmeterol 250/50 mcg BID N=403	FF/VI 100/25 OD PM N=260	FP/salmeterol 250/50 mcg BID N=259
N	352	347	401	401
LS Mean	2.364	2.400	2.34	2.36
LS Mean Change	0.341 (0.018)	0.377 (0.019)	0.31	0.33
FF/VI 100/25 mcg vs. FP/salmeterol 250/50 mcg	-0.037		-0.022	
95% CI	(-0.088, 0.015)		(-0.070, 0.027)	
p-value	0.162		0.380	

Source: Clinical Study Report HCA113091 Table 12 page 49

There is a separation of curves between FF/VI (a once a day dosing) and FP/Salmeterol (a twice a day dosing) favoring the FP/salmeterol group. The profiles appear to be similar at Days 1 and 168. The findings were the same (figures not shown) for the observed data.

Figure 12: LS Mean Change from baseline in FEV_1 (L) on Day 1 and Day 168 (ITT Population) – Study 3091



Source: Clinical Study Report HZA113091, Figure 3 page 52 and Figure 4 page 53
Note: Scale in the y-axis is the same.

In summary, studies 2532 and 3109 provided an additional benchmark comparison for FF/VI. The results of these studies demonstrated a similar or slightly increased mean change from baseline for FF/VI 100/25 compared to FP/Salmeterol 250/50. In the asthma study (study 3091), FP/Salmeterol 250/50 numerically outperformed FF/VI.

3.3 Evaluation of Safety

Safety evaluations for this submission will be evaluated by the Medical Reviewer, Sofia Chaudhry, M.D. Please refer to her review for more details regarding the safety findings.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The applicant evaluated the consistency of the treatment effect on the primary efficacy endpoints for studies 2206, 2207, 2871 and 2970 across subgroups by adding treatment-by-subgroup interaction into the primary analysis models. The statistical significance of the interaction term indicated whether the treatment effect was different among the subgroups. If any interaction p-value was less than 0.1 then further investigations were carried out.

The prespecified subgroup analyses that were considered included the following.

1. age (≤64 years and ≥65 years)
2. race (African American/African Heritage, American Indian or Alaskan Native, Asian, Native Hawaiian or other Pacific Islander, White and Mixed Race)
3. gender
4. region (US, European Union, other)
5. reversibility
6. percent predicted GOLD categories
7. smoking status
8. baseline FEV_1
9. center grouping

10. cardiovascular (CV) history/risk factors

In study 2206, there was a nominal significant quantitative interaction between treatment and reversibility for the primary endpoints, weighted mean FEV_1 0–4 hours at Day 168 (p=0.003) and change from baseline in clinic visit trough FEV_1 on treatment Day 169 (p=0.018), as well as, for weighted mean FEV_1 0–4 hours at Day 168 in study 2207 (p=0.004) (Table 22, Table 23 and Table 24, respectively). For both endpoints in study 2206, as expected, the magnitude of the treatment effect was greater in the reversible patients than in the non-reversible patients. For study 2207, the magnitude of the treatment effect was smaller in the non-reversible patients relative to the reversible patients in the FF 100, FF 200, VI 25 and FF/VI 100/25 groups. In the FF/VI 200/25 group the magnitude of the effect was larger in the non-reversible group. Both effects were in the same direction for both endpoints. On the other hand, a nominal significant quantitative interaction between treatment and smoking status at screening (p=0.0665), as well as, treatment and baseline FEV_1 for change from baseline in clinic visit trough FEV_1 on treatment Day 169 (p=0.096) was observed in study 2207 (Table 24). The treatment effects in former smokers were smaller than those of the current smokers in the VI versus placebo and FF/VI 100/25 versus placebo. There was a larger treatment effect seen in former smokers compared to current smokers for the FF/VI 200/25 versus the placebo group. In general, for the treatment by baseline FEV_1 interaction, larger effects were seen with the VI 25 and FF/VI 200/25 groups compared with the placebo group in those with baseline FEV1 values above the median of 1.3L than in those with baseline FEV1 values below the median. In both studies, no evidence of interaction was found with treatment and age, gender, race, region, center grouping, GOLD category, baseline disease severity (pre-dose Day 1 percent predicted FEV_1) or CV history.

For study 2871, there was a nominal significant quantitative interaction between treatment and reversibility for the negative binomial model (p=0.093) (Table 26). There was a greater reduction in the annual rate of moderate and severe exacerbation for FF/VI 50/25 and FF/VI 200/25 compared to VI in the reversible subjects than in the non-reversible subjects, however the effect was opposite in the FF/VI 100/25 versus VI group. This interaction was not observed in study 2970. Instead, there was a significant interaction between treatment and smoking status for the negative binomial model in study 2970 (p=0.065) (Table 28). There was a greater reduction in the annual rate of moderate and severe exacerbation for FF/VI 50/25 and FF/VI 200/25 compared to VI in former smokers than in the current smokers, however the effect was opposite in the FF/VI 100/25 versus VI group. For study 2871, there was a nominal significant quantitative interaction between treatment and smoking status at screening (p=0.060) (Table 27). There was a greater reduction in the LS mean treatment differences for VI in all three FF/VI doses in trough FEV_1 for former smokers compared to current smokers. In study 2970 there was a nominal significant quantitative interaction between treatment reversibility for trough FEV_1 (p=0.062) (Table 29). There was a greater LS mean treatment difference for VI in all three FF/VI doses in trough FEV_1 for reversible subjects compared to non-reversible subjects. No evidence of interaction was found with treatment and age, gender, race, region, baseline disease severity (pre-dose Day 1 percent predicted FEV_1), center grouping, Gold category, or CV history in either study. There were no significant interactions seen for the Poisson analysis.

