

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**204275Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Established Name Fluticasone furoate and  
Vilanterol  
(Proposed) Trade Name Breo Ellipta  
Therapeutic Class ICS/LABA  
Applicant GlaxoSmithKline

Formulation(s) Orally inhaled  
Dosing Regimen Once daily  
Indication(s) 1) Maintenance treatment of  
airflow obstruction  
2) Reduction in exacerbation

Intended Population(s) COPD

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### List of Commonly Used Abbreviations

AE	Adverse Event
WM	Weighted Mean
CMC	Chemistry, manufacturing and controls
COPD	Chronic Obstructive Pulmonary Disease
DPI	Dry Powder Inhaler
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
MACE	Major adverse cardiac events
mcg	Microgram
NDA	New drug application
PD	Pharmacodynamic
PK	Pharmacokinetic
S	Salmeterol
SABA	Short acting beta-agonist
SAE	Serious Adverse Event
VI	Vilanterol

## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

At the time of this review, the preliminary recommended regulatory action from a clinical perspective for fluticasone furoate/vilanterol (FF/VI) 100/25 mcg one inhalation once daily for the long-term once-daily maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD) is Approval. However, this recommendation is preliminary and subject to change after the Pulmonary Allergy Drugs Advisory Committee discussion of this application scheduled for April 17, 2013.

### 1.2 Risk Benefit Assessment

The proposed indication for FF/VI 100/25 mcg once daily is for the long-term once-daily maintenance treatment of airflow obstruction and for reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD).

To support the proposed indications, the development program included two, 24-week lung function trials (2206 and 2207) and two, 52-week exacerbation trials. The 24-week lung function trials had co-primary endpoints of change from baseline in trough FEV1 and weighted mean FEV1 (0-4). The effect on FEV1 is supplemented with trough FEV1 data, designated as a secondary endpoint, from the two exacerbation trials (871 and 970). The 52-week exacerbation trials had a primary endpoint evaluating the annual rate of moderate to severe COPD exacerbations.

The benefit vilanterol provides to the combination FF/VI product is demonstrated through a comparison of FF/VI 100/25 to FF 100 in the two 24-week lung function trials. In both trials, FF/VI 100/25 demonstrated a statistically significant improvement compared to FF 100 monotherapy. The efficacy of the VI monocomponent is also demonstrated in the same 24-week lung function trials through a comparison of VI to placebo. Both trials demonstrate a statistically significant improvement for VI compared to placebo.

The benefit FF provides to the combination product is demonstrated by the comparison of FF/VI 100/25 to VI 25 in the exacerbation trials and lung function trials. A statistically significant improvement in the annual rate of exacerbation for FF/VI 100/25 compared to VI 25 is seen in one of the 52-week exacerbation trials with the other trial demonstrating a numerical improvement with a nominal p-value <0.05. While the second trial demonstrated a similar treatment effect, the improvement was not statistically significant based on the statistical hierarchical testing procedure. In addition to the exacerbation

data, a consistent numeric improvement in trough FEV1 is demonstrated for FF/VI 100/25 compared to VI 25 monotherapy in both 24 week lung function trials as well as in the two 52-week exacerbation trials. The data do not support an efficacy advantage for doses higher than FF/VI 100/25 in terms of exacerbations or lung function.

In terms of risk, the common adverse event profile for FF/VI in COPD is similar to other ICS/LABA products in COPD. In terms of serious events, an increase in FF dose-related risk for pneumonia is seen in the FF/VI development program. However, pneumonia has been seen in other ICS/LABA development programs and current product labeling for other ICS/LABA product contains warning language regarding this risk. No direct comparison to an approved product of adequate treatment duration to assess pneumonia has been performed to directly assess the risk of pneumonia of FF/VI compared to approved products. However, keeping in the mind the limitations of cross study comparisons, the overall impression from this program is that the rates of pneumonia for the proposed FF/VI 100/25 mcg dose are not grossly disproportionate to what has been seen in other ICS/LABA products currently approved for COPD.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

No postmarket requirements or commitments are recommended at the time of this review.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

The proposed drug product is a new fixed-dose, inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination inhalation dry powder administered by a novel dry powder inhaler. The combination device contains fluticasone furoate (FF) as the ICS and vilanterol (VI) as the LABA in 2 double foil blister packs. Within the foil packs, one strip contains 100 mcg of FF and the second 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 approved indications for patients with chronic obstructive pulmonary disease (COPD).

- “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: Available treatments for maintenance treatment of airflow obstruction in COPD**

Class		Generic Name	Brand Name
Beta <sub>2</sub> -adrenergic agonists	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
		Indacaterol maleate	Arcapta Neohaler
	Anti-cholinergics	Short-acting	Ipratropium bromide
Long-acting		Tiotropium bromide	Spiriva Handihaler
		Acclidinium bromide	Tudorza Pressair
Combination	SABA/anti-cholinergic	Albuterol/Ipratropium Albuterol/Ipratropium	Combivent Combivent respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus
		Budesonide/Formoterol	Symbicort
Xanthines	Non specific phosphodiesterase inhibitor	Theophylline	Multiple

**Table 2: Available 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 is approved as an orally-inhaled product. Vilanterol is a new molecular entity.

Fluticasone furoate, was approved on April 27, 2007 in an intranasal formulation as Veramyst Nasal Spray at a dose of 110 mcg once daily for patients  $\geq$  12 years of age for the treatment of seasonal and perennial allergic rhinitis and at a dose of 55 mcg once daily for children age 2 to 11 years old for the same indications.

### 2.4 Important Safety Issues With Consideration to Related Drugs

As evidenced by previous ICS/LABA development programs in COPD, the use of ICS in this patient population has been associated with an increased risk of pneumonia and lower respiratory tract infections in an ICS-dose-dependent 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 observed in COPD.

### 2.5 Summary of Presubmission Regulatory Activity Related to Submission

The Division and GSK have had multiple prior interactions to discuss the proposed FF/VI COPD development program. The table below provides a timeline of regulatory interactions and outlines major discussion points relevant to the COPD program. In addition, discussion highlights pertinent to the COPD indication from the interactions regarding the sponsor's asthma program are also highlighted.

**Table 3: Key Presubmission Interactions between Division and Sponsor**

Date	Interaction	Highlights as they pertain to the COPD indication
January 31, 2007	Pre-IND (VI)	<ul style="list-style-type: none"><li>• Characterize VI monocomponents prior to developing FF/VI</li></ul>
April 29, 2008	Pre-IND	<ul style="list-style-type: none"><li>• Obtain dose regimen and ranging information for VI in COPD</li><li>• Asthma data may not apply to COPD, each monocomponent must be examined in addition to the combination product</li><li>• Compare once-daily regimen to twice daily regimen</li></ul>
May 23, 2008	IND	<ul style="list-style-type: none"><li>• Safe to proceed</li></ul>
March 31,	EOP2:	<ul style="list-style-type: none"><li>• Division noted need to directly compare QD to BID regimens to establish</li></ul>

Date	Interaction	Highlights as they pertain to the COPD indication
2009	asthma	the appropriate dosing frequency
June 17, 2009	EOP2: COPD	<ul style="list-style-type: none"> <li>• 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</li> <li>• 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</li> <li>• Phase 3 trial design options discussed; Division noted that replicate trials were expected to support a bronchodilator claim and an exacerbation claim</li> </ul>
December 9, 2009	Type C meeting: COPD mortality	<ul style="list-style-type: none"> <li>• Bronchodilator dose selection in COPD should be informed by bronchodilator-sensitive population</li> <li>• Discussion of mortality trial design</li> </ul>
March 24, 2010	Type C meeting: asthma dose selection	<ul style="list-style-type: none"> <li>• 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</li> <li>• FDA agreed that 25 mcg VI appeared reasonable for COPD (B2C111045), but that lower doses may be efficacious for asthma</li> </ul>
June 8, 2010	Type C meeting: asthma phase 3 asthma	<ul style="list-style-type: none"> <li>• Dose selection in COPD should be informed by bronchodilator sensitive population</li> <li>• Bronchodilator dose may differ between asthma and COPD</li> <li>• Asthma safety data should be submitted with COPD NDA to support FF/VI safety in COPD</li> </ul>
July 13, 2011	COPD Pre-NDA	<ul style="list-style-type: none"> <li>• Division noted a lack of replicate statistically significant benefit of FF/VI over VI alone for spirometry data</li> </ul>
October 12, 2012	Asthma Pre-NDA	<ul style="list-style-type: none"> <li>• Division requested that asthma application be submitted concurrently with COPD application</li> </ul>
EOP2 = end of phase 2, IND = investigational new drug, NDA = new drug application		

## 2.6 Other Relevant Background Information

In previous ICS/LABA COPD development programs, approval of the combination product has followed approval in asthma. As this is not the case for this clinical program, the NDA application includes comprehensive dose-ranging information in both asthma and COPD as well as safety data from the FF/VI asthma program.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

The submission is appropriately indexed and complete to permit review. The statistical reviewer determined that conducting a center effect analysis would not be helpful in identifying possible sites for an Office of Scientific Investigations (OSI) audit as each of the individual centers enrolled only a small number of subjects and many centers failed to enroll subjects in each treatment group; therefore, no center effect analysis is included in this review.

One site, center 189089, had two sub-investigators who are listed as current or former employees of GSK. This center enrolled 26% (7 of 27) subjects in the asthma trial HZA11326, which was submitted as secondary support. GSK ran an internal impact analysis that determined that the removal of data from this site decreased the FF/VI treatment, but remained statistically superior to placebo. Removal of this trial on the early asthmatic response retained a numeric positive treatment effect of FF/VI but statistical significance was lost. Given the results of GSKs internal analysis and that these asthma data only provide supplemental efficacy evidence for the sponsor's proposed COPD indication, no OSI audit of this site was requested.

Of note, the program had a disproportionate number of fatal cases of pneumonias from a single site in the Philippines with four of the seven fatal cases occurring at this site. In addition, trial 102871 had a disproportionate number of fatal pneumonia cases with all but one of the cases occurring in this study. An OSI audit of this site has been requested and may be informative in determining the cause of the imbalance.

An OSI audit of the two centers enrolling the largest number of subjects for a trial from each indication has also been requested (site 068982 for trial 102871 and site 069133 for trial 112206; Table 4).

While final OSI recommendations remain pending at the time of this review, a preliminary review has not revealed any issues that would impact the interpretation of overall efficacy results from the clinical development program.

**Table 4: Largest center enrollment for pivotal trials**

Site #	Contact Information	Protocol Number	Number of Subjects
068982	Martinez	102871	29 out of 1622 (1.79%)
069133	Kerwin	112206	28 out of 1030 (2.71%)

Source: CSR 112206 and 112207 table 5.09 and 102871 and 102970 table 5.08

### 3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in each complete study report and in the efficacy information amendment located in Module 2.5 Section 1.4.1.

### 3.3 Financial Disclosures

GSK provided financial disclosure information for trials with study sites in the United States. None of the investigators had a proprietary interest in the product, but one investigator (b) (6) reported significant equity interest.

- (b) (6) principal investigator for site (b) (6) recruited (b) (6) subjects in trial (b) (6) and reported an equity interest in GSK that peaked at \$72,000.

Given that (b) (6) site recruited only (b) (6) study participants, any potential conflict of interest would not impact the overall interpretation of the study results. Multiple additional investigators had financial disclosures to report; however, none are likely to have impacted the study results.

GSK failed to obtain follow-up financial information on 3 additional investigators: one investigator retired and was not available for follow up, another investigator died, and the third failed to fully complete the form. Again, the failed reporting from these investigators is unlikely to impact the overall interpretation of the trial results.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The preliminary recommendation from the CMC review team is Approval pending site inspection and analytical method validation.

The drug product is a plastic inhaler with a light grey body, a pale blue mouthpiece cover and a dose counter with two double-foil blister strips containing the active ingredients. One blister strip contains a white powder mix of 100 mcg of micronized FF with 124 mg lactose monohydrate (b) (4). The second blister strip contains a white powder mix of 40 mcg of micronized VI trifenatate with 125 mcg

magnesium stearate (b) (4) and 12.34 mg lactose monohydrate (b) (4)

Based on a cutoff date of February 15, 2012, 97,841 of the to-be-marketed devices were dispensed during both the asthma and COPD development programs. A total of 46,469 inhalers were dispensed in the asthma development program, with 89 inhalers (0.19%) reported as malfunctioning and 51,372 inhalers were dispensed in the COPD development program with 58 inhalers reported as malfunctioning (0.11%). The majority of malfunctioning units were due to problems with the dose counter. GSK has reported that modifications to this dose counter have been made to the commercial unit. These changes to the device have been reviewed by the CMC reviewer, who has determined that they do not impact drug delivery or the approvability of the product.

Design robustness and ruggedness of the inhaler were also evaluated by GSK throughout the development program. In addition, a Human Factors User Error study was conducted using the commercial inhaler. A total of 48 inhaler users and 12 caregivers of inhaler users aged 12 to 78 years were enrolled. A single subject (out of 62) failed to open the mouthpiece fully before inhaling. All other tasks were successfully performed by all 62 subjects. These data, in addition to the clinical trial data using the to-be-marketed product, support approval of the product from a device perspective.

## 4.2 Clinical Microbiology

An approval of this application is recommended from the product quality microbiology team. Additional details from the microbiology review are found in Dr. Stephen Langille's microbiology review dated November 27, 2012.

## 4.3 Preclinical Pharmacology/Toxicology

The recommendation from the preclinical review is Approval. Details of the preclinical pharmacology/toxicology review can be found in the nonclinical review.

### Fluticasone furoate

All FF non clinical data were previously submitted to and reviewed in NDA 22-051 (Veramyst nasal spray; approved April 27, 2007). Per the non clinical review, FF possesses a toxicity profile typical of inhaled corticosteroids and the drug is non-genotoxic, non-carcinogenic and non-teratogenic.

### Vilanterol

The general toxicity of inhaled VI was evaluated in mice, rats and dogs for 13, 26, and 39 weeks respectively. The following target organs for VI toxicity were identified: upper airways, heart, liver and testes. Per the nonclinical review, the findings are typical of

beta-agonists. The carcinogenicity of VI was evaluated in two traditional bioassays. The rat study showed a dose-related shortening of latency for pituitary neoplasms in both sexes and increases in the incidence of leiomyomas in mesovarian ligaments in females. In mice, females showed increases in the incidence of tubulostromal carcinomas in the ovaries, and in leiomyomas and leiomyosarcomas in the uterus. Per the nonclinical review, these findings are typical of beta agonists in rodents. In addition, maternal exposure of VI caused dose-dependent increases in fetal malformations in rabbits and variations in both rats and rabbits. Vilanterol alone did not affect fertility in either males or female rats.

#### FF and VI in combination

The potential for inhaled FF and VI interactions was evaluated in both rats and dogs. The nonclinical review did not find any significant toxicological interactions between inhaled VI and FF.

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

## **4.4 Clinical Pharmacology**

### **4.4.1 Mechanism of Action**

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

### **4.4.2 Pharmacodynamics**

Traditionally, approval of an ICS/LABA combination product for COPD follows the approval of orally inhaled formulations of the monocomponents and of the combination product in asthma. In this case, neither fluticasone furoate nor vilanterol are currently approved as an orally inhaled formulation, nor is the combination FF/VI approved in asthma. Instead, the sponsor has chosen to pursue approval 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. These data are reviewed in this section of the NDA review. Because single agent ICS therapy is not thought to be efficacious in COPD, dose ranging information for FF monotherapy in COPD was not obtained. The sponsor does have a small trial in COPD containing three FF doses coupled with a fixed dose of VI. While the primary objective of this trial was to evaluate the 24 hour treatment effect of FF/VI, this trial does provide some dose ranging information. Importantly, all three FF doses were carried forward into the phase 3 program for confirmation of the FF dose in the combination product in COPD.

### **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 asthma data is presented first followed by the COPD dose-ranging information and the dosing interval data obtained in asthma.

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

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

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. 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.

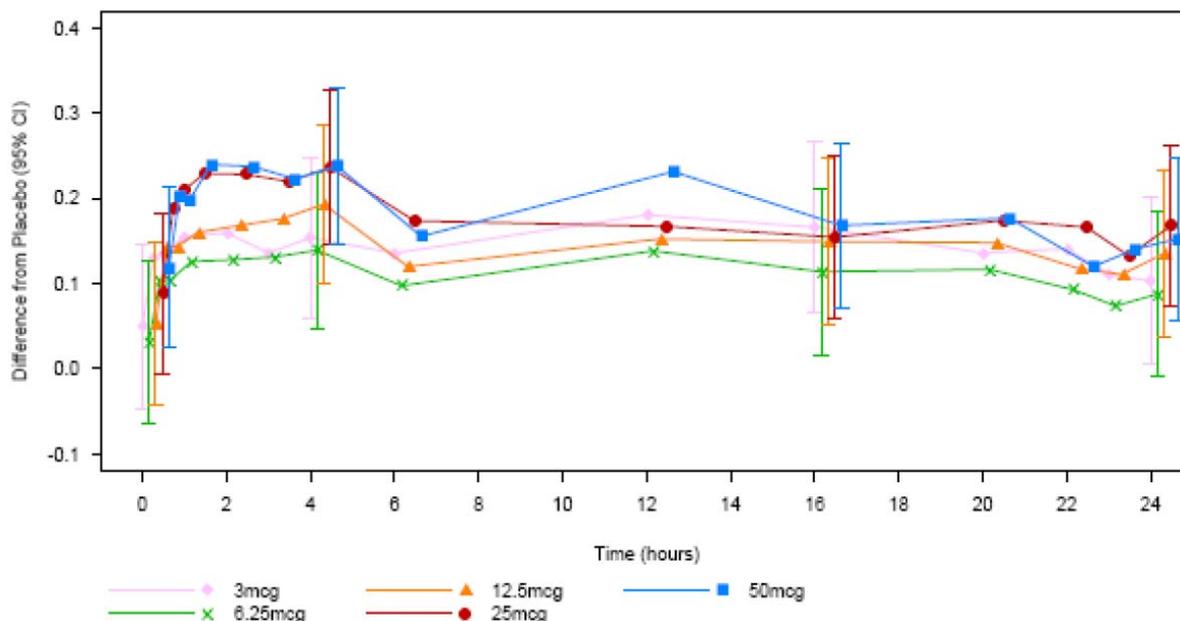
Trial B2C109575: VI Dose-Ranging in Asthma

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  $\geq 12$  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 5: 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
Source: CSR B2C109575 Table 12						

Figure 1: 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 increased benefit provided by the higher doses appears to diminish towards the end of the dosing. While the trough FEV1 point estimate for 12.5 mcg dose suggests that lower doses may be equally efficacious, a lower treatment effect is seen for this dose in the early part of the time curve suggesting that this dose may be too low.