In summary, there was some evidence of a quantitative interaction between treatment and reversibility, and between treatment and smoking in lung function and in exacerbation. The

magnitude of effect appears to be greater in reversible patients and in current smokers in some of the combination dose groups, but appears to be smaller in other combination dose groups. In the absence of a consistent effect, it is difficult to draw any definitive conclusion.

5 SUMMARY AND CONCLUSIONS

In study 2206, VI 25 showed a significant improvement compared to placebo for weighted mean 0–4 hours FEV_1 (Table 17). VI also showed a significant improvement compared to placebo for trough FEV_1. However, FF/VI 100/25 did not show a significant improvement over VI 25 for trough FEV_1, failing to show the contribution of FF in the FF/VI combination. This is in agreement with the applicant's conclusion. Change from baseline in trough FEV_1 for VI 25 was 100 mL compared to 150 mL for FF/VI 100/25; therefore, the difference, if any, was about 50 mL (95% CI: -6 mL, 100 mL).

Study 2207 showed similar results, but at the higher dosage of FF/VI, 200/25. VI also showed a significant improvement from placebo for trough FEV_1. However, FF/VI 200/25 did not show a significant improvement over VI 25 for trough FEV_1, failing to show the contribution of FF in the FF/VI combination. This is also in agreement with the applicant's conclusion. Change from baseline in trough FEV_1 for VI 25 was also 100 mL compared to 150 mL for FF/VI 100/25 and about 140 mL for FF/VI 200/25; therefore, the difference, if any, was about 45 mL (95% CI: -8 mL, 97 mL) and 32 mL (-19 mL, 83 mL), respectively.

Only one of the two exacerbation studies showed a significant improvement for all FF/VI doses over VI 25 for annual rate of moderate and severe exacerbations. In study 2970 there was a significant improvement for all FF/VI doses over VI 25 for annual rate of moderate and severe exacerbations. Study 2871 did not show a significant improvement for FF/VI 200/25 compared to VI 25 for annual rate of moderate and severe exacerbations, thus failing to show the contribution of FF in the FF/VI combination. However, there was a numeric improvement with FF/VI at all strengths with 13%, 34%, and 15% reduction in the annual rate of moderate and severe exacerbations for FF/VI 50/25, FF/VI 100/25 and FF/VI 200/25 respectively in study 2871. For the FF/VI 100/25 group in both studies, the rate of moderate and severe exacerbation was reduced by about a quarter to a third of an event in one year. Exploratory analyses of the change in trough FEV_1 showed a significant improvement at all FF/VI dosage strengths compared to VI 25 in study 2871 but not in study 2970. When compared to VI 25, the numeric improvements at all FF/VI dosage strengths were below 35 mL in study 2970 and about 50–60 mL in study 2871 that is consistent with the findings in studies 2206 and 2207.

Active comparator studies 2532 and 3109 provided an additional benchmark comparison for FF/VI. The results of these studies demonstrated a similar or slightly increased mean change from baseline for FF/VI 100/25 compared to FP/Salmeterol 250/50. In study 3091 (asthma study), FP/Salmeterol 250/50 numerically outperformed FF/VI.

In summary, there was evidence of efficacy for the VI 25 and all dosage strengths of FF/VI in the weighted mean FEV_1 (0–4 h) and change from baseline in trough FEV_1 when compared to

placebo (studies 2206 and 2207). These studies also successfully demonstrated the contribution of VI 25 in the FF/VI at all dosage strengths, based on the difference in weighted mean FEV_1 (0–4 h). However, neither study demonstrated the contribution of FF in the FF/VI combination at all dosage strengths based on trough FEV_1. Change from baseline in trough FEV_1 for VI 25 was 100 mL compared to 150 mL for FF/VI 100/25 and about 140 mL for FF/VI 200/25; therefore for the proposed dose of FF/VI 100/25, the difference was about 50 mL (95% CI: -6, 102). Since the confidence interval includes zero, this implies that the direction of the difference, if any, was not known with much confidence. In both studies, the higher dose FF/VI combination did not have a larger effect on the primary endpoints (weighted mean FEV_1 or trough FEV_1) compared to the lower dose FF/VI combination.

Only one of the two exacerbation studies showed a significant improvement for all FF/VI doses over VI 25 for annual rate of moderate and severe exacerbations. In this study, the mean rate of moderate and severe exacerbation in the VI 25 group was about 1 exacerbation per year. For the proposed dose of FF/VI 100/25, the rate of moderate and severe exacerbation was reduced by about a quarter of an event in one year.

Table 17: Summary of Efficacy Findings

	Study 2206		Study 2207		Study 2871		Study 2970	
	WMFEV **Diff** **P-Value**	**Trough** **Diff** **P-Value**	**WMFEV** **Diff** **P-Value**	**Trough** **Diff** **P-Value**	**%Reduction Exacerbation** **P-value**	**Trough at Week 52** **Diff** **P-Value**	**%Reduction Exacerbation** **P-Value**	**Trough at Week 52** **Diff** **P-Value**
VI 25 vs PBO	103 mL <0.001	67 mL 0.017	185 mL <0.001	100 mL <0.001				
FF/VI 200/25 vs PBO			209 mL <0.001	131 mL <0.001				
FF/VI 200/25 vs FF 200			168 mL <0.001					
FF/VI 200/25 vs VI				32 mL 0.224	15% 0.109	64 mL <0.001*	31% <0.001	26 mL 0.115
FF/VI 100/25 vs PBO	173 mL <0.001	115 mL <0.001	214 mL <0.001	144 mL <0.001*				
FF/VI 100/25 vs FF 100	120 mL <0.001		168 mL <0.001					
FF/VI 100/25 vs VI		48 mL 0.082		45 mL 0.093*	34% <0.001*	58 mL 0.001*	21% 0.024	24 mL 0.143
FF/VI 50/25 vs PBO	192 mL <0.001	129 mL <0.001*						
FF/VI 50/25 vs VI		62 mL 0.025*			13% 0.181*	41 mL 0.007*	19% 0.040	34 mL 0.034*

Key: * = nominal p-value; red font = p-value greater than 0.05

APPENDICES

Table 18: Study 2206-Summary of Demographics Characteristics-ITT Population

	FF 100 N=206	VI 25 N=205	FF/VI 50/25 N=206	FF/VI 100/25 N=206	Placebo N=207
Age (years)					
Mean (SD)	62.7 (9.47)	63.4 (9.58)	62.8 (9.13)	62.3 (8.49)	62.1 (8.80)
Sex n (%)					
Female	74 (36)	65 (32)	71 (34)	69 (33)	66 (32)
Male	132 (64)	140 (68)	135 (66)	137 (67)	141 (68)
Race and Racial Combinations, n (%)					
African American/African Heritage	3 (1)	7 (3)	6 (3)	9 (4)	7 (3)
American Indian or Alaska Native	0	0	1 (<1)	1 (<1)	1 (<1)
Asian	64 (31)	57 (28)	43 (21)	46 (22)	44 (21)
Central/South Asian Heritage	0	1 (<1)	0	0	0
White	139 (67)	141 (69)	156 (76)	150 (73)	155 (75)
Ethnicity, n (%)					
Hispanic or Latino	9 (4)	6 (3)	12 (6)	9 (4)	10 (5)
Not Hispanic or Latino	197 (96)	199 (97)	194 (94)	197 (96)	197 (95)
Height (cm)					
Mean (SD)	166.1 (8.46)	167.7 (9.09)	167.7 (9.24)	167.9 (9.66)	168.8 (8.16)
Weight (kg)					
Mean (SD)	71.4 (17.32)	72.2 (18.51)	73.7 (18.68)	76.5 (22.51)	74.5 (18.45)
BMI (kg/m^2)					
Mean (SD)	25.7 (5.44)	25.6 (5.98)	26.1 (5.73)	26.9 (6.80)	26.0 (5.61)

Source: Clinical Study Report-Protocol Number HZC112206 Table 8, page 76

Table 19: Study 2207-Summary of Demographic Characteristics-ITT Population

	FF 100	FF 200	VI 25	FF/VI 100/25	FF/VI 200/25	Placebo
Age (years)						
Mean (SD)	61.8 (8.28)	61.8 (9.02)	61.2 (8.62)	61.9 (8.79)	61.1 (8.67)	61.9 (8.14)
Sex n (%)						
Female	54 (26)	52 (26)	52 (26)	60 (29)	68 (33)	53 (26)
Male	150 (74)	151 (74)	151 (74)	144 (71)	137 (67)	152 (74)
Race and Racial Combinations, n (%)						
African American/African Heritage	2 (<1)	5 (2)	3 (1)	4 (2)	2 (<1)	0
American Indian or Alaska Native	0	1 (<1)	0	2 (<1)	0	0
Asian	5 (2)	14 (7)	4 (2)	8 (4)	11(5)	8 (4)
Japanese/East Asian Heritage/~ South East Asian Heritage	5(2)	14 (7)	4 (2)	8 (4)	11 (5)	8(4)
White	197 (97)	183 (90)	196 (97)	190 (93)	192 (94)	197 (96)
Ethnicity, n (%)						
Hispanic or Latino	1 (<1)	0	0	1 (<1)	0	0
Not Hispanic or Latino	203 (>99)	203 (100)	203 (100)	203 (>99)	205 (100)	205 (100)
Height (cm)						
Mean (SD)	171.7 (9.01)	169.7 (8.34)	171.2 (8.43)	171.1 (9.09)	170.3 (9.24)	170.9 (8.66)
Weight (kg)						
Mean (SD)	80.3 (19.38)	77.3 (20.24)	77.0 (17.18)	77.3 (18.81)	75.4 (16.08)	78.8 (17.08)
BMI (kg/m^2)						
Mean (SD)	27.1 (5.71)	26.7 (6.35)	26.2 (5.21)	26.2 (5.12)	25.9 (4.86)	26.9 (5.36)

Source: Clinical Study Report-Protocol Number HZC112207 Table 8, page 75

Table 20: Study 2871- Summary of Demographic Characteristics-ITT Population

n(%)		VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402	Total N=1622
Age (years)	n	409	408	403	402	1622
	Mean	63.6	63.6	63.6	63.8	63.6
	SD	9.43	9.06	9.06	9.30	9.21
	Min-Max	40-87	40-88	41-88	41-90	40-90
Sex	n	409	408	403	402	1622
	Female	170 (42)	163 (40)	172 (43)	153 (38)	658 (41)
	Male	239 (58)	245 (60)	231 (57)	249 (62)	964 (59)
Race	n	408	408	403	401	1620
	White	331 (81)	334 (82)	332 (82)	324 (81)	1321 (82)
	African American/African Heritage	9 (2)	8 (2)	6 (1)	9 (2)	32 (2)
	Asian	39 (10)	37 (9)	37 (9)	41 (10)	154 (10)
	Other	29 (7)	29 (7)	28 (7)	27 (7)	113 (7)
Ethnicity	n	409	408	403	402	1622
	Hispanic or Latino	78 (19)	73 (18)	72 (18)	76 (19)	299 (18)
	Not Hispanic or Latino	331 (81)	335 (82)	331 (82)	326 (81)	1323 (82)
Body Mass Index (kg/m^2)	n	407	408	402	402	1619
	Mean	26.17	26.94	27.14	26.52	26.69
	SD	5.596	5.771	6.144	6.191	5.936
	Min-Max	14.7-44.9	14.6-47.1	15.5-58.2	12.4-54.4	12.4-58.2