Overall, the results from this trial are supportive of the VI 25 mcg dose.

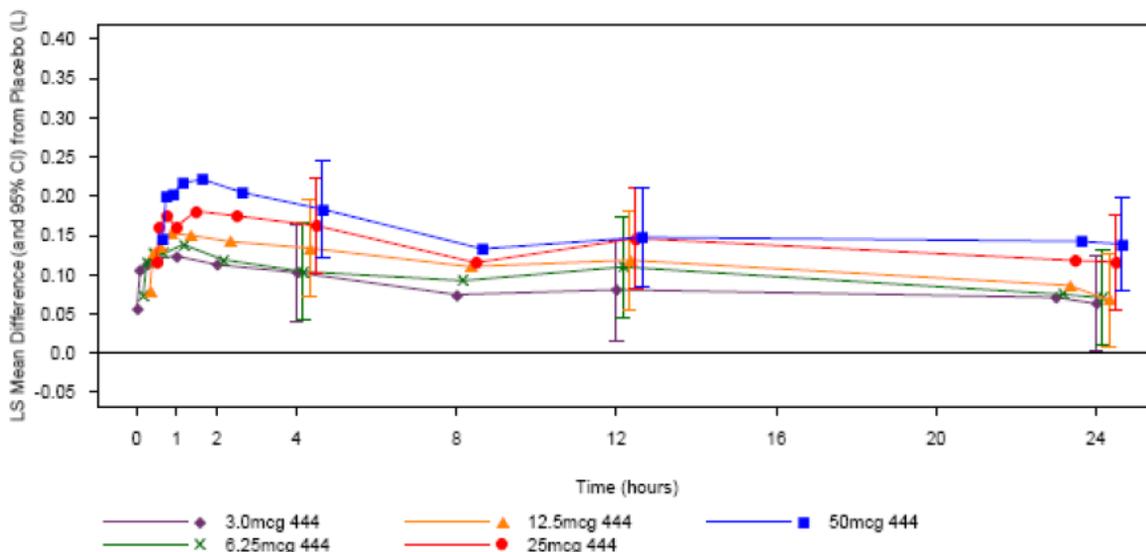
#### Trial B2C111045: VI Dose-Ranging Trial in COPD

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  $\geq 40$  years of age with COPD with a post-bronchodilator FEV1  $\leq 70\%$  and FEV1/FVC ratio  $\leq 0.70$  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  $\geq 12\%$  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 6: 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
<b>Primary Efficacy Endpoint: Day 29 Change from baseline in trough FEV1</b>						
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
<b>Secondary Efficacy Endpoint: Change from baseline Weighted Mean Serial FEV1 on 28</b>						
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 2: 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

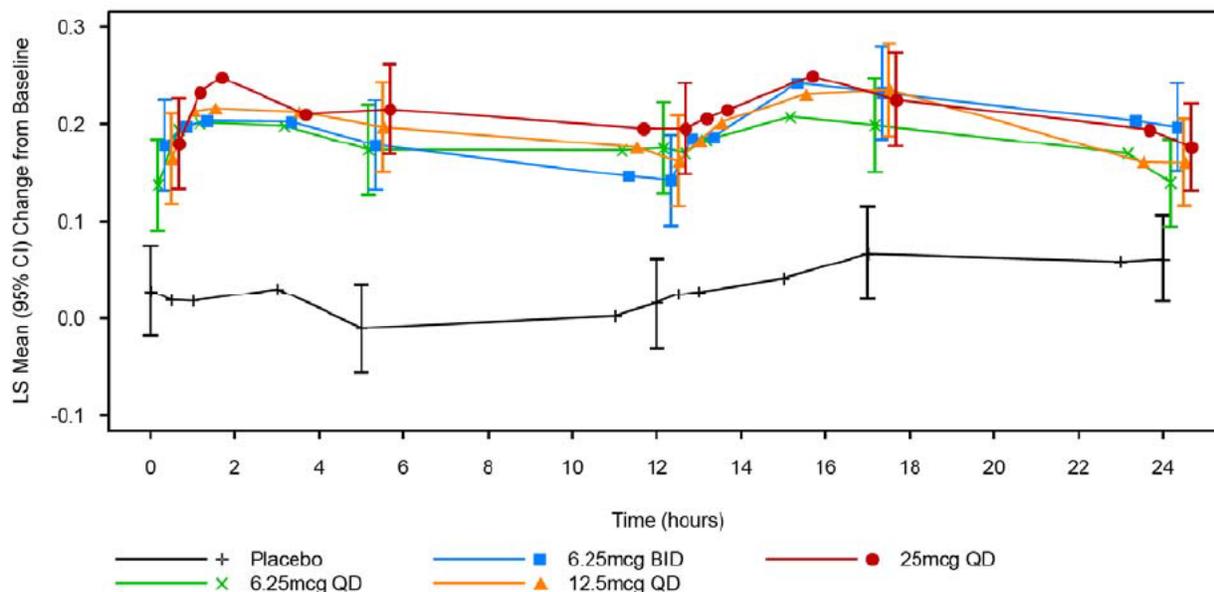
Based on the data from this VI dose-ranging trial in COPD, evaluating VI 25 mcg in the phase 3 trials was reasonable. All doses of VI demonstrated a statistically significant improvement over placebo in a dose-dependent manner for both the primary endpoint, trough FEV1, as well as the secondary endpoint, weighted mean FEV1 (0-24h). However, as shown in Figure 2, 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 HZA113310: VI Dose-Interval 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 7: 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
<b>Trough FEV1: day 7 change from baseline</b>				

	6.25 QD N = 73	6.25 BID N = 74	12.5 QD N = 73	25 QD N = 73
LS mean change from placebo (L)	0.094	0.140	0.102	0.125
P value	<0.001	<0.001	<0.001	<0.001
<b>Weighted mean FEV1 (0-24h): day 7 change from baseline</b>				
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 trough FEV1 results suggest that 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 with the 6.25 mcg twice daily dose demonstrating a lower treatment effect in the early part of the time curve. This finding is further supported by the weighted mean FEV1 (0-24h) data which demonstrates the larger treatment effect for the 25 mcg once-daily dose compared to the 6.25 mcg twice-daily and 12.5 mcg once-daily doses.

Given these results carrying forward the once-daily dose of VI into the phase 3 trials was not unreasonable.

### **FF Dose and Dosing Regimen Selection**

Since asthmatic patients are thought to be more steroid-sensitive, dose-ranging for FF monotherapy was primarily conducted in asthma. 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 8.

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 8: FF Dose-ranging in Asthma: 9685 and 9687**

	PBO	FF once daily						FP twice daily	
		25	50	100	200	300	400	100	250
<b>Trough FEV1: change from baseline at week 8</b>									
<b>Trial 9687</b>									
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	
<b>Trial 9685</b>									
N	106			102	101	102	97		99
LS mean change from Placebo (L)				0.207	0.238	0.293	0.279		0.225
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 Diskus 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 treatment 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 9 below.

**Table 9: FF Dose Regimen in Asthma: 1202**

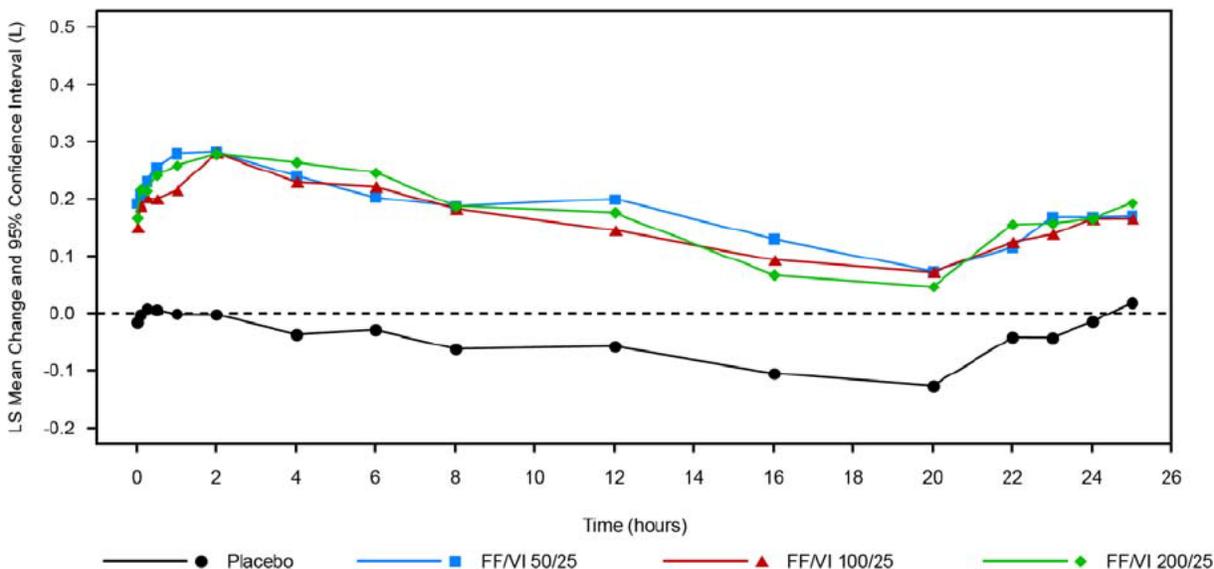
	FF 200 QD N=140	FF 100 BID N = 142	FP 200 QD N = 42	FP 100 BID N = 43
<b>Trough FEV1: LS mean change from baseline at Day 28</b>				
LS mean change from placebo (L)	0.108	0.098	0.087	0.132
P value	<0.001	<0.001	<0.001	<0.001
LS mean change from FF 100 BID (L)	0.011			
P value	0.641			
Source: CSR FFA112202 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 10: FF/VI Dose-ranging in COPD: 0946**

	FF/VI once a day		
	50/25 N = 34	100/25 N = 33	200/25 N = 31
<b>Trough FEV1: LS mean change from baseline at Day 29</b>			
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. Given the argument that the benefit of FF may be better seen through an evaluation of non-spirometric variables, it was reasonable to carry forward all three FF/VI doses into the phase 3 program for further evaluation.

Trial HZA11464: AM vs PM Dosing for FF/VI in Asthma

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.

### **4.4.3 Pharmacokinetics**

The preliminary assessment of the clinical pharmacology review is for Approval; however, final recommendations are pending at the time of this review.

The FF C<sub>max</sub> and AUC are 47% and 46% lower in COPD patients compared to healthy subjects and for VI, C<sub>max</sub> is 67% lower while AUC(0-24) is 24% higher in COPD patients compared with healthy subjects.

VI clearance is decreased by 27% in patients > 65 years of age resulting in a higher AUC<sub>(0-24)</sub> in these patients. No difference in exposure for patients > 65 years of age is seen for FF. No influence of gender on PK of either FF or VI is seen. Systemic exposure for East Asian, Japanese and South Asian patients are, on average, 23% higher compared to white Caucasians.

For patients with hepatic impairment, systemic FF exposure is higher and VI exposure is unchanged. For patients with renal impairment, systemic FF exposure is lower and systemic VI exposure is higher. The clinical pharmacology team is recommending no dose adjustments for patients with renal impairment. For hepatic impairment, while no dose adjustment is recommended, the team recommends use with caution.

Co-administration with ketoconazole results in a modest increase in mean FF and VI AUC<sub>(0-24)</sub> and C<sub>max</sub> (FF 36% and 33%; VI 65% and 22%); however no dose adjustment is recommended. In addition, no dose adjustment is recommended for use with verapamil.

## **5 Sources of Clinical Data**

### **5.1 Tables of Studies/Clinical Trials**

Traditionally, ICS/LABA combination products in COPD have drawn on the experience from the individual monocomponent development programs as well as from the combination product's development program in asthma. As this is 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 11 below. Of note, all of the following trials included the to-be-marketed formulation which was administered via the to-be-marketed novel dry powder inhaler device<sup>1</sup>. The results of these trials are reviewed in Section 4.4.2.

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<sup>1</sup> Trial B2C111401 also included treatment arms containing an older formulation of VI

**Table 11: FF and VI Dose Selection Trials**

Trial (dates)	Design	Population (N)	Treatment	Time (weeks)	Primary Endpoint	Sites (Countries)
<b>Vilanterol</b>						
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)
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)
<b>Fluticasone furoate</b>						
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	8	Trough FEV1	98 (US, Canada, Mexico, Europe)

Trial (dates)	Design	Population (N)	Treatment	Time (weeks)	Primary Endpoint	Sites (Countries)
			FP 250 BID Placebo BID			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)
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)
<b>Fluticasone furoate with fixed dose vilanterol</b>						
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 12. The phase 3 trial designs are presented in detail in Section 5.3, 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 6.1.10.

**Table 12: Pivotal Phase 3 Trials**

Study dates	Design	Population	Wks	Treatments	N	Primary Endpoint	Sites Countries (n)
<b>24-week lung function trials: 2206 and 2207</b>							
112206 <i>Oct 2009</i>	R, DB, PC	COPD	24	FF/VI 50/25 FF/VI 100/25	206 206	Trough FEV1	<i>Chile (36), Estonia (58), Germany (132), Japan (42), Korea (124),</i>

Clinical Review  
Sofia Chaudhry, MD  
NDA 204275  
Breo Ellipta (fluticasone furoate and vilanterol)

Study dates	Design	Population	Wks	Treatments	N	Primary Endpoint	Sites Countries (n)
to Feb 2011				FF 100 VI 25 PBO	206 205 207	WM FEV1 (0-4h)	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 FEV1  WM FEV1 (0-4h)	Czech Republic (77), Germany (282), Japan (47), Poland (103), Romania (270), Russian Fed. (103), Ukraine (34), U.S. (308)
<b>52-week exacerbation trials: 2871 and 2970</b>							
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 exacerb.	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 exacerb.	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)
<b>3 month active comparator trials: 3107, 3109, 2353</b>							
113107 Feb 2011 to Oct 2011	R, DB, AC, PG	COPD: FEV1≤70%, exacerbation within 3 yrs	12	FF/VI 100/25 FP/S 500/50	266 262	WM FEV1 (0-24h)	Philippines (101), Germany (96), Russian Federation (80), Poland (79), Italy (63), Spain (53), Belgium (20), Ukraine (19), France (17)
113109 Mar 2011 to Dec 2011	R, DB, AC, PG	COPD: FEV1≤70%, exacerbation within 3 yrs	12	FF/VI 100/25 FP/S 250/50	260 259	WM FEV1 (0-24h)	Romania (149), United States (147), Germany (68), Poland (61), Czech Republic (52), Russian Federation (42)
112352 Mar 2011 to	R, DB, AC, PG	COPD: FEV ≤ 70%	12	FF/VI 100/25 FP/S 250/50	259 252	WM FEV1 (0-24h)	United States (150), Ukraine (134), S Africa (90), Sprain (76), Italy (61),

Study dates	Design	Population	Wks	Treatments	N	Primary Endpoint	Sites <i>Countries (n)</i>
Jan 2012							
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 Kingdom U.S. = United States; mod = mod/sev = moderate/severe; exac. = exacerbation							

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 13 summarizes the main trials comprising the COPD safety database. Table 70 in Section 7.7 outlines the studies included in the 120-day safety update.

**Table 13: COPD Safety Database**

Trial	Design	Weeks	Population	Treatment Arms	N
<b>24-week Lung function Trials</b>					
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
<b>52-week Exacerbation Trials</b>					
2871	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
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
<b>Supplemental one month COPD trials</b>					
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

Trial	Design	Weeks	Population	Treatment Arms	N
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
<b>Advair Comparator Trials</b>					
3107	R, DB, AC, PG	12 week	COPD: FEV1≤70%, exacerbation within 3 yrs	FF/VI 100/25 FP/S 500/50	266 262
3109	R, DB, AC, PG	12 week	COPD: FEV1≤70% exacerbation within 3 yrs	FF/VI 100/25 FP/S 250/50	260 259
2352	R, DB, AC, PG	12 week	COPD: FEV ≤ 70%	FF/VI 100/25 FP/S 250/50	259 252
Source: Module 5.2 Tabular listing of all clinical studies					

## 5.2 Review Strategy

The focus of this review is on the clinical development program conducted in support of FF/VI in COPD. The dose ranging trials and results are reviewed in Section 4.4.2. The pivotal phase 3 protocol designs are reviewed in this section and the efficacy and safety results are reviewed in Section 6 and Section 7 respectively. Any supportive efficacy and safety data generated from other trials are reviewed in the applicable efficacy or safety section. This includes a review of GSK's integrated summary of safety for its asthma database in Section 7.4.5.

## 5.3 Discussion of Individual Studies/Clinical Trials

### 5.3.1 Lung Function Trials: HZC112206 and HZC11207

Studies HZC112206 and HZC112207, hereafter referred to as 2206 and 2207, respectively, were similarly designed trials initiated in 2009 and completed in February and March of 2011, respectively. The only difference between the two trials is the dosage strengths of FF/VI and corresponding FF comparator arms. Trial 2206 evaluated FF/VI 50/25 and 100/25 with 100 mcg FF and 2207 evaluated FF/VI 100/25 and 200/25 with corresponding FF 100 and 200 mcg doses. Both trials also evaluated a VI 25 mcg arm and placebo. The use of a placebo control arm 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.

The protocol for 2206 is detailed below and serves as the protocol description for both trials. This is followed by the administrative information for trial 2207.