Source: Clinical Study Report-Protocol Number HZC102871 Table 6, page 58

Table 21: Study 2970- Summary of Demographics Characteristics-ITT Population

n(%)		VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409	Total N=1633
Age (years)	n	409	412	403	409	1633
	Mean	63.6	63.7	64.0	63.5	63.7
	SD	9.29	9.56	9.28	8.84	9.24
	Min-Max	40-85	40-88	40-88	40-86	40-88
Sex	n	409	412	403	409	1633
	Female	174 (43)	181 (44)	181 (45)	191 (47)	727 (45)
	Male	235 (57)	231 (56)	222 (55)	218 (53)	906 (55)
Race	n	409	412	403	409	1633
	White	360 (88)	359 (87)	353 (88)	359 (88)	1431 (88)
	African American/African Heritage	9 (2)	14 (3)	7 (2)	9 (2)	39 (2)
	Asian	4 (<1)	3 (<1)	5 (1)	3 (<1)	15 (<1)
	Other	36 (9)	36 (9)	38 (9)	38 (9)	148 (9)
Ethnicity	n	409	412	403	409	1633
	Hispanic or Latino	70 (17)	68 (17)	74 (18)	73 (18)	285 (17)
	Not Hispanic or Latino	339 (83)	344 (83)	329 (82)	336 (82)	1348 (83)
Body Mass Index (kg/m^2)	n	409	412	403	408	1632
	Mean	27.31	27.10	26.97	26.82	27.05
	SD	6.184	5.737	5.638	5.979	5.886
	Min-Max	14.5-63.2	15.1-51.6	14.9-50.4	13.7-56.5	13.7-63.2

Source: Clinical Study Report-Protocol Number HZC102970 Table 6, page 57

Table 22 Subgroup Analysis for 0-4 Hours Weighted Mean FEV_1 (L) at Day 168 by Reversibility for Study 2206 (ITT Population)

	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25	Placebo
	N=206	N=205	N=206	N=206	N=207
Not Reversible					
LS Mean (SE)	1.284 (0.0224)	1.328 (0.0218)	1.380 (0.0227)	1.395 (0.0219)	1.236 (0.0228)
Drug vs Placebo					
Difference	0.048	0.092	0.145	0.160	
95% CI	-0.014, 0.111	0.030, 0.154	0.081, 0.208	0.098, 0.222	
p-value	0.132	0.004	<0.001	<0.001	
Drug vs VI 25					
Difference			0.052	0.067	
95% CI			-0.009, 0.114	0.007, 0.128	
p-value			0.097	0.029	
Drug vs FF 100					
Difference				0.111	
95% CI				0.050, 0.173	
p-value				<0.001	
Reversible					
LS Mean (SE)	1.306 (0.0304)	1.373 (0.0325)	1.510 (0.0299)	1.453 (0.0311)	1.236 (0.0228)
Drug vs Placebo					
Difference	0.062	0.129	0.266	0.209	
95% CI	-0.023, 0.148	0.040, 0.217	0.182, 0.351	0.122, 0.295	
p-value	0.153	0.004	<0.001	<0.001	
Drug vs VI 25					
Difference			0.138	0.080	
95% CI			0.051, 0.224	-0.008, 0.168	
p-value			0.002	0.076	
Drug vs FF 100					
Difference				0.146	
95% CI				0.061, 0.232	
p-value				<0.001	

Source: Clinical Study Report-Protocol Number HZC112206 Table 6.74, page 1377-1386

Table 23 Subgroup Analysis for Trough FEV_1 (L) at Day 169 by Reversibility for Study 2206

	FF 100	VI 25	FF/VI 50/25	FF/VI 100/25	Placebo
	N=206	N=205	N=206	N=206	N=207
Not Reversible					
LS Mean (SE)	1.278 (0.0244)	1.313 (0.0236)	1.346 (0.0247)	1.355 (0.0238)	1.246 (0.0246)
Drug vs Placebo					
Difference	0.032	0.067	0.100	0.109	
95% CI	-0.036, 0.100	0, 0.134	0.031, 0.168	0.042, 0.176	
p-value	0.359	0.050	0.004	0.001	
Drug vs VI 25					
Difference			0.033	0.042	
95% CI			-0.034, 0.100	-0.024, 0.108	
p-value			0.340	0.208	
Drug vs FF 100					
Difference				0.077	
95% CI				0.010, 0.144	
p-value				0.024	
Reversible					
LS Mean (SE)	1.289 (0.0330)	1.328 (0.0352)	1.428 (0.0324)	1.386 (0.0338)	1.257 (0.0343)
Drug vs Placebo					
Difference	0.031	0.070	0.171	0.129	
95% CI	-0.062, 0.125	-0.026, 0.167	0.078, 0.263	0.034, 0.223	
p-value	0.511	0.153	<0.001	0.008	
Drug vs VI 25					
Difference			0.100	0.058	
95% CI			0.006, 0.194	-0.037, 0.154	
p-value			0.036	0.231	
Drug vs FF 100					
Difference				0.098	
95% CI				0.005, 0.190	
p-value				0.039	

Source: Clinical Study Report-Protocol Number HZC112206 Table 6.75, page 1387-1406

Table 24 Subgroup Analysis for 0–4 Hours Weighted Mean FEV1 (L) at Day 168 by Reversibility for Study 2207 (ITT Population)