### **HCZ112206**

#### **Administrative Information:**

- 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)
- Study Dates: October 19, 2009 – February 16, 2011
- Study Sites: Chile (36), Estonia (58), Germany (132), Japan (42), Korea (124), Philippines (87), Poland (86), Russian Federation (65), United States (400)
- Study Report Date: May 2012

#### **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 2 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 obtain baseline assessments and compliance with study procedures. Subjects who remained eligible were then randomized and entered the 24-week treatment period. Subjects were stratified according to smoking status. All subjects 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 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. It was performed after withholding morning dose of COPD medications at Visit 1 and after withholding morning dose of single-blind and during the run-in and prior to am dose of double-blind study medications during the treatment period. Rescue medication was withheld for  $\geq 4$  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 14: 2206 Time and Events Table**

Visit	1	2	3	4	5	6	7	8	9	10	11	12	Early WD	Follow up +7
Day <sup>1</sup>	-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	
<b>Safety Assessments</b>														
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
<b>Efficacy Assessment</b>														

Visit	1	2	3	4	5	6	7	8	9	10	11	12	Early WD	Follow up +7
Day <sup>1</sup>	-14	1	2	7	14	28	56	84	112	140	168	+1		+7
Week	-2			1	2	4	8	12	16	20	24			
Spirometry	X												X	
Serial spirometry <sup>2</sup>		X			X		X	X			X			
Trough spirometry			X	x	X	X	X	X	X	X	X	X		
<b>Additional Assessments</b>														
Resource utilization		X	X	X	X	X	X	X	X	X	X	X		
PK sampling								X			X			
<b>Medications</b>														
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	
<b>Diary</b>														
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														
<sup>1</sup> (±2) for each day except Day 1( Visit 1) <sup>2</sup> Serial spirometry performed 30 minutes pre-dose, 5 minutes pre-dose and post dose at 5, 15, 30 minutes and 1, 2, and 4 hours. At visits with serial and trough spirometry pre-dose serial measurements include 23 and 24 h trough measurements  WD = withdrawal; IC = informed consent; PG = pharmacogenomic; CXR = chest xray, VS = vital signs, PE = physical exam, OP = oropharyngeal, AE = adverse event; PE = physical exam; VS = vital signs; ECG = electrocardiogram; SABA = short acting bronchodilatory therapy, SB = single blind, DB = double blind, PEF = peak expiratory flow,														

The study was designed appropriately 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.

**Study Population**  
Inclusion Criteria

- Male or female subjects  $\geq 40$  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
  - $FEV_1/FVC \leq 0.70$
  - Post SABA  $FEV_1 \leq 70\%$  of predicted
- Current or prior history  $\geq 10$  year pack year history of cigarette use
- $\geq 2$  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,  $\alpha$ -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 must 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 study 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 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., <b>tiotropium</b> )	1 week
Theophylline preparations	48 hours
Oral leukotriene inhibitors (zafirlukast, montelukast, zileuton)	48 hours
Inhaled long acting beta <sub>2</sub> -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 <sub>2</sub> -agonists <sup>1</sup>	4 hours (albuterol/salbutamol will be supplied for rescue during the study)
Short-acting anti-cholinergics (e.g., <b>ipratropium bromide</b> <sup>2</sup> )	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 PRN oxygen use
- Clinically significant sleep apnea
- Pulmonary rehabilitation within 4 weeks of screening or will enter a program during the study. Subjects 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 subject at risk

Randomization Criteria:

- COPD exacerbation/LRTI during run-in
- Abnormal, clinically significant laboratory finding at screening
- Abnormal and clinically significant 12-lead ECG at screening reviewed by independent, centralized cardiologist. Abnormal changes include but are not limited to:
  - Sinus bradycardia < 45 bpm or sinus tachycardia  $\geq$  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 2<sup>nd</sup> degree heart block or third degree
  - Sinus pause  $\geq$  2 seconds (p wave to p wave)
- Non-compliance

Withdrawal Criteria:

- 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

Permitted Medications and non-drug therapy during screening or treatment period

- Study-supplied albuterol/salbutamol (MDI or nebulas)
- 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  $\leq 12$  hours a day
  - Cardioselective beta-blockers (stable dose) and ophthalmic beta-blockers.
  - Antihistamines and nasal decongestants
  - OTC cough suppressants (for short term treatment  $\leq 7$  days)
  - Intranasal cromolyn or nedocromil
  - Intranasal, ophthalmic and topical corticosteroids
  - Antibiotics that are not strong inhibitors of cytochrome P450 3A4 for short term treatment ( $\leq 14$  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.

### **Study 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 administered using the to-be-marketed NDPI which contains two blister foil packs. The FF/VI formulation administered was the to-be-marketed product. For the monotherapy treatment arms and placebo, the NDPI contained the same foil packs with the active drug moieties removed with all other excipients remaining 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  $\leq 80\%$  or  $\geq 120\%$  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 subject temporally associated with the use of medicinal product.
  - A 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 a 80ml difference between FF/VI and VI in trough FEV1 on day 169. 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 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 removed the sleep apnea exclusion criteria, clarified the ECG exclusion criteria for patients with right bundle branch block, in addition to other minor editorial changes. 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.

### **HZC112207**

#### **Administrative Information:**

- 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)

- Study Dates: October 19, 2009 – March 16, 2011
- Study Sites: Czech Republic (77), Germany (282), Japan (47), Poland (103), Romania (270), Russian Federation (103), Ukraine (34), United States (308)
- Study Report Date: May 2012

The trial design for 2207 is the same as trial 2206 described above.

### **5.3.2 Exacerbation trials: HZC102871 and HZC102970**

Studies HZC102871 and HZC102970 were replicate trials initiated at the same time and both completed in October 2011. The protocol for HZC102871, hereafter referred to as 871, is detailed below and serves as the protocol description for both trials. This is followed by the administrative information for trial HZC102970, hereafter referred to as 970.

#### **HZC102871**

##### **Administrative Information:**

- 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
- Study Dates: September 25, 2009 – October 31, 2011
- Study Sites: 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)
- Study Report Date: April 2012

##### **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 3, 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 short-acting anticholinergics to be used on an as needed basis, 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 an early withdrawal visit. All patients were provided with supplemental albuterol/salbutamol MDI and/or nebulas to be used on an as needed basis.

#### COPD Exacerbation Assessment:

Exacerbations were identified based on an IVRS diary review which subjects completed on a daily basis via telephone. In the daily diary, subjects 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 subjects 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 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

COPD exacerbation severity was categorized using the follow definitions. 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 per investigator judgment, if the two exacerbations were separated by no more than three exacerbation free days.

- 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  $\leq$  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 was not considered a COPD exacerbations unless the symptoms met the COPD exacerbation definition outlined above.

#### Pneumonia Identification

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 to be 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 15: Trial 871 Time and Events Table**

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		
<b>Procedures</b>													
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											
<b>Efficacy Assessments</b>													
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	
<b>Safety Assessments</b>													
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											
<b>Laboratory Assessments</b>													

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		
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											
<b>Study supplies And Investigational Product (IP)</b>													
Dispense OL product													
Collect OL													
Dispense IP													
Assess compliance													
Collect IP													
Dispense rescue SABA													
Collect rescue SABA													
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;													
Source: Table 3 Time and Events Table from Protocol 871													

The study was overall designed appropriately to assess the effects of FF/VI compared to VI on exacerbations. In addition, the sponsor’s definition and classification for exacerbations also are reasonable as they include objective parameters which decrease the impact of local practice patterns.

### Study Population

#### Key Inclusion Criteria:

Trial 871 enrolled a similar patient population as trial 2206. However instead of baseline dyspnea symptoms requirement, subjects had to have a documented history of ≥ 1 COPD exacerbation within 12 months of screening.

#### Key Exclusion Criteria

Trial 871 had similar exclusion criteria as 2206, with the following modifications and additions.

- 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 to be over-read by a central vendor
- 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
  - 2<sup>nd</sup> degree Mobitz block of 3<sup>rd</sup> 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  $\leq 14$  days) for the short term treatment of COPD exacerbations were allowed in trial 871 but were not allowed in trial 2206.

### **Study 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  $\leq 80\%$  or  $\geq 120\%$  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  $\geq 2$  consecutive days of symptoms
- Annual rate of exacerbations requiring oral/systemic corticosteroids
- Pre-dose 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.
  - a 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. These 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 tested.

### **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 reflected the amended protocol. The protocol amendment included addition of systemic corticosteroid use in addition oral corticosteroid use to the exacerbation inclusion criteria and secondary endpoint data for annual rate of exacerbations. 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, as well as other editorial changes.

### **Protocol Results**

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

### **HZC102970**

#### **Administrative Information:**

- 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
- Study Dates: September 25, 2009 – October 17, 2011
- Study Sites: Argentina (69), Australia (68), Canada (67), Chile (60), Denmark (79), Germany (55), Italy (127), Mexico (83), Netherlands (97), Peru (66), South Africa (165), Spain (36), Sweden (42), United Kingdom (39), United States (580)
- Study Report Date: April 2012

The trial design for 2970 is the same as trial 2871 described above.

## **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 proposed indications data are drawn from two, 24-week lung function trials (2206 and 2207) and two 52-week exacerbation trials (2871 and 2970). To

evaluate the effect on lung function, the 24-week lung function trials specified 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).

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 the lung function benefit provided FF/VI, they do not assess whether the efficacy of FF/VI is driven by VI alone.

Data for the reduction in exacerbation indication is drawn from the replicate, 52-week exacerbation trials (2871 and 2970), which evaluated the effect on the annual rate of moderate to severe exacerbations as the primary endpoint.

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 24-week lung functions (2206 and 2207).

The benefit FF provides to the combination product is demonstrated in two 52 week exacerbation trials with support drawn from the trough FEV1 results obtained in the four pivotal phase 3 trials.

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). Trial 2970 demonstrates a statistically significant reduction, while trial 2871 demonstrates a similar treatment effect, this result is nominally significant due to failure of the FF/VI 200/25 to VI 25 comparison in this trial.

In addition to a consistent treatment effect for FF/VI 100/25 on exacerbations, numeric improvements in trough FEV1 are 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). This 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. Furthermore, an FF/VI 100/25 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. These data provide supplemental data indicating a treatment benefit for FF/VI over VI.

While the two 52 week exacerbation trials do not provide replicate evidence of statistically significant improvement based on the testing hierarchy for FF/VI 100/25 over VI 25, the totality of the efficacy data comparing FF/VI 100/25 to VI 25 demonstrates the benefit added by the steroid component to the combination product

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, 3109 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 3109 demonstrates a statistically significant difference between the two treatments, the comparison from trial 2352 is not statistically significant. While these data do not provide an assessment of whether FF/VI provides an additional treatment benefit over VI treatment alone, the results suggest that FF/VI has a similar effect on FEV1 as an approved ICS/LABA product,.

## **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 6.1.10.

### **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<sup>2</sup> 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 32.

Overall, the demographics are similar to other ICS/LABA combination development programs for approved products.

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<sup>2</sup> Global Strategy for Diagnosis, Management, and Prevention of COPD: Global Initiative for Chronic Obstructive Lung Disease (GOLD) report revised 2011.

**Table 16: 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
<b>Age</b>						
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
<b>Sex</b>						
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)
<b>Race</b>						
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)
<b>Duration of COPD</b>						
<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)
<b>Smoking Status at screening</b>						
Current Smoker	112 (54)	111 (54)	111 (54)	111 (54)	111 (54)	556 (54)
Former Smoker	95 (46)	95 (46)	94 (46)	95 (46)	95 (46)	474 (46)
<b>Baseline Lung Function</b>						
Mean pre-bronchodilator FEV1 percent predicated	42.4	41.5	44.5	42.5	42.3	42.6
<b>GOLD Stage at Baseline</b>						
≥80% (Stage I)	0	0	0	0	0	0
≥50% (Stage II)	94 (46)	94 (46)	108 (53)	102 (50)	89 (43)	487 (47)
≥30% (Stage III)	93 (45)	88 (43)	83 (40)	84 (41)	97 (47)	445 (43)
<30% (Stage IV)	18 (9)	24 (12)	14 (7)	19 (9)	19 (9)	94 (9)
<b>Reversibility</b>						
Reversible	77 (38)	71 (34)	64 (31)	73 (36)	66 (32)	351 (34)
Non-Reversible	128 (62)	135 (66)	140 (69)	131 (64)	138 (68)	672 (66)
<b>Concomitant Medications</b>						
Short acting anticholinergics	62 (30)	53 (26)	40 (20)	44 (21)	46 (22)	245 (24)
Other respiratory medications	26 (13)	19 (9)	26 (13)	24 (12)	11 (5)	106 (10)

	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
Source: CSR 2206 Tables 8, 9, 10, 11, 12,14						

**Table 17: 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
<b>Age</b>							
Mean	61.9	61.8	61.8	61.2	61.9	61.1	61.6
Median	62	61.5	62	62	62	61	62
Min - Max	40-81	41-84	40-85	41-80	41-84	42-83	40-85
<b>Sex</b>							
Female	53 (26)	54 (26)	52 (26)	52 (26)	60 (29)	68 (33)	339 (28)
Male	152 (74)	150 (74)	151 (74)	151 (74)	144 (71)	137 (67)	885 (72)
<b>Race</b>							
African Heritage	0	2 (<1)	5 (2)	3 (1)	4 (2)	2 (<1)	16 (1)
Amer. Indian or Al. Native	0	0	1 (<1)	0	2 (<1)	0	3 (<1)
Asian	8 (4)	5 (2)	14 (7)	4 (2)	8 (4)	11 (5)	50 (5)
White	197 (96)	197 (97)	183 (90)	196 (97)	190 (93)	192 (94)	1155 (94)
<b>Duration of COPD</b>							
<1 year	24 (12)	22 (11)	29 (14)	19 (9)	18 (9)	18 (9)	130 (11)
≥1 to <5 years	79 (39)	77 (38)	79 (39)	76 (37)	78 (38)	77 (38)	466 (3)
≥5 to <10 years	57 (28)	69 (34)	49 (24)	57 (28)	62 (30)	70 (34)	364 (30)
≥10 to <15 years	30 (15)	24 (12)	31 (15)	25 (12)	30 (15)	21 (10)	161 (13)
≥15 to <20 years	8 (4)	5 (2)	12 (6)	14 (7)	10 (5)	8 (4)	57 (5)
≥20 to <25 years	2 (<1)	5 (2)	2 (<1)	6 (3)	5 (2)	6 (3)	26 (2)
≥25 years	5 (2)	2 (<1)	1 (<1)	6 (3)	1 (<1)	5 (2)	20 (2)
<b>Smoking Status at Screening</b>							
Current	108 (53)	114 (56)	112 (55)	111 (55)	109 (53)	112 (55)	666 (54)
Former	97 (47)	90 (44)	91 (45)	92 (45)	95 (47)	93 (45)	558 (46)
<b>Baseline Lung Function</b>							
Mean Percent Predicted pre-bronchodilator FEV1	43.5	44.6	42.7	43.7	43.8	43	43.6
<b>GOLD Stage at Baseline</b>							
≥80% (Stage I)	0	0	0	0	1 (<1)	1 (<1)	2 (<1)
≥50% (Stage II)	94 (46)	95 (47)	85 (42)	102 (50)	93 (46)	91 (45)	560 (46)
≥ 30% (Stage III)	96 (47)	91 (45)	101 (50)	81 (40)	90 (45)	89 (44)	548 (45)
<30% (Stage IV)	13 (6)	15 (7)	16 (8)	19 (9)	18 (9)	22 (11)	103 (8)

	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
<b>Reversibility</b>							
Reversible	61 (30)	57 (29)	54 (27)	60 (30)	58 (29)	54 (27)	344 (29)
Non-Reversible	142 (70)	142 (71)	147 (73)	140 (70)	142 (71)	144 (73)	857 (71)
<b>Concomitant Medications</b>							
Short acting anticholinergics	41 (20)	35 (17)	39 (19)	42 (21)	41 (20)	46 (22)	244 (20)
Other respiratory medications	13 (6)	5 (2)	11 (5)	9 (4)	10 (5)	13 (6)	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 patient 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 18: 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)
<b>Primary reason for withdrawal</b>						
Adverse event	15 (7)	23 (11)	24 (12)	17 (8)	14 (7)	93 (9)
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 19: 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)
<b>Primary Reason for Withdrawal</b>							
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)

	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
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-dose 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. While not typically evaluated to demonstrate the benefit added by a steroid component, the comparison of FF/VI to VI for weighted mean FEV1 is also presented below as this provides data evaluating FF’s effect on FEV1.

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, this treatment effect appears to be maintained throughout the course of the trial (see Figure 6).

For the lung function benefit provided by FF, improvements of 24ml to 58 ml in trough FEV1 are seen for the FF/VI to VI comparisons. 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 100/25 for both 2206 (0.71 ml) and 2207 (0.29 ml), providing some support for an additional benefit provided by the steroid component.

Of note, 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. However, 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.