	FF 100	FF 200	VI 25	FF/VI 100/25	FF/VI 200/25	Placebo
	N=204	N=203	N=203	N=204	N=205	N=205
Not Reversible						
LS Mean	1.368	1.351	1.479	1.503	1.512	1.326
(SE)	(0.0224)	(0.0215)	(0.0222)	(0.0227)	(0.0222)	(0.0225)
Drug vs Placebo						
Difference	0.042	0.025	0.153	0.176	0.186	
95% CI	-0.020,0.104	-0.036,0.086	0.091,0.215	0.114,0.239	0.124,0.248	
p-value	0.187	0.424	<0.001	<0.001	<0.001	
Drug vs VI 25						
Difference				0.023	0.033	
95% CI				-0.039,0.086	-0.029,0.095	
p-value				0.460	0.293	
Drug vs FF 100						
Difference				0.135		
95% CI				0.072,0.197		
p-value				<0.001		
Drug vs FF 200						
Difference					0.161	
95% CI					0.101,0.222	
p-value					<0.001	
Reversible						
LS Mean	1.403	1.423	1.599	1.642	1.609	1.338
(SE)	(0.0344)	(0.0364)	(0.0330)	(0.0351)	(0.0344)	(0.0346)
Drug vs Placebo						
Difference	0.065	0.085	0.260	0.304	0.271	
95% CI	-0.031,0.161	-0.014,0.183	0.166,0.354	0.207,0.400	0.175,0.366	
p-value	0.184	0.092	<0.001	<0.001	<0.001	
Drug vs VI 25						
Difference				0.043	0.010	
95% CI				-0.051,0.138	-0.083,0.104	
p-value				0.369	0.829	
Drug vs FF 100						
Difference				0.239		
95% CI				0.142,0.335		
p-value				<0.001		
Drug vs FF 200						
Difference					0.186	
95% CI					0.087,0.284	
p-value					<0.001	

Source: Clinical Study Report-Protocol Number HZC112207 Table 6.68, page 1243-1262

Table 25 Subgroup Analysis for Trough FEV_1 (L) at Day 169 by Smoking Status for study 2207 (ITT Population)

	FF 100	FF 200	VI 25	FF/VI 100/25	FF/VI 200/25	Placebo
	N=204	N=203	N=203	N=204	N=205	N=205
Current Smoker						
LS Mean	1.398	1.345	1.457	1.504	1.443	1.347
(SE)	(0.0247)	(0.0248)	(0.0260)	(0.0263)	(0.0259)	(0.0265)
Drug vs Placebo						
Difference	0.051	-0.002	0.110	0.157	0.096	
95% CI	-0.020,0.122	-0.073,0.069	0.037,0.183	0.084,0.230	0.023,0.169	
p-value	0.157	0.958	0.003	<0.001	0.010	
Drug vs VI 25						
Difference				0.047	-0.014	
95% CI				-0.026,0.119	-0.086,0.058	
p-value				0.205	0.705	
Drug vs FF 100						
Difference				0.106		
95% CI				0.035,0.176		
p-value				0.003		
Drug vs FF 200						
Difference					0.098	
95% CI					0.028,0.168	
p-value					0.006	
Former Smoker						
LS Mean	1.382	1.368	1.433	1.477	1.518	1.348
(SE)	(0.0287)	(0.0280)	(0.0265)	(0.0279)	(0.0264)	(0.0271)
Drug vs Placebo						
Difference	0.033	0.020	0.085	0.129	0.169	
95% CI	-0.044,0.111	-0.056,0.096	0.010,0.159	0.053,0.205	0.095,0.243	
p-value	0.397	0.605	0.026	<0.001	<0.001	
Drug vs VI 25						
Difference				0.044	0.085	
95% CI				-0.031,0.120	0.011,0.158	
p-value				0.250	0.024	
Drug vs FF 100						
Difference				0.095		
95% CI				0.017,0.174		
p-value				0.017		
Drug vs FF 200						
Difference					0.149	
95% CI					0.074,0.225	
p-value					<0.001	

Source: Clinical Study Report-Protocol Number HZC112207 Table 6.69, page 1263-1302

Table 26 Subgroup Analysis for Annual Rate of Moderate and Severe Exacerbations by Reversibility for Study 2871(ITT Population)

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402
Not Reversible				
LS Mean Annual Rate	0.94	0.88	0.61	0.91
Drug vs VI 25 Ratio		0.93	0.64	0.97
95% CI		0.74,1.19	0.50,0.83	0.76,1.23
p-value		0.576	<0.001	0.794
Percent Reduction		7	36	3
95% CI		-19, 26	17, 50	-23, 24
Reversible				
LS Mean Annual Rate	1.32	1.04	0.97	0.80
Drug vs VI 25 Ratio		0.79	0.69	0.61
95% CI		0.56,1.11	0.49,0.98	0.42,0.88
p-value		0.177	0.037	0.008
Percent Reduction		21	31	39
95% CI		-11, 44	2, 51	12,58

Source: Clinical Study Report-Protocol Number HZC102871 Table 6.48, page 714-715

Table 27 Subgroup Analysis for Trough FEV_1 (L) at Week 52 by Smoking Status for Study 2871 (ITT Population)

	VI 25 N=409	FF/VI 50/25 N=408	FF/VI 100/25 N=403	FF/VI 200/25 N=402
Former Smoker				
LS Mean (SE)	1.167 (0.0150)	1.224 (0.0146)	1.251 (0.0148)	1.267 (0.0147)
Drug vs VI 25 Difference		0.057	0.084	0.100
95% CI		0.016,0.098	0.042,0.125	0.059,0.142
p-value		0.007	<0.001	<0.001
Current Smoker				
LS Mean (SE)	1.197 (0.0176)	1.215 (0.0174)	1.220 (0.0171)	1.208 (0.0181)
Drug vs VI 25 Difference		0.018	0.023	0.012
95% CI		-0.030,0.067	-0.025,0.071	-0.038,0.061
p-value		0.454	0.342	0.639

Source: Clinical Study Report-Protocol Number HZC102871 Table 6.49, page 716-733

Table 28 Subgroup Analysis for Annual Rate of Moderate and Severe Exacerbations by Smoking Status for Study 2970 (ITT Population)