**Table 20: Change from Baseline in Mean 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
<b>Trial 2206</b>							
N <sup>1</sup>	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 <sup>3</sup>		0.067 0.017	0.129 <0.001	0.115 <0.001	
Difference from VI 25 mcg P value					0.062 0.025 <sup>2</sup>	0.048 0.082	
Difference from FF 100 P value						0.082 0.003	
<b>Trial 2207</b>							
N <sup>1</sup>	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 <sup>3</sup>	0.008 0.756 <sup>3</sup>	0.1 <0.001		0.144 <0.001 <sup>2</sup>	0.131 <0.001
Difference from VI 25 mcg P value						0.045 0.093 <sup>2</sup>	0.032 0.224
Difference from FF 100 P value						0.1 <0.001 <sup>3</sup>	
Difference from FF 200 P value							0.123 <0.001 <sup>3</sup>
<b>Trial 2871</b>							

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<b>Trial 2970</b>							
N <sup>1</sup>				409	408	403	402
Week 52 LS mean change				-0.04	0.00	0.018	0.024
Difference from VI					0.041	0.058	0.064
P value					0.011 <sup>2</sup>	<0.001 <sup>2</sup>	<0.001 <sup>2</sup>
<b>Trial 2970</b>							
N <sup>1</sup>				409	412	403	409
Week 52 LS mean change				-0.019	0.015	0.005	0.006
Difference from VI 25					0.034	0.024	0.026
P value					0.034 <sup>2</sup>	0.143 <sup>2</sup>	0.115 <sup>2</sup>
Source: Table 21 CSR 2206 and 2207 and Table 18 CSR 2871 and 2970							
<sup>1</sup> number randomized							
<sup>2</sup> nominal p values only due to statistical hierarchal testing procedures							
<sup>3</sup> comparison not included in statistical hierarchal testing procedures							

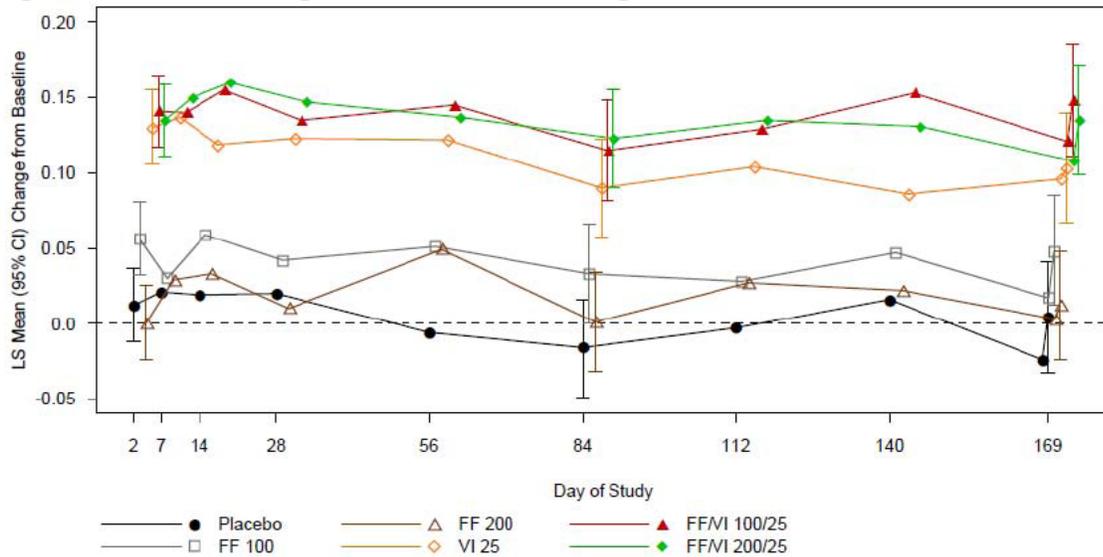
**Table 21: Change from Baseline in Weighted Mean FEV1 (L): 2206 and 2207**

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<b>Trial 2206</b>							
N <sup>1</sup>	207	206		205	206	206	
Day 169 LS mean change	0.029	0.098		0.139	0.239	0.205	
Difference from placebo		0.053		0.103	0.192	0.173	
P value		0.04 <sup>3</sup>		<0.001	<0.001 <sup>2</sup>	<0.001	
Difference from VI 25 mcg					0.090	0.071	
P value					<0.001 <sup>2,3</sup>	0.006 <sup>3</sup>	
Difference from FF 100						0.120	
P value						<0.001	
<b>Trial 2207</b>							
N <sup>1</sup>	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		0.046	0.041	0.185		0.214	0.209
P value		0.085 <sup>3</sup>	0.123 <sup>3</sup>	<0.001		<0.001	<0.001
Difference from VI 25 mcg						0.029	0.024
P value						0.274 <sup>2,3</sup>	0.357 <sup>3</sup>
Difference from FF 100						0.168	
P value						<0.001	
Difference from FF 200							0.168
P value							<0.001
Source: CSR 2206 and 2207 Table 19							
<sup>1</sup> number randomized							

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<sup>2</sup> nominal p values only due to statistical hierarchal testing procedures <sup>3</sup> comparison not included in statistical hierarchal testing procedures							

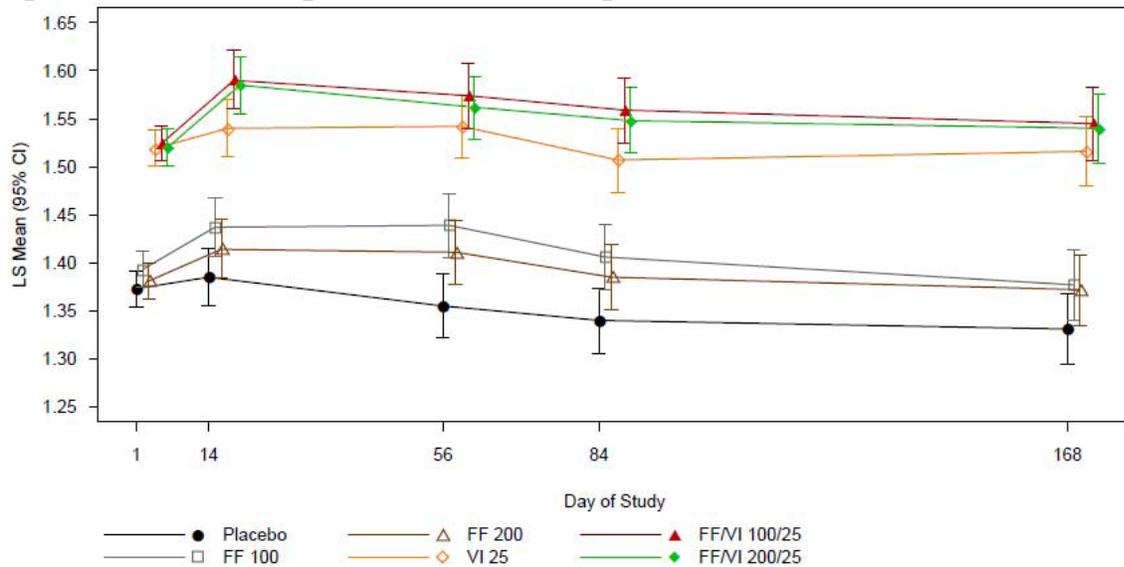
In addition to the weighted mean FEV1 data and trough FEV1 data obtained at the end of the treatment periods, all four trials evaluated these same measures at additional time points throughout the trials. In general, the separation between FF/VI and VI is maintained throughout the course of each study. 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 over Time: 2207**



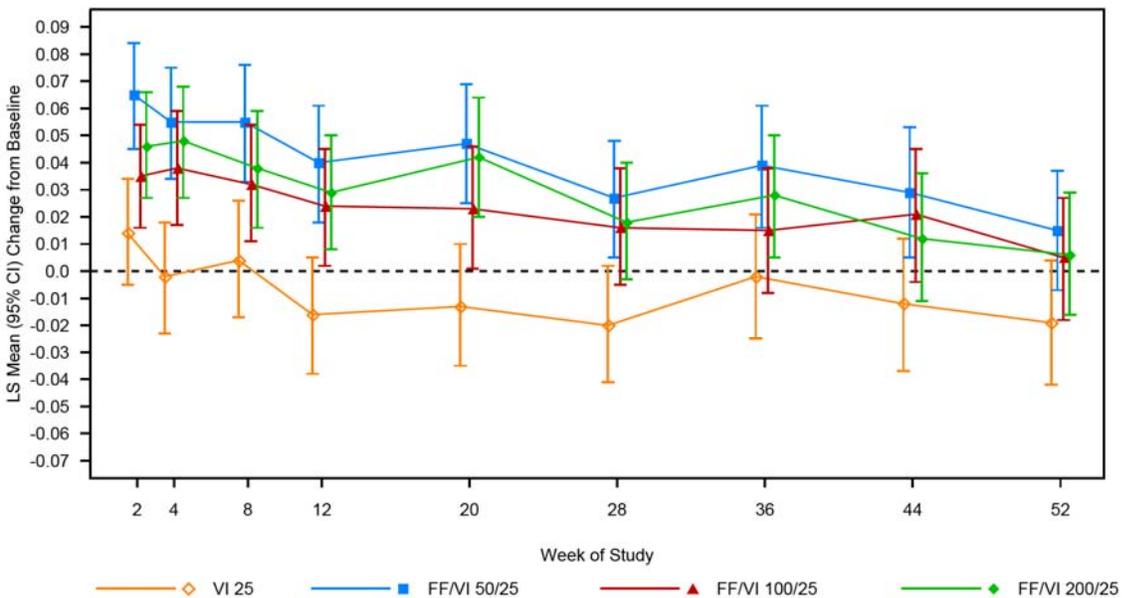
Source: CSR 2207 Figure 3; data presented are the LS means with 95% confidence intervals in trough FEV1 for the ITT using a repeated measures model

**Figure 6: LS Mean Change from Baseline in Weighted Mean FEV1 over Time: 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 over Time: 2970**



Note: Analysis performed using a repeated measures model with covariates of treatment, smoking status at screening (stratum), baseline (pre-dose Day 1), centre grouping, Week, Week by baseline and Week by treatment interactions.

rx91516: /arenv/arprod/gw685698\_gw642444/hzc102970/final/drivers/f\_e\_pf\_trcfblsm.sas 04JAN2012 09:16

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.

GSK’s proposed label includes a time to onset claim. As described below, consistent results are seen in the two trials supporting inclusion of this information into the product label.

#### 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 22: 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
<b>Trial 2206</b>							
N <sup>1</sup>	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	
<b>Trial 2207</b>							
N <sup>1</sup>	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							
<sup>1</sup> 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). While the importance of onset of action for a chronically administered drug is questionable, onset of action information has been included in the product labels of other bronchodilators approved for COPD.

**Table 23: 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
<b>Trial 2206</b>							
N <sup>1</sup>	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 <sup>2</sup> , n (%)	117 (57)	109 (53)		30 (15)	31 (15)	31 (15)	
Median <sup>3</sup> , 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 <sup>2</sup> , n (%)	142 (69)	131 (64)		49 (24)	53 (26)	57 (28)	
Median <sup>3</sup> , min				32	30	59	
<b>Trial 2207</b>							
N <sup>1</sup>	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 <sup>2</sup> , n (%)	103 (50)	85 (42)	96 (48)	21 (10)		31 (15)	28 (14)
Median <sup>3</sup> , 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 <sup>2</sup> , n (%)	141 (69)	132 (65)	132 (65)	53 (26)		51 (25)	61 (30)
Median <sup>3</sup> , min				35		33	61
Source: CSR 2206 and 2207 Table 27, 29							
<sup>1</sup> number randomized							
<sup>2</sup> censored defined as a subject who had at least one post-dose measurement but did not meet criteria.							
<sup>3</sup> 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 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 24: 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
<b>Trial 2206</b>							
N <sup>1</sup>	207	206		205	206	206	
<b>Cough Scores</b>							
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	
<b>Sputum Scores</b>							
LS Mean	1.32	1.24		1.26	1.18	1.21	
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	
<b>Breathlessness Scores</b>							
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	
<b>Trial 2207</b>							
N <sup>1</sup>	205	204	203	203		204	205

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<b>Cough Scores</b>							
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
<b>Sputum Scores</b>							
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
<b>Mean Breathlessness Scores</b>							
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
Difference from FF 100						-0.21	
Difference from FF 200							-0.19
Source: CSR 2206 and 2207 Table 32, 33, 34 <sup>1</sup> 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 25: 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
<b>Trial 2206</b>							
N <sup>1</sup>	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	
<b>Trial 2207</b>							
N <sup>1</sup>	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							
<sup>1</sup> 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 26: 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
<b>Trial 2206</b>							
N <sup>1</sup>	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	
<b>Trial 2207</b>							
N <sup>1</sup>	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

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
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  
<sup>1</sup> 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. 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 27: 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
<b>Trial 2206</b>							
N <sup>1</sup>	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	
<b>Trial 2207</b>							
N <sup>1</sup>	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

Source: CSR 2206 and 2207 Table 38  
<sup>1</sup> 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.

**Table 28: 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
<b>Trial 2206</b>							

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<b>Trial 2206</b>							
N <sup>1</sup>	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	
<b>Trial 2207</b>							
N <sup>1</sup>	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							
<sup>1</sup> 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.” There is no regulatory precedent for a claim based on this questionnaire. 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<sup>3</sup>.

**Table 29: 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
<b>Trial 2206</b>							
N <sup>1</sup>	207	206		205	206	206	
Day 168 LS mean change from baseline	0.23	0.29		0.37	0.42	0.53	

<sup>3</sup> 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
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	
<b>Trial 2207</b>							
N <sup>1</sup>	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							
<sup>1</sup> 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 is seen.

**Table 30: 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
<b>Trial 2206</b>							
N <sup>1</sup>	207	206		205	206	206	
Total Symptom free, mean %							
Baseline,	3	2.8		5	1.8	5	
Week 1-24	6.1	7		10.1	9.7	8.4	
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	

	Placebo	FF 100	FF 200	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<b>Trial 2207</b>							
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	
<b>Trial 2207</b>							
N <sup>1</sup>	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							
<sup>1</sup> 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 31: 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
<b>Trial 2206</b>							
N <sup>1</sup>	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	
<b>Trial 2207</b>							
N <sup>1</sup>	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
Source: CSR 2206 and 2207 Table 31							
<sup>1</sup> 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 32: 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
<b>GOLD Stage 1 and 2<sup>1</sup></b>			
Difference from VI	0.047	0.027	0.033
P value	0.153	0.332	0.32
<b>GOLD Stage 3</b>			
Difference from VI	0.07	0.082	0.036
P value	0.056	0.005	0.315
<b>GOLD Stage 4<sup>2</sup></b>			
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			
<sup>1</sup> No patients with GOLD stage 1 were enrolled			
<sup>2</sup> 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 Analysis of Clinical Information Relevant to Dosing Recommendations**

Only a single dosage strength of FF/VI, 100/25 mcg once daily, is being proposed by GSK for this NDA. A discussion of the dose-selection and regimen trials used to determine which doses to carry forward into the Phase 3 trials is found in Section 4.4.2., and Phase 3 data do not suggest an efficacy benefit for doses higher than FF/VI 100/25.

### **6.1.9 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, the dose-ranging trial of VI in COPD did not demonstrate tachyphylaxis over the first month of treatment (see Table 6). 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).

### **6.1.10 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 for use in COPD 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 comparison 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 trials 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. 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 33: Efficacy data from COPD Advair Comparator Trials**

	FF/VI 100/25	Advair 250/50	Advair 500/50
<b>Trial 3107</b>			
Change from baseline in 24 hour weighted mean FEV1, L	0.130		0.107
Day 84 LS mean $\Delta$ from FF/VI			0.022
P value <sup>1</sup>			0.282
<b>Trial 2352</b>			
Change from baseline in 24 hour weighted mean FEV1, L	0.143	0.113	
Day 84 LS mean $\Delta$ from FF/VI		0.029	
P value <sup>1</sup>		0.267	
<b>Trial 3109</b>			
Change from baseline in 24 hour weighted mean FEV1, L	0.170	0.096	
Day 84 LS mean $\Delta$ from FF/VI		0.080	
P value <sup>1</sup>		P<0.001	
Source: CSRs 3107 2352 and 3109 Tables 12, 13			
<sup>1</sup> 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