	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
Former Smoker				
LS Mean Annual Rate	1.19	0.90	0.98	0.66
Drug vs VI 25 Ratio		0.76	0.82	0.55
95% CI		0.57,1.01	0.62,1.09	0.41,0.74
p-value		0.056	0.175	<0.001
Percent Reduction		24	18	45
95% CI		-1, 43	-9, 38	26, 59
Current Smoker				
LS Mean Annual Rate	1.09	0.94	0.81	0.94
Drug vs VI 25 Ratio		0.86	0.74	0.86
95% CI		0.64,1.16	0.55,1.01	0.64,1.16
p-value		0.330	0.055	0.324
Percent Reduction		14	26	14
95% CI		-16, 36	-1, 45	-16, 36

Source: Clinical Study Report-Protocol Number HZC102970 Table 6.47, page 714-715

Table 29 Subgroup Analysis of Trough FEV_1 (L) by Reversibility for Study 2970 (ITT Population)

	VI 25 N=409	FF/VI 50/25 N=412	FF/VI 100/25 N=403	FF/VI 200/25 N=409
Not Reversible				
LS Mean (SE)	1.213 (0.0135)	1.231 (0.0131)	1.229 (0.0134)	1.229 (0.0130)
Drug vs VI 25				
Difference		0.017	0.015	0.016
95% CI		-0.019,0.054	-0.022,0.053	-0.021,0.053
p-value		0.354	0.417	0.396
Reversible				
LS Mean (SE)	1.204 (0.0204)	1.279 (0.0195)	1.258 (0.0195)	1.250 (0.0199)
Drug vs VI 25				
Difference		0.075	0.055	0.046
95% CI		0.020,0.130	-0.001,0.110	-0.010,0.102
p-value		0.008	0.052	0.107

Source: Clinical Study Report-Protocol Number HZC102970 Table 6.48, page 716-733

The Clinical Pharmacology Summary

The clinical pharmacology program, including selection of dose, dosing frequency and timing of the dose, was conducted in patients with COPD as well as asthma.

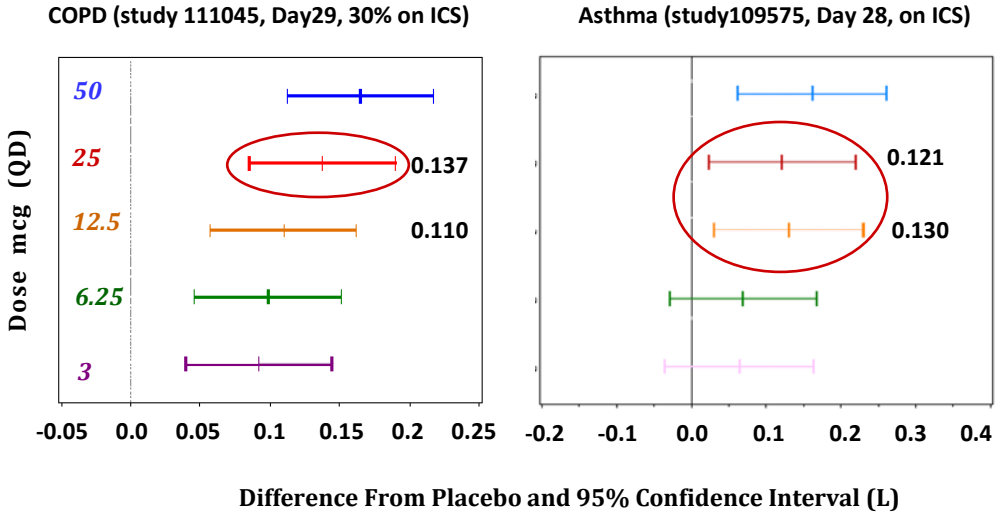
RATIONALE FOR DOSE AND DOSING FREQUENCY SELECTION

The proposed dose of FF/VI is 100/25 mcg once daily, preferably in the morning. Three dosing regimens, FF/VI 50/25, 100/25 and 200/25 mcg, were tested in Phase III studies in COPD patients. The dose regimens, including selection of dose, dosing frequency and timing of the dose, was established in dose ranging studies in COPD population as well as asthma patients.

Dose for VI

The 25 mcg dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with COPD (Study B2C111045), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint trough FEV1 (Figure 1) and secondary endpoint weighted mean FEV1 as well as the safety profile, 25 mcg was the appropriate dose. The 25 mcg dose was also supported by study B2C109575 in patients with asthma (Figure 1).

Fig 1. Effect of VI on lung function (trough FEV_1) across doses ranging from 3 mcg to 50 mcg QD

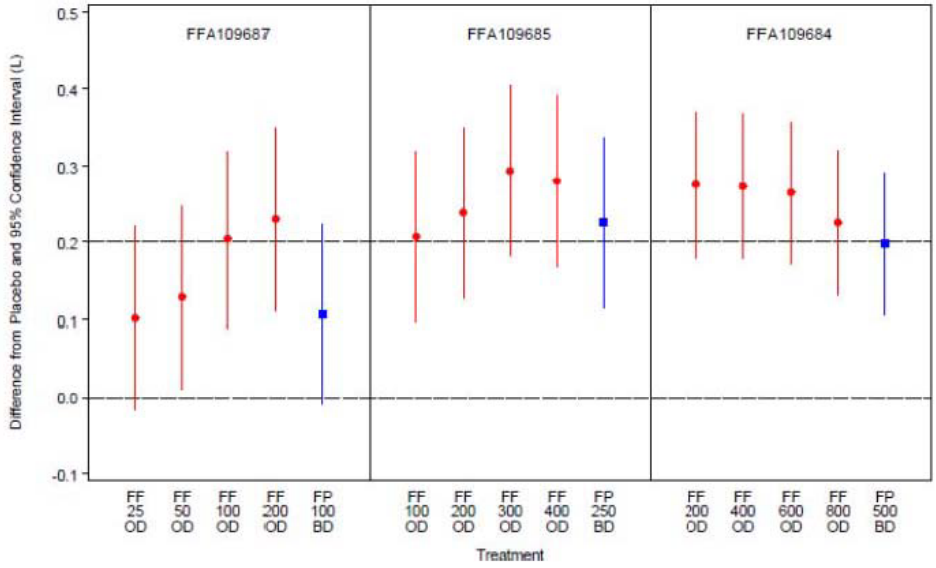


Dose for FF

Results for different FF doses on trough FEV_1 from the three Phase 2 dose ranging studies (FFA109687, FFA109685, FFA109684) in subjects with varying severity of asthma are summarized in Figure 2, which show substantial efficacy with FF 100 and near maximal efficacy with FF 300. In study FFA109685 and FFA109684, there is linear PK for FF 200 mcg to 800 mcg. The systemic exposure is not correlated with clinical

response (FEV1). Sponsor selected three doses of FF (50, 100 and 200 mcg) for further evaluation in combination with VI in the COPD phase III program.

Fig 2. Adjusted Treatment Differences From Placebo of Change from Baseline in Trough FEV1 (L) (LOCF) at Week 8 in Asthma for FF doses ranging from 25-800 mcg QD



Following selection of doses for individual components of FF and VI, sponsor compared the efficacy of FF/VI 50/25, 100/25 and 200/25 mcg in Phase III studies in COPD patients.

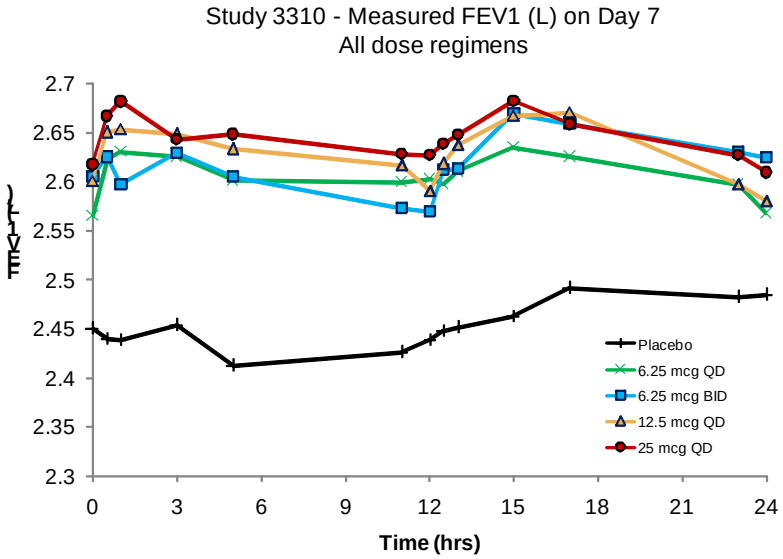
Dosing Frequency (QD vs BID)

Study FF112202 in subjects with asthma supported the comparability of once and twice daily dosing for FF (Table 1). HZA113310 in subjects with persistent asthma supported the comparability of once and twice daily dosing for VI. Figure 3 demonstrates that the improvement of mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing.

Table 1. Effect of FF dosing in Asthma; Trough FEV1 (L) on Day 28; Trial FFA-112202. Also shown is the Effect of FP dosing in Asthma.

	FF 100 BD	FF 200 QD	FP 100 BD	FP 200 QD
LS Mean difference (L)	0.098	0.108	0.132	0.087
95% CI	(0.064, 0.153)	(0.054, 0.142)	(0.059, 0.205)	(0.014, 0.161)

Fig 3. Effect of VI dosing on FEV1 in subjects with persistent asthma (studyHZA113310)



Morning vs. Evening Dosing

Study HZA114624 was a three-way crossover study in subjects with asthma that demonstrated that FF/VI 100/25, whether dosed in the morning or evening, resulted in a similar FEV1 time curve relative to placebo (data not shown).

PHARMACOKINETICS

Absorption

- The absolute systemic bioavailability for FF and VI (administered as FF/VI) was 15.2% and 27.3%, respectively. However, the systemic bioavailability of both FF and VI was low after oral administration, on average 1.26% and <2%, respectively. Therefore, systemic exposures for both inhaled FF and VI are primarily due to absorption of the inhaled portion of the dose delivered to the lung. For these reasons food effect for FF/VI would be negligible.
- Systemic exposure for FF/VI increased in proportion to the dose in the dose range of 200 to 800 mcg for FF ($AUC_{0-\infty}$, C_{max}), and 25 to 100 mcg for VI (C_{max}).
- T_{max} was reached by approximately 0.5-1 hours for both FF and VI following oral inhalation administration.
- Upon once-daily dosing, steady-state was reached by the 6th day. Based on $AUC_{(0-t)}$, accumulation ranged from 74% to 158% for FF and 24 to 140% for VI.

Distribution

- FF and VI have high *in-vitro* plasma protein binding, which are independent of concentration with average values of ≥99.6% and 93.9%, respectively. FF was predominantly bound to albumin (96%) and α1-acid glycoprotein (90%).
- Steady-state volume of distribution (Vd_{ss}) for FF and VI following oral inhalation were 661 L and 165 L, respectively.

Metabolism and Transporters

- FF and VI are both substrates of CYP3A4 and P-glycoprotein (P-gp).
- Based on in vitro studies, the potential for FF and VI to inhibit and induce metabolic enzymes is negligible at low inhalation doses.

Elimination

- In humans, FF is eliminated primarily by metabolism with metabolites excreting predominantly in feces. VI is also primarily eliminated by metabolism with metabolites excreting both in urine and feces (approximately 70% and 30% of the recovered radioactive dose, respectively).
- The apparent terminal phase elimination half-lives of FF and VI following oral inhalation administration of FF/VI were on average, 23.7 h and 2.47 h, respectively.

PK in asthma and COPD patients

- For FF systemic exposure, COPD< Asthma<healthy subjects. In subjects with COPD, FF Cmax and AUC were 47% and 46% lower compared to healthy subjects.