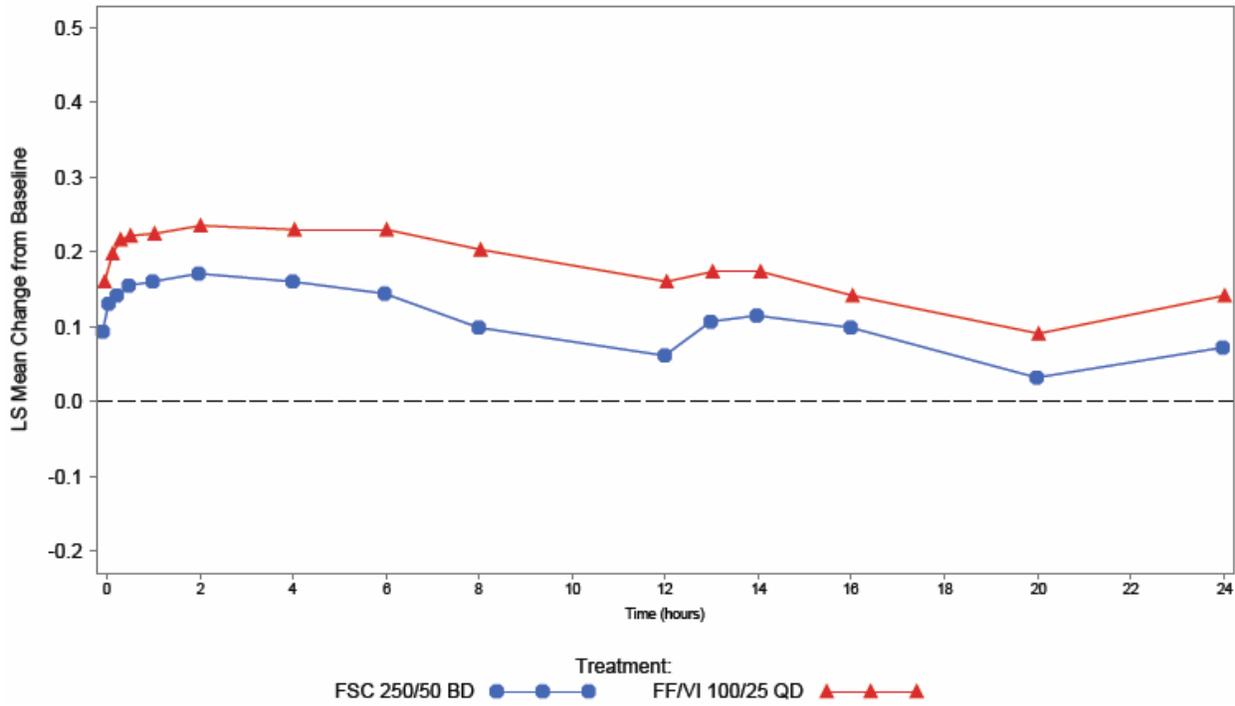
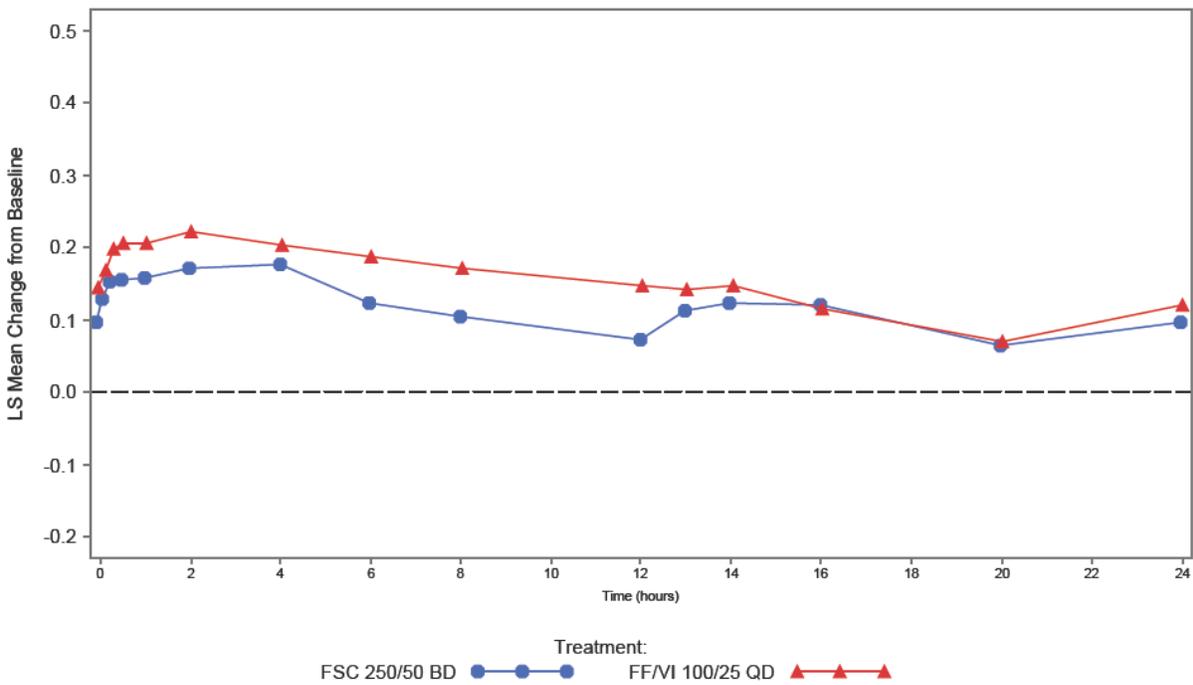
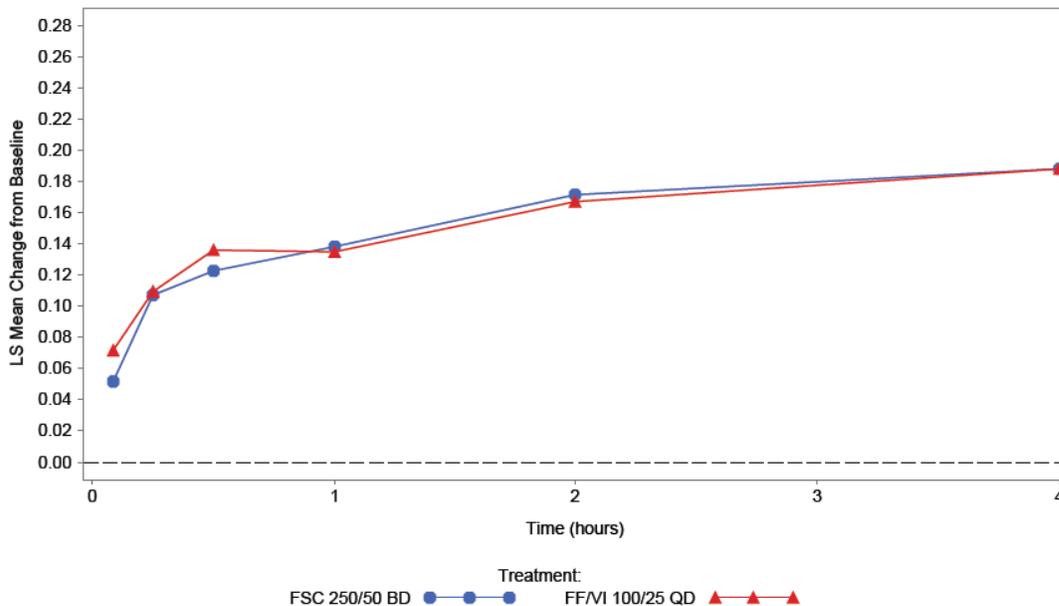


Figure 9: LS Mean Change from baseline in FEV1 on Day 84: 2352



In addition to a general sense of efficacy for FF/VI compared to an approved product, comparisons of the Day 1 post-dosing FEV1 time curves from the Advair comparator trials provide additional support that an excessively high dose of VI was not chosen to compensate for the once daily dosing regimen. While direct comparisons between VI and salmeterol were not performed in these trials, the ICS is unlikely to contribute to the FEV1 effect at this early timepoint. Below is the FEV1 time curve from trial 2352 which demonstrates that the FF/VI and FP/S behaved similarly. This curve is representative of data from trial 3107 and 3109.

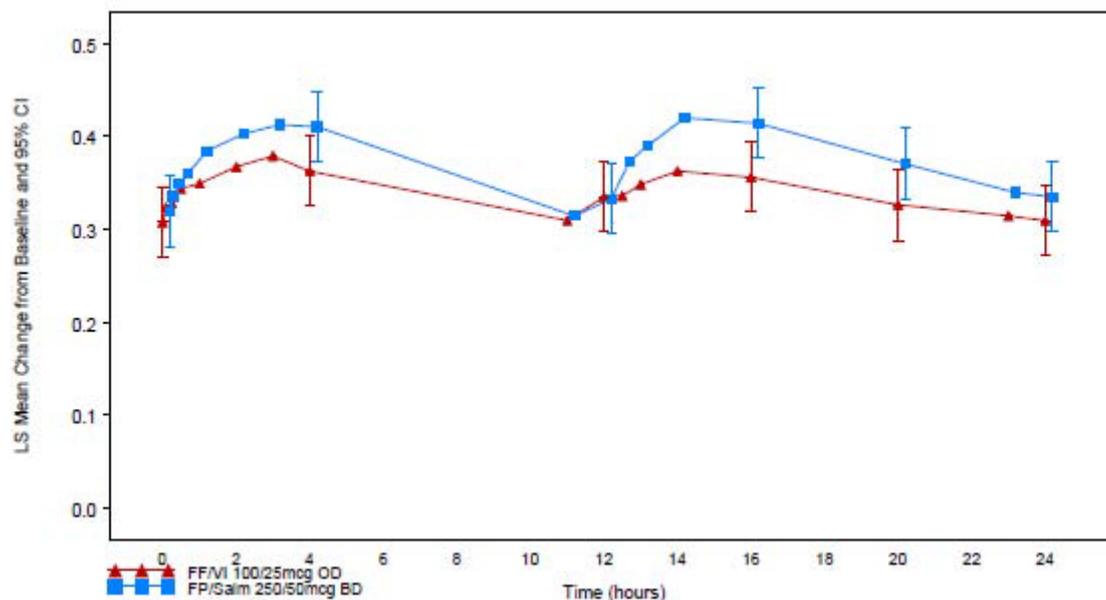
**Figure 10: Day 1 LS Mean Change from Baseline in FEV1: Trial 2352**



Source: CSR 2352 Figure 7.04

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 11: 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 and similar to other ICS/LABA combination development programs for approved products.

The 52-week exacerbation trials enrolled a greater 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 34: Demographic and Baseline Characteristics: 2871**

Clinical Review  
Sofia Chaudhry, MD  
NDA 204275  
Breo Ellipta (fluticasone furoate and vilanterol)

	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
<b>Age</b>					
Mean	63.6	63.6	63.6	63.8	63.6
Min - Max	40-87	40-88	41-88	41-90	40-90
<b>Sex</b>					
Female	170 (42)	163 (40)	172 (43)	153 (38)	658 (41)
Male	239 (58)	245 (60)	231 (57)	249 (62)	964 (59)
<b>Race</b>					
White	331 (81)	334 (82)	332 (82)	324 (81)	1321 (82)
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)
<b>Duration of COPD</b>					
<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)
<b>Smoking Status at screening</b>					
Current Smoker	174 (43)	171 (42)	174 (43)	166 (41)	685 (42)
Former Smoker	235 (57)	237 (58)	229 (57)	236 (59)	937 (58)
<b>Baseline Lung Function</b>					
Mean post-bronchodilator FEV1 percent predicted	44.3	45.6	45.7	45.1	45.2
<b>Reversibility<sup>1</sup></b>					
Reversible	125 (31)	116 (29)	121 (30)	106 (27)	468 (29)
Non-Reversible	282 (69)	287 (71)	279 (70)	290 (73)	1138 (71)
<b>Concomitant Medications</b>					
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, <sup>1</sup> Reversibility defined as: post-SABA increase in FEV1 ≥ 12% and ≥ 200 ml					

**Table 35: 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

	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
<b>Age</b>					
Mean	63.6	63.7	64	63.5	63.7
Min - Max	40-85	40-85	40-88	40-86	40-88
<b>Sex</b>					
Female	174 (43)	181 (44)	181 (45)	191 (47)	727 (45)
Male	235 (57)	231 (56)	222 (55)	218 (53)	906 (55)
<b>Race</b>					
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)
<b>Duration of COPD</b>					
<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)
<b>Smoking Status at screening</b>					
Current Smoker	190 (46)	193 (47)	185 (46)	186 (45)	754 (46)
Former Smoker	219 (54)	219 (53)	218 (54)	223 (55)	879 (54)
<b>Baseline Lung Function</b>					
Mean post-bronchodilator FEV1 percent predicated	46.1	45.2	46.4	45.3	45.7
<b>Reversibility<sup>1</sup></b>					
Reversible	126 (31)	130 (32)	127 (32)	122 (30)	505 (31)
Non-Reversible	276 (69)	276 (68)	271 (68)	282 (70)	1105 (69)
<b>Concomitant Medications</b>					
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, <sup>1</sup> 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 2871 and 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 36: 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)
<b>Primary reason for withdrawal</b>					
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)
<b>Protocol deviation</b>					
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 37: 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)
<b>Primary reason for withdrawal</b>					
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)
<b>Protocol Deviation</b>					
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%).

A numeric treatment benefit of FF/VI to VI is seen for all doses in both trials. 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. However, a similar treatment effect for FF/VI 100/25 to VI 25 is seen between the two trials and the treatment effect over VI monotherapy for all combination doses in both trials trend in the same direction.

The consistency of these results is supportive of the efficacy of FF/VI 100/25 compared to VI treatment alone in reducing the rate of exacerbations. However, no incremental increase in benefit is seen for the higher dose FF/VI 200/25 that would outweigh the dose dependent increase in pneumonia that is seen with the product (see section 7.3.5).

**Table 38: Annual Rate of Moderate and Severe Exacerbations: 2871 and 2970**

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
<b>Trial 2871</b>				
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 <sup>1</sup>	<0.001 <sup>1</sup>	0.109
Percent Reduction		13	34	15
95% Confidence Intervals		(-6, 28) <sup>1</sup>	(19, 46) <sup>1</sup>	(-4, 30)
<b>Trial 2970</b>				
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				
* 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 **Error! Reference source not found.**), the exacerbation protocols specified the following secondary endpoints.

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

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.

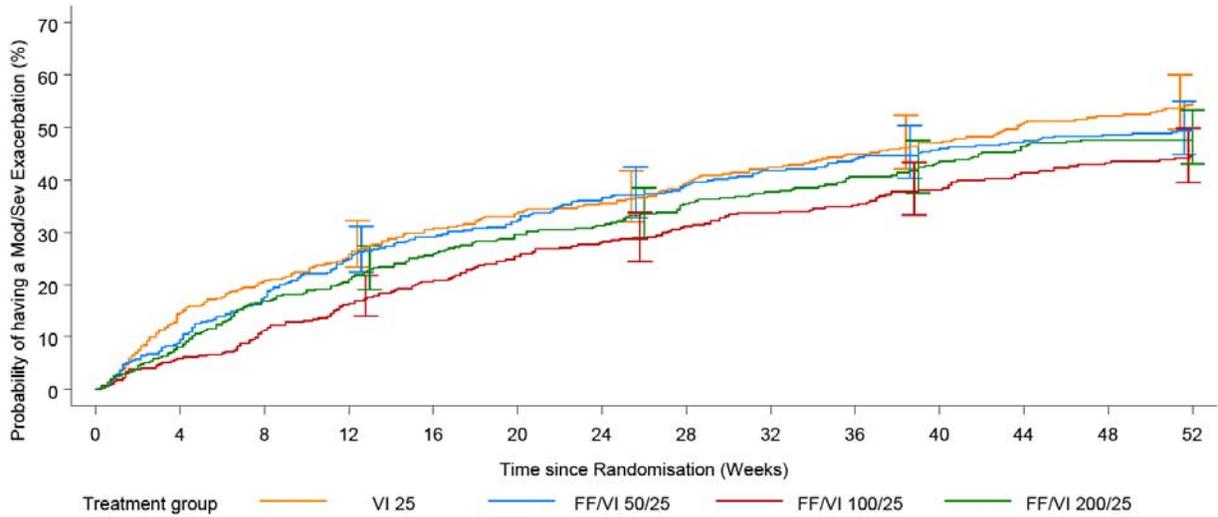
The data from these endpoints are supportive of the results from the primary efficacy endpoints. Numeric improvements compared to VI are seen for all dosage groups in both trials. These occur in a dose-dependent manner for trial 2970 but not for 2871.

#### 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 12: Kaplan-Meier Plot: Time to First Moderate or Severe Exacerbation: 2871**

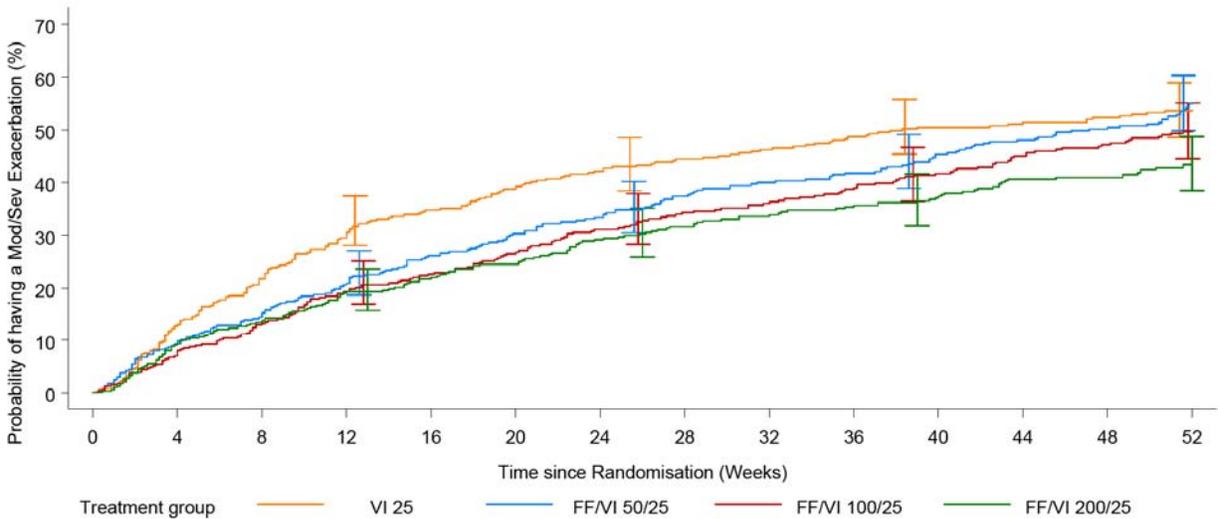


Number of Subjects at Risk:

Week	0	13	26	39	52
VI 25	408	288	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 13: 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 39 below summarizes these data.

**Table 39: Annual Rate of Exacerbations Requiring Systemic/oral Corticosteroids: 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		0.84	0.62	0.81		0.84	0.77	0.65
P value		0.125	<0.001	0.064		0.154	0.041	<0.001
Percent reduction		16	38	19		16	23	35
Confidence Interval		(-5,33)	(22,51)	(-1,36)		(-7,35)	(1,40)	(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”<sup>4</sup>. Instead a post-hoc analysis of time to first severe exacerbation was performed which demonstrates a 29% 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 40: 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
<b>All exacerbations</b>								
LS mean annual rate	1.37	1.17	0.92	1.35	1.55	1.31	1.25	1.06
<b>Compared to VI</b>								
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 41.

<sup>4</sup> CSR 2970 Section 6.5.1 “Annual Rate of Severe Exacerbation” page 74.

**Table 41: 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
<b>Compared to VI</b>						
Hazard Ratio	0.87	0.68	0.86	0.82	0.8	0.72
Source: CSR 2871 and 2970 Table 20						

### 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 42.

### *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 42: 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
<b>Night time awakenings/24 hours</b>								
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
<b>Use Rescue Medication/24 hours</b>								
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
<b>Dyspnea</b>								
Compared to VI LS mean difference		-0.11	-0.08	-0.11		-0.05	-0.11	-0.12
<b>Sputum</b>								
% 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

Overall, a distinct conclusion for these subpopulation analyses that differs from the primary analysis can not be made.

### **6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

Only a single dosage strength of FF/VI, 100/25 mcg once daily, is being proposed by GSK for this NDA. A discussion of the dose-selection and regimen trials used to determine which doses to carry forward into the Phase 3 trials is found in Section 4.4.2 of this review. Three difference dosage strengths of FF combined with 25 mcg of VI were carried forward into the phase 3 development program and the efficacy data is discussed throughout Section 6.

### **6.2.9 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 12) are not suggestive of a loss of efficacy over time. 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**

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. Over 7000 patients have received FF/VI in GSKs COPD development program. Of these, 1,249 patients received at least one dose of the proposed FF/VI 100/25, and 1,087 patients have received higher doses of FF/VI.

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. 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.

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 included in this review. 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.

Overall, imbalances in pneumonia and fracture are noted in the FF containing treatment arms compared to VI monotherapy arms. These are both known effects for steroid use in COPD and currently product labeling includes warnings regarding these increased risks. Ultimately, there are no data of adequate treatment duration directly comparing FF/VI to an already marketed product to compare the pneumonia-related risk . However, keeping in mind the limitations of cross study comparisons, a review of the frequencies of these events for the proposed dose from this development program do not appear disproportionately increased compared to other development programs.

## **7.1 Methods**

### **7.1.1 Studies/Clinical Trials Used to Evaluate Safety**

Table 13 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<sup>5</sup>. 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
- 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

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<sup>5</sup> 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.

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 review relies on pooled data from the lung function trials and pooled data from the exacerbation trials. The replicate nature of the trial designs and reasonable number of patients enrolled allows for more straightforward comparisons 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 exceeds the size of the initial safety databases used for approval of other ICS/LABA COPD development programs and is adequate for review. However, unlike other ICS/LABA COPD development programs, FF/VI is not already 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%). Enrollment of patients with reversible disease was approximately equal in the two trials with 31% of patient in the lung function trials and 30% of patients in the exacerbation trials having reversible disease. In addition, patients in the 52-week exacerbation trials were required by protocol to have had a recent COPD exacerbation.

**Table 43: 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
<b>Exposure (Days)</b>							
Mean	136.2	138.7	140.2	146.4	144.3	139.9	143.4
<b>Range of Exposure, n (%)</b>							
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 44: 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
<b>Exposure (Days)</b>				
Mean	306.2	306.6	308.3	295.2
<b>Range of Exposure, n (%)</b>				
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)
>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)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF 200/25 N=811	VI 25 N=818
>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 59 and discussed in Section 7.3.5.

### **7.2.3 Special Animal and/or In Vitro Testing**

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

### **7.2.4 Routine Clinical Testing**

Routine testing in this development program included serum chemistry, hematology, 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.

### **7.2.5 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.

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

#### *ICS*

The pivotal trials incorporated monitoring for toxicities associated with ICS use by evaluating AEs for episodes of pneumonia, bone disorders, local and systemic corticosteroid effects, and ocular disorders. Details of the AE analyses are found in Section 7.1.2 and the results in Section 7.3.5.

#### *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 7.3.5 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 45 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 45, 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 46 provides details, including the preferred term, for each cause of the death from the completed trials in GSK's COPD development program. In general, the tabulation of the Preferred Terms appears consistent with a review of the individual case narratives. The discrepancies that do occur are few enough in number that they do not impact the overall assessment. Additional details from the case narratives that this reviewer believes are pertinent are provided in the notes section of the table.

**Table 45: 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
<b>24-week Lung function Trials: 2206 and 2207</b>							
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) <sup>1</sup>	0	0	0	0	0
Cerebral hemorrhage	0	1 (<1) <sup>1</sup>	0	0	0	0	0
Thrombotic stroke	0	0	0	1 (<1)	0	0	0
Gastrointestinal hemorrhage	0	1 (<1)	0	0	0	0	0
Anaphylactic reaction	0	0	0	0	1 (<1) <sup>2</sup>	0	0
Pulmonary embolism	0	0	0	0	0	1 (<1)	0
<b>52-week Exacerbation Trials: 2871 and 2970</b>							
N		820	806	811	818		
System Organ Class, n (%)							
Preferred Term <sup>3</sup> , n (%)							
All Events		16 (2)	10 (1)	14 (2)	13 (2)		
Cardiac Disorders		5 (<1)	4 (<1)	3 (<1)	5 (<1)		
Myocardial infarction <sup>4</sup>		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)		

	Placebo	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25	FF 100	FF 200
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  
<sup>1</sup> both events in same patient  
<sup>2</sup> anaphylactic reaction to nuclear stress test injection  
<sup>3</sup> Preferred Terms occurring in > 1 patient  
<sup>3</sup> 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

**Table 46: Details of On and Post Treatment deaths**

Treatment	Patient ID	Study	Age/ Sex	Time since 1 <sup>st</sup> /last dose	Cause of Death preferred term	Additional notes
VI 25	136226	2206	61/M	2/2	Sudden cardiac death	
FF/VI 50/25	136284	2206	63/M	126/1	Alcohol poisoning Cerebral hemorrhage	
FF/VI 50/25	135717	2206	45M	133/2	GI hemorrhage	
Placebo post treatment	139459	2206	47/F	52/24	Sudden death	
FF 100 post treatment	137033	2206	62/M	66/3	Pulmonary embolism	
Placebo	153689	2207	78/M	99/1	Myocardial ischemia chronic ischemic heart disease	
VI 25	148010	2207	67/M	15/1	Anaphylactic reaction <sup>6</sup>	anaphylaxis to nuclear stress test injection
VI 25	151830	2207	55/M	67/1	Accidental poisoning/accidental ingestion methanol	
FF/VI 100/25	145006	2207	57/M	94/1	Thrombotic stroke	
FF/VI 200/25	152912	2207	62/M	78/1	Myocardial infarction	
FF/VI 100/25 Post treatment	152916	2207	62/M	191/38	Death-unknown cause	
VI 25	104877	871	59/M	168/2	Cardiac failure	congestive heart failure

Clinical Review  
Sofia Chaudhry, MD  
NDA 204275  
Breo Ellipta (fluticasone furoate and vilanterol)

Treatment	Patient ID	Study	Age/ Sex	Time since 1 <sup>st</sup> /last dose	Cause of Death preferred term	Additional notes
VI 25	110978	871	54/F	132/<1	Acute coronary syndrome	
VI 25	11092	871	67/M	251(-1)	Abdominal pain lower	no additional details
VI 25	111126	871	62/M	94(<1)	Arrhythmia, cardiorespiratory arrest	
FF/VI 50/25	100687	871	51/M	172/<1	Death	no additional details
	102558	871	68/M	167/-32	Intervetebral disc protrusion	d/c to hospice with end stage COPD
	111168	871	67/M	134/ <1	Loss of consciousness	hospitalized in prior month for COPD/PNA
	111459	871	54/M	35/<1	Myocardial Infarction	
	110101	871	60/M	250/-18	Acute lymphocytic Leukemia	
	109887	871	77/M	264/2	Shock, hemorrhagic	
	112550	871	55/M	48/<1	COPD, UTI bacterial	
FF/VI 100/25	103678	871	75/M	342/<1	Cardiac arrest	
	109853	871	69/M	60/<1	Myocardial infarction	
	111368	871	65/M	71/-34	Abdominal pain	malignancy admitted with bowel obstruction
	112531	871	63/M	286/<1	Acute respiratory failure COPD	
	107461	871	63/M	355/<1	Acute respiratory failure	
FF/VI 200/25	101434	871	60/F	257/<1	Pneumonia	
	111084	871	72/M	181/-8	COPD	
	111089 <sup>7</sup>	871	69/M	210/-15	COPD	pneumonia on eCRF
	111128	871	70/M	5/-2	Pneumonia	
	111129	871	76/M	44/-14 51/-7	COPD Pneumonia	
	111165	871	63/F	138/-2	Angina unstable Pneumonia, Septic Shock	
	111302	871	62/M	294/<1	COPD	
	111364	871	67/M	51/2	Myocardial Infarction	
	111426	871	53/M	234/<1	Coronary Artery Thrombosis	
	109996	871	60/M	235/<1	Aortic Aneurysm rupture	
	111958	871	70/F	73/<1	Pancreatic carcinoma	
	112538	871	59/M	265/2	Pneumonia	
	112548	871	74/M	181/<1	Pneumonia	

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Breo Ellipta (fluticasone furoate and vilanterol)

Treatment	Patient ID	Study	Age/ Sex	Time since 1 <sup>st</sup> /last dose	Cause of Death preferred term	Additional notes
VI 25 Post treatment	107586	871	64/M	77/33	Sepsis	
	111338	871	72/M	371/4	Myocardial infarction	
	111343	871	58/M	316/52	Death	Found dead at home
FF/VI 50/25 Post Treatment	102558	871	68/M	202/4	COPD	
	109995	871	68/M	357/7	Cardiopulmonary failure	sudden cardiac arrest
	110555	871	76/M	331/10	Cerebrovascular accident	
FF/VI 100/25 post treatment	107659	871	55/M	332/36	Diffuse large B-cell lymphoma	
	112531	871	63/M	288/3	Hypertension	respiratory failure requiring VATS lung resection and subsequent shock
FF/VI 200/25 post treatment	112538	871	59/M	267/4	Respiratory failure	pneumonia, COPD exacerbation, UTI
VI 25	116012	970	67/M	293/-14	Metastatic squamous cell carcinoma	primary: lung
	119011	970	65/F	24/-1	Arteriosclerosis	
	124912	970	55/M	262<1	COPD	
	125934	970	65/M	?	COPD, LRTI	
FF/VI 50/25	117509	970	59/M	160/-9	Squamous cell carcinoma	poorly differentiated
	112582	970	66/F	343//2	Myocardial infarction	
	127061	970	72/M	204/-1	COPD	
	125117	970	65/M	340/<1	Acute myocardial infarction	
	123761	970	69/M	188/-77	Neuroendocrine tumor, metastasis to GI tract	
	126775	970	78/F	35/2	Lung squamous cell carcinoma	
	118504	970	48/M	195/<1	Cardiac arrest	cause of death unknown
FF/VI 100/25	119103	970	59/F	251/<1	Cardiac arrest	possible allergic reaction per ER physician
	116955	970	67/M	285/-25 310/<1	COPD, pna	
	127454	970	67/M	201/-3	Cholelithiasis	
VI post	127070	970	55/M	367/11	COPD, respiratory tract	

Treatment	Patient ID	Study	Age/ Sex	Time since 1 <sup>st</sup> /last dose	Cause of Death preferred term	Additional notes
treatment					infection, pna	
	126522	970	58/F	365/3	Cardiopulmonary failure	Died in sleep,
FF/VI 100/25 post treatment	118469	970	69/M	61/3	Cardiac failure congestive	
FF/VI 200/25 post treatment	124354	970	76/M	352/3	Metastasis to bone, liver, lung	primary: unknown
VI 6.25	151	1045	66M		Subdural hematoma	
FF/VI 100/25 post treatment	721	3107	52/M	87/2	Congestive heart failure	
FP/salmeterol	2858	3109	55/M	54/1	Cardiopulmonary arrest	found dead at home
FF/VI 100/25	10345	2352	77/F	26/NA 33/NA	Cardiac failure, respiratory failure, myocardial infarction	lesion on xray, biopsy negative for carcinoma, ? infective
FF/VI		782			Multiorgan failure	Interstitial lung disease

Source: CSR 2206 + 2207 Table 49; 871 + 970 Table 34 and individual case narratives; 120-day safety update

### **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 7.3.5 of this review. Of note, the data presented in Section 7.3.5 of the review uses a comprehensive list of pneumonia related Preferred Terms, while data in this section of the review does not.

Table 47 presents the SAE data as Preferred Terms occurring in >1 patient across treatment arms in the two 24-week lung function trials. Table 48 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 7.3.5. Interpretation of additional SAEs is limited by the rarity of occurrences.

**Table 47: 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 <sup>1</sup> , 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 <sup>2</sup>	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)	2 (<1)
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 <sup>3</sup>	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. <sup>4</sup>	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							
<sup>1</sup> Preferred terms occurring > 1 patient across treatment arms presented							
<sup>2</sup> Injury poisoning and procedural complications							
<sup>3</sup> Neoplasms Benign, Malignant, and Unspecified							
<sup>4</sup> General Disorders and Administration Site Conditions							

**Table 48: 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 <sup>1</sup> , 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
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)
Acute myocardial infarction	2 (<1)	2 (<1)	0	1 (<1)
Angina pectoris	3 (<1)	0	0	2 (<1)
Supraventricular tachycardia	0	0	0	3 (<1)
Nervous System Disorders	6 (<1)	6 (<1)	6 (<1)	8 (<1)
Cerebrovascular accident	1 (<1)	2 (<1)	3 (<1)	2 (<1)
Musculoskeletal and Connective Tissues Disorders	3 (<1)	1 (<1)	4 (<1)	6 (<1)
Musculoskeletal chest pain	0	0	0	4 (<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				
<sup>1</sup> 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 7-11% in the active treatment groups. Discontinuation due to COPD exacerbation is the most common reason (placebo: 2%; active treatment: 0%-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 Significant Adverse Events**

Adverse events of special interest for LABAs and ICS, including laboratory abnormalities, are discussed in Section 7.3.5. Rates of study drug discontinuation and withdrawals due to Adverse Events are discussed in Section 7.3.3.

#### **7.3.5 Submission Specific Primary Safety Concerns**

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 inherent 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 49: Pneumonia in 52-week Exacerbation trials<sup>1</sup>: 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) <sup>2</sup>	1 (<1) <sup>3</sup>
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	

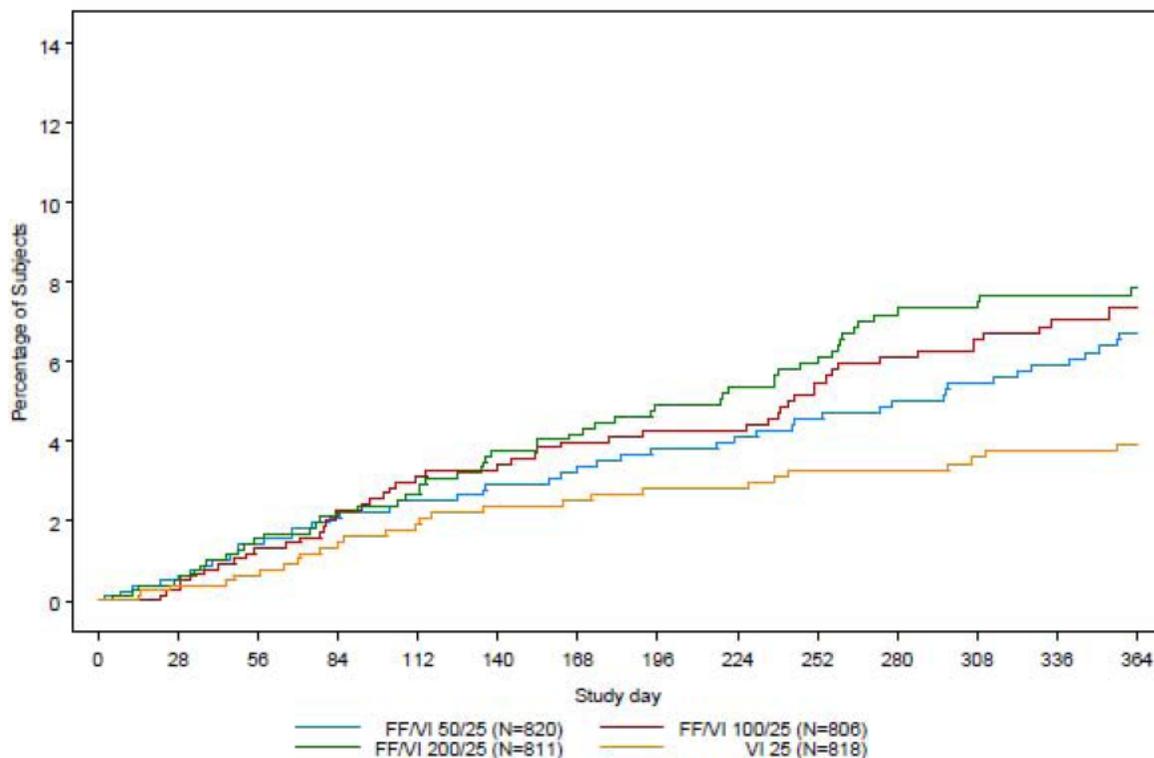
Source: ISS Tables 59, 69, 2.168

<sup>1</sup> No pneumonia related fatalities in the 24-week lung function trials

<sup>2</sup> 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.

<sup>3</sup> Patient 127070 in trial 2970: pneumonia fatality occurred in the post-treatment follow up phase

**Figure 14: 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 data 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%)<sup>8</sup>. 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.<sup>9</sup> In addition, a post-hoc analysis by Crim et al<sup>10</sup> 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 Table 50.

**Table 50: Pneumonia Data From Previous FP/S Trials**

	Placebo	S 50	FP 500	FP/S 500/50	FP/S 250/50
<b>TORCH Trial<sup>1</sup></b>					
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		1.09	1.53	1.64	
95% Confidence Interval		(0.87, 1.37)	(1.24, 1.89)	(1.33, 2.02)	
P-value		0.465	<0.001	<0.001	
<b>Advair Diskus: Two 52-week Exacerbation Trials<sup>2</sup></b>					
Pneumonia, % of patients		3			7
Sources: <sup>1</sup> Crim et al <sup>8</sup> <sup>2</sup> 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%;

<sup>8</sup> Advair Diskus; NDA 21-077; Prescribing Information

<sup>9</sup> Calverley et al; Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease; N Engl J Med 2007; 256:775-89.

<sup>10</sup> 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.

placebo: 6.2%). This pattern was not seen when looking at specific rates of pneumonia<sup>11</sup> it is unclear if this is due to a difference in trial design.

GSK also conducted a new meta-analysis of its Advair data using the same composite list of pneumonia-related preferred terms that is used for the FF/VI AE of Interest analysis<sup>12</sup>. This analysis was run on multiple different groupings of the clinical data including:

- 11 trials evaluating Advair 500/50 ranging from 13 weeks to 156 weeks
- 11 trials evaluating Advair 250/50 ranging from 6 weeks to 104 weeks
- 10 trials evaluating Advair 500/50 excluding TORCH (13 weeks to
- 2 52-week exacerbation trials used to support approval of Advair exacerbation indications (SCO40043 and SC100250)
- TORCH trial alone

The data from the pooling of the 11 Advair 250/50, 11 Advair 500/50 and 10 Advair 500/50 (minus TORCH) must be analyzed cautiously given the wide range of treatment durations contained in these trials, and the presumed differences in trial designs. However, imbalances between steroid-containing treatment arms and non-steroid-containing treatment arms in the treatment year-adjusted rates are seen in these groupings of the Advair 250/50 and Advair 500/50 data.