- For VI systemic exposure, Asthma<healthy subjects≠COPD. In subjects with COPD, VI C_{max} was 67% lower while $AUC_{(0-24)}$ was 24% higher compared with healthy subjects.

POPULATION PHARMACOKINETIC ANALYSIS

Population PK models were developed to describe the FF and VI systemic exposure in subjects with COPD.

Age

- VI clearance is decreased by 27% in elderly patients (>65 years), resulting in higher $AUC_{(0-24)}$ in older subjects. The higher exposure of VI in older subjects was not associated with an increase in heart rate. There is no effect of age on the exposure of systemic FF in subjects with COPD and VI exposure is higher in elderly (>65 years) patients.

Weight

- There is no influence of weight or body mass index on the pharmacokinetics of either FF or VI in subjects with COPD.

Gender

- There is no influence of gender on the pharmacokinetics of either FF or VI in subjects with COPD.

Race

- Systemic exposure of FF for East Asian, Japanese and South Asian subjects were on average 23% to 49% higher compared with white Caucasian subjects. This finding is consistent with results seen previously in healthy subjects of East Asian origin. There was no effect of race on the pharmacokinetics of VI in subjects with COPD.

SPECIAL POPULATIONS

Renal Impairment

- Systemic FF exposure is lower and systemic VI exposure is higher in severe renal impairment patients. At day 7, subjects with severe renal impairment had a mean (90%CI) increase in VI AUC by 56% (27%, 92%) and had similar VI C_{max} compared to subjects with normal renal function.
- The increased PK exposure of VI did not result in significant heart rate increase or serum potassium decrease in severe renal impairment patients compared to healthy subjects.
- No dose adjustments are recommended for subjects with renal impairment.

Hepatic Impairment

- Systemic FF exposure is higher and systemic VI exposure is not affected in patients with all severities of hepatic impairment. Mean percentage change in FF AUC (90%CI) for subjects with mild, moderate and severe hepatic impairment vs. normal hepatic function were respectively: 34% (-18%, 120%), 83% (11%, 199%) and 75% (5%, 191%). Mean percentage change in FF C_{max} (90% CI) for these cases were respectively: 18% (-17%, 69%), 43% (0%, 104%) and 37% (-5%, 98%). There was no evidence for reduced plasma protein binding of either FF or VI in plasma from subjects with varying degrees of hepatic impairment.
- The weighted mean (0-24h) serum cortisol was on average 34% lower with moderate hepatic impairment subjects compare to the healthy subjects. There is no change in VI related systemic effects (maximum heart rate and minimum blood potassium) in hepatic impairment subjects.
- Use with caution in patients with hepatic impairment. No dose adjustments are recommended for subjects with hepatic impairment.

DRUG-DRUG INTERACTIONS (DDI)

Drug-Drug and Formulation Interactions

There were no clinically relevant differences (<20% difference between the geometric means) in the pharmacokinetics of either FF or VI when administered in combination compared with administration alone.

Effect of coadministered drugs on FF/VI exposure

- Co-administration with strong CYP3A4 and potent P-gp inhibitor ketoconazole, resulted in modest increases in mean FF $AUC_{(0-24)}$ and C_{max} (by 36% and 33%, respectively) and mean VI $AUC_{(0-t)}$ and C_{max} (by 65% and 22%, respectively). Co-administration did not result in an increase in beta-adrenoceptor-mediated systemic effects (maximum heart rate and minimum blood potassium), while steroid-mediated systemic effects were observed with a 27% reduction in weighted mean serum cortisol (0-24 h). No dose adjustment is recommended for FF/VI when coadministered with ketoconazole.
- Co-administration with potent P-glycoprotein and moderate CYP3A4 inhibitor verapamil did not affect the VI C_{max} or AUC. No dose adjustment is recommended for FF/VI when coadministered with verapamil.

Effect of FF/VI on exposure of coadministered drugs

- With low systemic exposures for both FF and VI after oral inhalation administration, potential for inhibition and induction of metabolic enzymes is negligible.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR SAFETY

FF/VI is administered by oral inhalation and efficacy is presumed to be driven by local effects in the lung. Systemic exposures of FF and VI are considered more relevant for safety.

Effect of VI on QTc and HR

- Based on the FDA analysis of the through QT study, supratherapeutic doses of FF/VI (800/100mcg) yielded a placebo corrected QTcF of 9.6 ms and the upper bound of the 90%CI (12.2) superseded the threshold of regulatory concern (10 ms). Of note, the purported "therapeutic" dose of 200/25 mcg used in the study showed only minimal prolongation of QTcF (see Table 2 below).

Table 2. Effect of VI on ΔΔQTc from devoted through QT study

Treatment	Time (hour)	ΔΔQTcF (ms)	90% CI (ms)
FF/VI 200/25 mcg	30 min	4.9	(2.3, 7.5)
FF/VI 800/100 mcg	30 min	9.6	(7.0, 12.2)
Moxifloxacin 400 mg*	4	14.3	(11.9. 16.6)

- Heart rate increases were seen at both combination doses of FF/VI with maximum effects seen 10 minutes after dosing. The mean difference from placebo in maximum heart rate at 0 to 4 hours postdose was 3.9 beats/min (90% CI: 2.7, 5.1) and 12.4 beats/min (90% CI: 11.2, 13.6) following the lower and higher dose combinations, respectively.

Effect of FF on Serum Cortisol

- Although HPA suppression was observed with FF, serum cortisol reduction was not apparent at the proposed dosing. A pharmacokinetic/pharmacodynamic meta-analyses 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 1,556 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 (see Figure 4 below).

Fig 4. Effect of FF on serum cortisol (nmol/L) across doses ranging from placebo to 4000 mcg QD. Left plot is dose-response while right plot is concentration-response relationship.