GSKs re-analysis of the two 52-week Advair 250/50 exacerbation trials and the TORCH trial are largely in agreement with the data presented in Table 50 of this review. A total of 55 out of 788 (7%) patients in the Advair 250/50 arm reported pneumonia compared to 25 out of 791 (3.2%) in the salmeterol treatment group from the pooling of the two 52 week Advair exacerbation trials (SCO40043 and SC100250). The data from GSKs re-analysis of the TORCH trial using its composite list of Preferred Terms is also similar to the data presented in Table 50. A total of 149 patients out of 1544 (9.7%) in the placebo group, 255 out of 1546 (16.5%) in the Advair 500/50 group, 166 out of 1542 (10.8%) in the salmeterol 50 and 236 out of 1552 (15.2%) in the fluticasone propionate group had events of pneumonia.

#### *Bone Disorders:*

A 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.

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<sup>11</sup> Symbicort®; NDA 021-929; Prescribing Information

<sup>12</sup> Clinical information submitted to NDA 204275 dated February 28, 2013 (SDN 27)

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 51: 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 <sup>1</sup> , n (%)	24 (3)	27 (3)	21 (3)	9 (1)
Absolute Risk Difference	0.018	0.023	0.015	
NNTH (95% CI)	55 (30, 216)	44 (26, 121)	67 (34, 597)	
Fractures <sup>2</sup>	14 (2)	19 (2)	14 (2)	8 (<1)
Absolute Risk Difference	0.007	0.014	0.008	
NNTH (95% CI)	137 (51, ∞)	72 (36, 857)	134 (50, ∞)	

Source:

<sup>1</sup> ISS Table 2.160

<sup>3</sup> 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 (see tables Table 52 and Table 53). 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.

**Table 52: Osteocalcin measurements: 871**

	VI 25	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25
N (Baseline)	402	396	389	390
Osteocalcin, mcg/L (geom. mean)	15.16	14.18	14.89	14.12
n (End of study)	348	353	356	341
Osteocalcin, mcg/L (geom. mean)	16.45	15.51	15.12	14.11
n Ratio (EOS/Baseline)	342	341	345	330
Geom Mean Ratio (EOS/Baseline)	1.09	1.07	1.02	0.99
Ratio compared to VI25		0.98	0.93	0.91
P-value		0.683	0.128	0.047

Source: Clinical Study Report HZC102871 Tables 7.54, 7.55, 7.57

**Table 53: Serum CTX measurements: 871**

	FF/VI 50/25	FF/VI 100/25	FF/VI 200/25	VI 25
N (Baseline)	397	389	388	402
sCTX, mcg/L (geom.. mean)	0.337	0.335	0.320	0.347
n (End of study)	353	357	340	347
sCTX, mcg/L (geom.. mean)	0.354	0.353	0.352	0.387
n Ratio (EOS/Baseline)	342	346	328	341
Geom Mean Ratio (EOS/Baseline)	1.058	1.056	1.078	1.133
Ratio compared to VI25	0.933	0.932	0.952	
P-value	0.184	0.172	0.345	

Source: Clinical Study Report HZC102871 Tables 7.54, 7.55, 7.56

Similar to the pneumonia data, it can be helpful to consider these data in the context of previous ICS/LABA COPD development programs. However, again, one must keep in mind the limitations of cross study comparisons. Bone disorder data was assessed during the two, 52-week pivotal trials supporting Advair's decrease in exacerbations indication. These trials, SCO40043 and SCO100250, evaluated 788 patients treated with Advair and 791 with salmeterol. A total of 29 bone disorder events were seen in 3% (25) of the Advair treated patients compared to 21 events in 2% (19) of the salmeterol treated patients. Of these, 24 of the 29 events in the Advair treatment group were fractures, 4 were osteoporosis/osteopenia and 1 was osteonecrosis. The salmeterol-treated group had 17 fractures, 3 events of osteoporosis/osteopenia, and 1 event of osteonecrosis<sup>13</sup>. Bone disorder data was assessed in the 3-year COPD mortality trial (TORCH) evaluating Advair 500/50 versus salmeterol and placebo. In this trial, the Advair 500/50 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<sup>14</sup>.

<sup>13</sup> NDA 21-077, page 28 Primary Clinical Review by Dr. Carol Bosken, April 3, 2008

<sup>14</sup> Pulmonary and Allergy Advisory Committee FDA Clinical Briefing Document for sNDA 21-077; May 1, 2007

**Table 54: Fracture Data from Previous ICS/LABA Clinical Trials**

	Placebo	S 50	FP 500	FP/S 250/50	FP/S 500/50
<b>SC030003 (TORCH: 3 year Advair mortality trial) *</b>					
N	1544	1542	1552		1546
All Fractures, n(%)	57(3.7)	61(4)	65(4.2)		78(5)
Rate per 1000 treatment years*	18.6	20.4	20.3		22.4
Hazard Ratio to placebo		1.353	0.696		0.931
95% CI		0.766, 2.393	0.525, 1.788		0.505, 1.718
Kaplan Meier estimate of probability for all fracture at 3 years	5.1	5.1	5.4		6.3
<b>SC040043 + SCO100250 (52 week Advair exacerbation trials)+</b>					
N		791		788	
All fractures, n(%)		17(2)		24(3)	
Source: * Pages 109-110 and Table 57 briefing document for PADAC meeting May 1, 2007; + Page 28 Primary Clinical Review dated April 3, 2008 for NDA 21-077 s029					

**Additional Corticosteroid Effects:**

The development program for FF/VI also evaluated for other known effects of corticosteroid 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 the non-FF-containing treatment arms. These 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 these data.

**Table 55: ICS-related AEs<sup>1</sup> 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
<b>Adverse Event of Special Interest related to ICS use, n (%)</b>							
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

	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
Source: ISS Table 57 <sup>1</sup> Excluding pneumonia and bone disorders							

**Table 56: ICS-related AEs<sup>1</sup> 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
<b>Adverse Events of Special Interest related to ICS use, n (%)</b>				
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 <sup>1</sup> 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 50/25: 1.12; FF/VI: 100/25 1.04; FF/VI 200/25 0.95; VI 25: 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).

Other LABA development programs have used a MACE analysis to better assess cardiovascular risk. While a specific MACE analysis was not done for this clinical development program, GSK's list of cardiac-related PTs is in many ways a more comprehensive evaluation of cardiac safety than many MACE analyses. However, GSK's analysis is limited by the lack of inclusion of cardiovascular related fatalities and stroke-related SAEs. The fatal SAE event data are discussed above. To supplement GSK's analysis of cardiac safety, a review of stroke-related SAEs was compiled by this reviewer. The 24-week lung function trial data was used given the availability of placebo and non-VI containing comparator arms. As seen in Table 60 no imbalance in stroke-related risk is evident between VI and non-VI containing treatment arms.

These data provide additional support for the safety of VI 25 in terms of LABA-related AEs.

**Table 57: 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
<b>Adverse Event of Special Interest, n(%)</b>							
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
<b>Special MedDRA Query (SMQ), n(%)</b>							
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

	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
<b>Adverse Event of Special Interest, n(%)</b>							
Source: ISS Table 57 and 58							

**Table 58: 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
<b>Adverse Event of Special Interest, n(%)</b>				
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)
<b>Special MedDRA Query (SMQ), n(%)</b>				
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)
Source: ISS Table 59, Table 60				

**Table 59: 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
<b>Adverse Events of Special Interest, n, (%)</b>						
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.						

**Table 60: On-treatment Stroke-related SAEs<sup>\*</sup>: 24-week Lung Function Trials**

	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
<b>Nervous System Disorders</b>							
<b>Preferred Term, n (%)</b>							
Any event	0	2 (<1)	4 (<1)	1 (<1)	1 (<1)	4 (<1)	2 (<1)
Carotid artery stenosis	0	0	0	0	0	2 (<1)	0
Ischemic stroke	0	0	2 (<1)	0	0	0	0
Cerebral hemorrhage	0	1 (<1)	0	0	0	0	0
Cerebral infarction	0	0	0	1 (<1)	0	0	0
Cerebrovascular accident	0	0	1 (<1)	0	0	0	0
Subarachnoid hemorrhage	0	0	0	0	0	1 (<1)	0
Thrombotic stroke	0	0	1 (<1)	0	0	0	0
Transient ischemic attack	0	0	0	0	1 (<1)	0	0
Total stroke-related events	0	3 (<1)	4 (<1)	1 (<1)	1 (<1)	3 (<1)	0
<sup>*</sup> Excludes the following Preferred Terms: syncope, hypertonia, intracranial aneurysm, myasthenia gravis. Vascular System Disorders SOC included events of arteriosclerosis, peripheral arterial occlusive disease and venous insufficiency. None of these events were included.  Source: ISS Table 2.25							

**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 59 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 61 below.

**Table 61: 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
<b>Change from Baseline Trough (mmol/L)</b>							
Day 84 trough, median	-0.2	-0.1	-0.1	-0.05	-0.1	-0.1	-0.1

	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
Day168 trough, median	-0.1	-0.1	-0.1	-0.1	0	-0.1	-0.1
<b>Change from Baseline 30-minute post dose (mmol/L)</b>							
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
<b>Anytime shift to high</b>							
Anytime post baseline n (%)	30 (9)	6 (4)	22 (7)	15 (8)	24 (7)	16 (5)	11 (7)
<b>Adverse Event of Special Interest:</b>							
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 62: 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
<b>Change from Baseline Trough (mmol/L)</b>							
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	-0.1	-0.1	-0.1
<b>Change from Baseline 30 min post-dose</b>							
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
<b>Anytime Shift to High</b>							
Anytime post baseline, n (%)	53 (16)	33 (20)	57 (17)	24 (14)	49 (14)	52 (16)	27 (16)
<b>Adverse Event of Special Interest</b>							
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 63. Specific adverse events of interest are discussed in detail in Section 7.3.5.

**Table 63: 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
<b>Preferred Term, n %</b>							
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 <sup>1</sup>	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  
<sup>1</sup> includes the following preferred terms: oral candidiasis, oropharyngeal candidiasis, candidiasis, oropharyngitis fungal

**Table 64: 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
<b>Preferred Term, n(%)</b>				
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)

	FF/VI 50/25 N=820	FF/VI 100/25 N=806	FF/VI 200/25 N=811	VI 25 N=818
Pneumonia	46 (6)	49 (6)	45 (6)	23 (3)
Cough	35 (4)	31 (4)	35 (4)	34 (4)
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  
<sup>1</sup> includes the following preferred terms: oral candidiasis, oropharyngeal candidiasis, candidiasis esophageal candidiasis,

### 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 7.3.5.

**Table 65: Shift Table of Hematology Parameters<sup>1</sup> 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
<b>WBC, n (%)</b>							
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)
<b>Lymphocyte, n (%)</b>							
N	396	196	388	198	387	392	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	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)
<b>Neutrophil, n (%)</b>							
N	396	196	388	198	387	392	193
To low	14 (4)	4 (2)	7 (2)	2 (1)	9 (2)	13 (13)	6 (3)
To high	27 (7)	11 (6)	29 (7)	17 (9)	22 (6)	28 (7)	17 (9)
<b>Eosinophil, n (%)</b>							
N	396	196	388	198	383	392	193
To high	21 (5)	6 (3)	2 (6)	5 (3)	21 (5)	16 (4)	9 (5)
<b>Platelets, n (%)</b>							
N	387	196	383	197	383	388	192
To low	5 (1)	4 (2)	9 (2)	3 (2)	9 (2)	6 (2)	5 (3)
To high	4 (1)	4 (2)	6 (2)	6 (3)	2 (<1)	7 (2)	3 (2)
<b>Hemoglobin, n (%)</b>							
N	396	197	388	199	385	393	194
To low	26 (7)	5 (3)	21(5)	9(5)	12(3)	25(6)	14(7)
<b>Platelets, n (%)</b>							
N	387	196	383	197	383	388	192
To low	5 (1)	4 (2)	9(2)	3(2)	9(2)	6(2)	5(3)
To high	4 (1)	4 (2)	6(2)	6(3)	2(<1)	7(2)	3(2)
Source: ISS Table 3.16							
*includes labs performed at scheduled, unscheduled and early withdrawal visits							

**Table 66: Shift table of Chemistry Parameters<sup>1</sup> 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
<b>Alkaline phosphatase, n (%)</b>							
N	397	198	388	200	396	396	192
To high	7 (2)	5(3)	6(2)	2(1)	9(2)	8(2)	3(2)
<b>Aspartate aminotransferase, n (%)</b>							
N	397	198	388	199	395	396	192
To high	13 (3)	8(4)	13(3)	10(5)	9(2)	12(3)	4(2)
<b>Calcium, n (%)</b>							
N	397	197	388	199	395	396	192
To low	13 (3)	4(2)	8(2)	5(3)	16(4)	17(4)	8(4)
To high	9 (2)	6(3)	8(2)	9(5)	13(3)	9(2)	4(2)
<b>Bicarbonate, n (%)</b>							

	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
N	397	198	388	199	395	396	192
To low	38 (10)	21(11)	50(13)	21(11)	43(11)	36(9)	23(12)
To high	1 (<1)	0	0	0	0	0	0
<b>Creatinine Kinase, n (%)</b>							
N	397	198	388	200	396	395	192
To high	19 (5)	16 (8)	23 (6)	12 (6)	26 (7)	22 (6)	8(4)
<b>Total Bilirubin, n (%)</b>							
N	397	197	388	200	396	396	192
To high	5 (1)	2 (1)	2 (<1)	1 (<1)	6 (2)	5 (1)	3 (2)
<b>Direct Bilirubin , n (%)</b>							
N	397	198	388	200	396	396	192
To high	3 (<1)	0	2 (<1)	1 (<1)	0	0	2
<b>GGT, n (%)</b>							
N	397	198	398	200	396	396	192
To high	17 (4)	16 (8)	21 (5)	4 (2)	21 (5)	14 (4)	7 (4)
<b>Phosphorus, n (%)</b>							
N	397	197	388	200	396	396	192
To high	16 (4)	3 (2)	9 (2)	9 (5)	24 (6)	12 (3)	8 (4)
<b>Sodium, n (%)</b>							
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)
<b>Albumin, n (%)</b>							
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)
<b>Creatinine, n (%)</b>							
N	397	198	388	200	396	395	192
To low	34 (9)	16 (8)	29 (7)	14 (7)	34 (9)	29 (7)	13 (7)
To high	7 (2)	7(4)	4 (1)	2 (1)	4 (1)	3 (<1)	2 (1)
<b>Total Protein, n (%)</b>							
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)
<b>Urea/BUN, n (%)</b>							
N	397	198	388	200	396	396	192
To low	7 (2)	3 (2)	3 (<1)	1 (<1)	5 (1)	5 (1)	4 (2)

	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 high	11 (3)	7 (4)	11 (3)	8 (4)	11 (3)	12 (2)	5 (3)
<b>Uric Acid, n (%)</b>							
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							
*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 67: 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
<b>Systolic Blood Pressure (mmHg)</b>							
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	95	85	92	90	90	80	88
Max	171	172	180	160	170	168	170
Day 84 10 min post dose							
Median	130	126	126	130	130	129	130
Min	90	94	97	90	80	96	81
Max	191	175	175	162	170	170	176
<b>Diastolic Blood Pressure (mmHg)</b>							
Baseline							

	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
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	143	102	140	106	100	105	100
<b>Pulse (beats/minute)</b>							
Baseline							
Median	74	75	74	76	76	75	75
Min	45	49	49	51	49	50	50
Max	125	109	112	106	119	122	106
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 68: 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
<b>Heart Rate, beats per minute</b>							
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
<b>QTcF, msec</b>							
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
<b>Abnormality of potential clinical importance at any time post baseline<sup>12</sup></b>							
N (%)	57(14)	28(14)	50(12)	34(17)	49(12)	44(11)	28(14)
Source: ISS Table 85, 88, 90							
<sup>1</sup> per central cardiologists read of the ECG							
<sup>2</sup> 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 msec 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 msec. Overall, the team concluded that while FF/VI 800/100 effects exceed the regulatory threshold, 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 69.

**Table 69: 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
<b>Death</b>										
Total	0	1 (<1)	0	1 (<1)	0	0	0	1 (<1)	0	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
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
<b>Hospitalization</b>										
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
PNA	0	4 (<1)	1 (<1)	5 (<1)	0	0	1 (<1)	0	0	0
Other	0	1 (<1)	0	1 (<1)	0	0	0	0	0	0
Non-respiratory	0	27 (2)	6 (1)	17 (1)	0	0	4 (1)	0	0	0
<b>Intubations</b>										
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										

### **7.4.6 Immunogenicity**

The ICS/LABA combination product is a small molecule product and not anticipated to have immunogenic effects. Therefore, no special immunogenicity testing was performed.

### **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  $\leq 64$  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 Carcinogenicity**

No specific trials were conducted to assess for carcinogenicity in humans. See Division Memorandum for an overview of the toxicology program.

### **7.6.2 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.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

The sponsor has submitted a request for waiver of pediatric studies under PREA. The clinical review finds the request reasonable since COPD is a disease generally limited to adults.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Given the nature of the drug components, drug abuse, withdrawal, and rebound are not anticipated 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 70. Specific details from this safety update are included in relevant Sections above.

**Table 70: Studies from 120-day safety update**

<b>Trial</b>	<b>Design</b>	<b>Duration</b>	<b>Population</b>	<b>Treatment Arms</b>	<b>N</b>
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

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Sofia Chaudhry, MD  
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FFA115354* concluded	Retrospective pharmacogenetic 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.

## **9 Appendices**

### **9.1 Literature Review/References**

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

A PubMed search performed by this Reviewer [search term: fluticasone furoate AND vilanterol; no limits] was conducted on January 14, 2013, and yielded 10 references. A brief review of these reports was performed. No new safety signals were identified from these reports.

### **9.2 Labeling Recommendations**

A discussion of final labeling recommendations is deferred until after the Advisory Committee process is complete. Preliminary recommendations include the inclusion of class-effect warnings and precautions, dose-ranging data and efficacy and safety data from all dose levels evaluated in the phase 3 program into the product label.

### **9.3 Advisory Committee Meeting**

The advisory committee meeting was postponed and will be held after the finalization of this review. The anticipated focus of the discussion will be the strength of the efficacy data to support FF/VI 100/25 for the proposed indications, including the relative benefit FF/VI 100/25 offers over VI monotherapy. Therefore, the conclusions in this review are preliminary pending discussion of this application by the AC.

### **9.4 Additional Table and Figures**

This review contains no additional Tables or Figures.

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/s/  
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SOFIA S CHAUDHRY  
03/18/2013

SUSAN L LIMB  
03/18/2013

**MEDICAL OFFICER FILING REVIEW**  
**Division Of Pulmonary And Allergy Drug Products (HFD-570)**

<b>Application #:</b> NDA 204275	<b>Trade Name:</b> Breo Ellipta
<b>Applicant/Sponsor:</b> GlaxoSmithKline	<b>Generic Name:</b> Fluticasone furoate/vilanterol
<b>Medical Officer:</b> Sofia Chaudhry, MD	
<b>Team Leader:</b> Susan Limb, MD	<b>Category:</b> Inhaled ICS/LABA
<b>Completion Date:</b> September 4, 2012	<b>Route:</b> Inhaled

**REVIEW SUMMARY:**

This is a filing and planning review for the NDA application for the fixed-dose, orally-inhaled, ICS/LABA combination product, Breo Ellipta, containing fluticasone furoate (FF) as the ICS component and Vilanterol (VI) as the LABA component. The sponsor has submitted information to support two indications: treatment of airflow obstruction and a reduction in exacerbations in patients with COPD. GSK is proposing a single dosage strength of the FF/VI: 100/25 mcg administered once daily.

Neither the ICS, nor the LABA, are approved for use in asthma or COPD. To support its application, GSK has provided dose-ranging information for VI in asthma and COPD, for FF in asthma and for FF/VI in COPD. In addition, to further characterize the FF component in asthma, it carried forward three dosage strengths of FF combined with a single dose of VI into the phase 3 program.

The pivotal phase 3 trials consist of replicate COPD exacerbation trials, both of which evaluated the same three dosage strengths of FF/VI, and 2 airflow obstruction trials which were similar in design but evaluated different doses of FF/VI (only the 100/25 FF/VI dose replicated).

- HZC102871 and HZC102970: 52 week exacerbation trials
  - FF/VI 50/25 mcg once daily
  - FF/VI 100/25 mcg once daily
  - FF/VI 200/25 mcg once daily
  - VI 25 mcg once daily
- HZC112206: 24 week airflow obstruction trial
  - FF/VI 50/25 mcg once daily
  - FF/VI 100/25 mcg once daily
  - VI 25 mcg once daily
  - FF 100 mcg once daily
  - Placebo
- HZC 112207: 24 week airflow obstruction trials
  - FF/VI 100/25 mcg once daily
  - FF/VI 200/25 mcg once daily
  - VI 25 mcg once daily
  - FF 200 mcg once daily
  - Placebo

In addition to the pivotal dose ranging and phase 3 trials, the sponsor has submitted additional supportive data in both COPD and asthma. As this product is not approved, appropriate CMC, non-clinical, clinical pharmacology data have also been submitted.

The clinical study section and reports are appropriately indexed and organized to allow review. In addition, the sponsor has provided the requisite information to file the NDA, including appropriate disclosures, risk assessments and its REMS proposal. The filing checklist attached to this review provides a detailed list of the location for each required component of the NDA application. The review below will provide a brief overview of the application and the review strategy for the primary clinical review.

From a clinical standpoint, the submission is adequate to allow clinical review and the submission is fileable.

**OUTSTANDING ISSUES: None**

**RECOMMENDED REGULATORY ACTION: NDA application is Fileable**

### 1. Drug Product Information

The proposed drug product is a new fixed-dose, inhaled corticosteroid (ICS)/long-acting beta agonist (LABA) combination 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; 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.

- “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).”

In addition, the sponsor has included an onset of action claim in its proposed labeling.

(b) (4)

*Reviewer's comment: If approved, Breo Ellipta will be the first once-daily ICS/LABA approved. While neither of the proposed indications, nor the use of an ICS/LABA product in COPD is novel, this NDA application has not followed the previous approval pathway used by other COPD ICS/LABA programs. In this case, neither of the monocomponents are approved products; nor has the efficacy and safety of the combination product been demonstrated in asthma. Therefore, this application contains supportive dose ranging information for each of the monocomponents, as well as supportive safety data in asthma.*

*There are two approved ICS/LABA combination products for the maintenance treatment of airflow obstruction in COPD: Advair and Symbicort. In addition, Advair carries a reduction in exacerbation claim. Neither product has an onset of action claim. The product label for formoterol, contain the following statement in the Clinical Trials Section of the label (asthma):*

- *“In a placebo-controlled, single-dose clinical trial, the onset of bronchodilation (defined as a 15% or greater increase from baseline in FEV1) was similar for FORADIL AEROLIZER and albuterol 180 mcg by metered-dose inhaler.”*

*And the following language in the COPD clinical trial section:*

- *“In multiple-dose clinical trials in patients with COPD, FORADIL AEROLIZER 12 mcg was shown to provide onset of significant bronchodilation (defined as 15% or greater increase from baseline in FEV1) within 5 minutes of oral inhalation after the first dose. Bronchodilation was maintained for at least 12 hours.”*

*Similar to formoterol, salmeterol also contains onset of action information for both asthma and COPD.*

## 2. Regulatory History

The Division and GSK have had multiple prior interactions to discuss the proposed FF/VI development program in both COPD and asthma. A timeline of regulatory interactions is provided in the table below with major discussion points relevant to the COPD program outlined.

Date	Interaction	Highlights as they pertain to the COPD indication
April 29, 2008	Pre-IND	<ul style="list-style-type: none"> <li>• Dose regimen and ranging information for VI in COPD</li> <li>• Asthma data may not apply to COPD, each monocomponents must be examined in addition to the combination product</li> </ul>
May 23, 2008	IND submission	<ul style="list-style-type: none"> <li>• Safe to proceed</li> </ul>
June 17, 2009	End of Phase 2 COPD Indication	<ul style="list-style-type: none"> <li>• GSK Identified VI 25 mcg as dose to carry into phase 3 trials, FDA could not agree at this time</li> <li>• dose regimen and ranging information may differ between asthma and COPD</li> <li>• FDA agreed that QD and BID FF dosing regimens produced similar efficacy results</li> <li>• FDA agreed that 50, 100, and 200 mcg FF were reasonable doses to pursue in phase 3 COPD program</li> <li>• Phase 3 trial design options discussed</li> </ul>
December 9, 2009	Type C meeting: COPD mortality	<ul style="list-style-type: none"> <li>• Bronchodilator dose selection in COPD should be informed by bronchodilator-responsive population such as asthmatics</li> <li>• Discussion of mortality trial design</li> </ul>
March 24, 2010	Type C meeting: asthma dose selection	<ul style="list-style-type: none"> <li>• once daily VI dosing appeared reasonable (HZA113310), with caveat that 12.5 mcg BID was not compared to 25 mcg QD</li> <li>• FDA agreed that 25 mcg VI appeared reasonable for COPD (B2C111045), but that data suggested that lower doses may be efficacious in asthma</li> </ul>

June 8, 2010	Type C meeting: phase 3 asthma program	<ul style="list-style-type: none"> <li>• Dose selection in COPD should be informed by bronchodilator sensitive population such as asthmatics</li> <li>• Bronchodilator dose may differ between asthma and COPD, although this would be unprecedented</li> <li>• Asthma safety data should be submitted with COPD NDA to support FF/VI safety in COPD</li> </ul>
October 17, 2011	COPD pre-NDA	<ul style="list-style-type: none"> <li>• No replicate evidence of efficacy for any dose from bronchodilator trials</li> <li>• Completed trials do not appear to support multiple dose levels of FF/VI in COPD</li> <li>• Active comparator trials should not be included in the pooled ISS results</li> </ul>
April 20, 2012	Asthma Pre-NDA	<ul style="list-style-type: none"> <li>• COPD efficacy data would be reviewed in the context of equivocal results in the pivotal phase 3 asthma trials</li> </ul>

### 3. Dose Selection

The following table outlines the pivotal dose-ranging trials cited to support FF/VI dosing in COPD. As monotherapy ICS is not efficacious in COPD, dose selection for FF was initially conducted in asthma. However, a trial evaluating three dosage strengths of FF coupled with a fixed dose of VI was conducted in COPD. The same three dosage strengths were also evaluated in the COPD phase 3 trials. Dose selection for VI was conducted in both COPD and asthma and a single dosage strength was evaluated in the combination product in the phase 3 trials.

Study	Objective	Design	Population	Treatment	Time wks	Primary Endpoint
Vilanterol						
B2C111401	PK PD	R, DB, PC, XO	Asthma (24)  FEV1 ≥ 70%	VI 6.25 VI 25 VI 100 GW64244M6.25 GW64244M 25 GW64244M100 Placebo	SD	XXX
B2C109575	dose ranging	R, PC, DB, PG,	Asthma (605)  Uncontrolled on ICS FEV1 ≥ 40, ≤ 90%	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD Placebo QD	4	Trough FEV1
HZA113310	VI dose frequency	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	1 wk per period.	Trough FEV1

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B2C111045	dose ranging	R, DB, PG	COPD (602)	VI 3 QD VI 6.25 QD VI 12.5 QD VI 25 QD VI 50 QD Placebo QD	4	Trough FEV1
<b>Fluticasone furoate</b>						
FFA109687	Low dose FF dose ranging	R, PC, DB, PG	Asthma (598)  Uncontrolled without ICS	FF 25 QD FF 50 QD FF 100 QD FF 200 QD FP 100 BID Placebo BID	8	Trough FEV1
FFA109685	Med dose FF dose ranging	R, PC, DB, PG	Asthma (615)  Uncontrolled on low dose ICS	FF 100 QD FF 200 QD FF 300 QD FF 400 QD FP 250 BID Placebo BID	8	Trough FEV1
FFA109684	High dose FF dose ranging	R, PC, DB, PG	Asthma (622)  Uncontrolled on med dose ICS	FF 200 QD FF 400 QD FF 600 QD FF 800 QD FP 500 BID Placebo	8	Trough FEV1
FFA112202	FF dose frequency  non inferiority	R, DB, XO	Asthma (190)  Uncontrolled without ICS	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
<b>Fluticasone furoate and vilanterol</b>						
HZC110946	24 hour effect	R, DB, PC, 3 way XO	COPD (54)	1st group FF/VI 50/25 FF/VI 100/25 FF/VI 200/25 placebo	4	Serial spirometry
FF = fluticasone furoate, VI = Vilanterol, GW642444 = M salt of vilanterol (earlier formulation), R = randomized, PC = placebo controlled, DB = double blind, PG = parallel group, XO = cross over, SD = single dose,						
Sources: Module 5.2 Tabular listing of all studies and individual CSR						

*Reviewer's comment: To evaluate the dose selection for VI, three, monotherapy, dose ranging trials will be reviewed: B2C111401 (single dose VI in asthmatics); B2C111045 (multiple dose in COPD) and B2C109575 (multiple dose in asthmatics). This single-dose trial was chosen for review as this is the only trial in the application to include to-be-marketed formulation of VI administered with the to-be-marketed device as a treatment arm. In addition, while COPD is the intended patient population, traditionally LABA dose selection has been based on information from a bronchodilator responsive population such as asthmatics. Therefore, the totality of the dose ranging data will be reviewed to ensure an appropriate dose was carried forward into the phase 3 safety and efficacy trials. In addition, Trial HZA113310 will be reviewed to help determine that an appropriate dosing regimen was chosen.*

*Because ICS monotherapy has not been shown to be effective in the treatment of COPD, dose-ranging for the FF component is reliant on trials conducted in the asthma population. For this NDA application, the low dose and medium dose dose-ranging trials (trials FFA109687 and FF109685) will be reviewed as these trials contain the proposed to-be-marketed dose. Data evaluating the dosing regimen will be obtained from trial FFA112202. While the primary objective for trial HZC11096 was to evaluate the 24-hour effect of the combination product in COPD, this trial included three dosage strengths of FF combined with a single dosage strength of VI. This trial will be reviewed to evaluate the dose selection of the combination product in COPD. However, importantly, the same doses were carried forward into the phase 3 COPD program to ensure the appropriate dose of FF was selected in the COPD population.*

**4. Pivotal Safety and Efficacy Trials**

Study	Design	Population	Treatment (mcg QD)	Time (Wks)	Primary Endpoint
Airflow Obstruction Trials					
HZC112206	R, DB, PC	COPD	FF/VI 50/25 FF/100/25 FF 100 VI 25 PBO	24	Trough FEV FEV1 AUC
HZC112207	R, DB, PC	COPD	FF/VI 100/25 FF/VI 200/25 FF 200 VI 25 PBO	24	Trough FEV1 FEV AUC
Exacerbation trials					
HCZ102871	R, DB, AC	COPD with history of exacerbation	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25	52	Annual rate of moderate/severe exacerbations
HCZ102970		COPD with history of exacerbation	FF/VI 50/25 FF/VI 100/25 FF/VI 200/25	52	Annual rate of moderate/severe exacerbations
Sources: Module 5.2 Tabular listing of all studies and individual CSRs					

*Reviewer's Comment:*

The airflow obstruction trials were factorial designed trials with treatment arms for the combination product, both monocomponents and placebo. Co-primary endpoints of trough FEV1 and post-dose FEV1 AUC (0-4) were designated to evaluate efficacy of the combination product compared to the monocomponents as well as placebo. Overall, this design is consistent with the airflow obstruction trials used by previous COPD programs. In addition to the airflow obstruction claim, the sponsor has also provided data to support a reduction in exacerbation claim. Given the ethical considerations of a placebo arm in a year-long trial in the chosen patient population, the trial included a VI comparator arm but was not placebo controlled. The primary endpoint, a comparison in the frequency of moderate to severe exacerbation is a reasonable assessment. Importantly, the sponsor has included specific measures in the exacerbation definition to maintain consistency across trial sites.

Traditionally, trough FEV1 has been used to demonstrate the contribution of the ICS, and post dose FEV1 has been used to demonstrate the contribution of the LABA. However, recent COPD bronchodilator programs have successfully utilized trough FEV1 as a primary endpoint to demonstrate bronchodilator efficacy<sup>1</sup>. Overall, efficacy review for VI will be based on the totality of the data, including an analysis of both co-primary endpoints as well as the 24 hour spirometric time curve. For the ICS contribution, the sponsor stated in earlier meetings with the division that it felt the ICS contribution would be better demonstrated through an analysis of the exacerbation data. This was chosen because ICS/LABA effect on decreasing exacerbations is believed to be related to the ICS component and not the bronchodilator. While this is reasonable, previous ICS/LABA COPD programs have successfully demonstrated the benefit of ICS/LABA over LABA monotherapy with bronchodilator endpoints, presumably because the ICS is decreasing airway inflammation in addition to the direct bronchodilatory effect of the LABA. Again, the efficacy review for the ICS will rely on the totality of the data from the 4 pivotal trials.

The phase 3 program is appropriately designed to provide replicate evidence of efficacy for both intended claims and for the benefit of the combination product over the monocomponents. Whether these trials effectively do so, for one or both claims, will be determined during the NDA review.

### Preliminary bronchodilator trial results

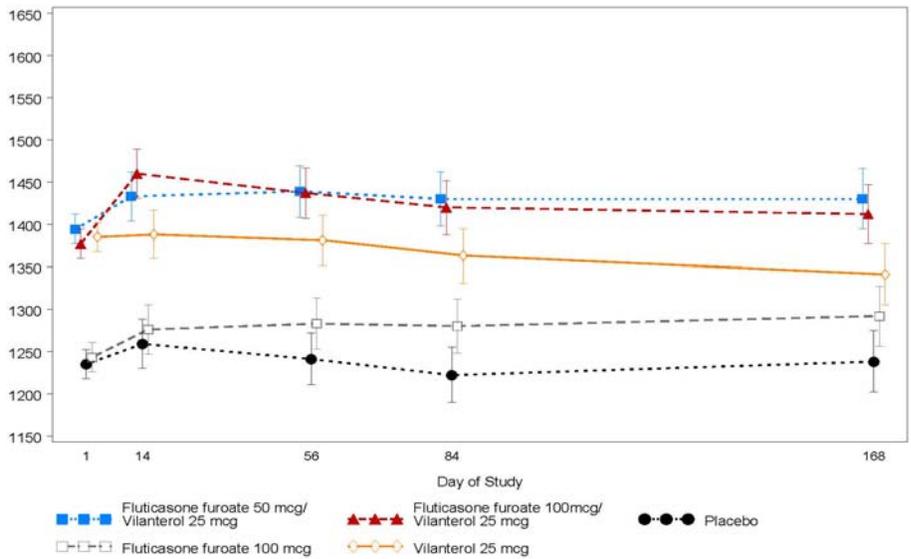
Summary table of co-primary efficacy endpoints

	FF/VI 50/25 versus			FF/VI 100/25 versus			FF/VI 200/25 versus		
	25 VI	50 FF	PBO	25 VI	100 FF	PBO	25 VI	200 FF	PBO
<b>Study 2206</b>									
Trough FEV1	0.062 P=0.025		0.129 P<0.001	0.048 P=0.082	0.082 P=0.003	0.115 P<0.001			
FEV1 AUC (0-4)	0.09 P< 0.001		0.192 <0.001	0.071 P=0.006	0.120 P<0.001	0.173 P<0.001			
<b>Study 2207</b>									
Trough FEV1				0.045 P=0.093	0.100 P<0.001	0.144 P<0.001	0.032 P=0.224	0.123 P<0.001	0.131 P<0.001
FEV1				0.029	0.168	0.214	0.024	0.168	0.209

<sup>1</sup> NDA 202-450; Aclidinium bromide approved July 23, 2012; Dr. Jenifer Rodriguez Pippins primary clinical review dated May 25, 2012 Section 6.1.4.

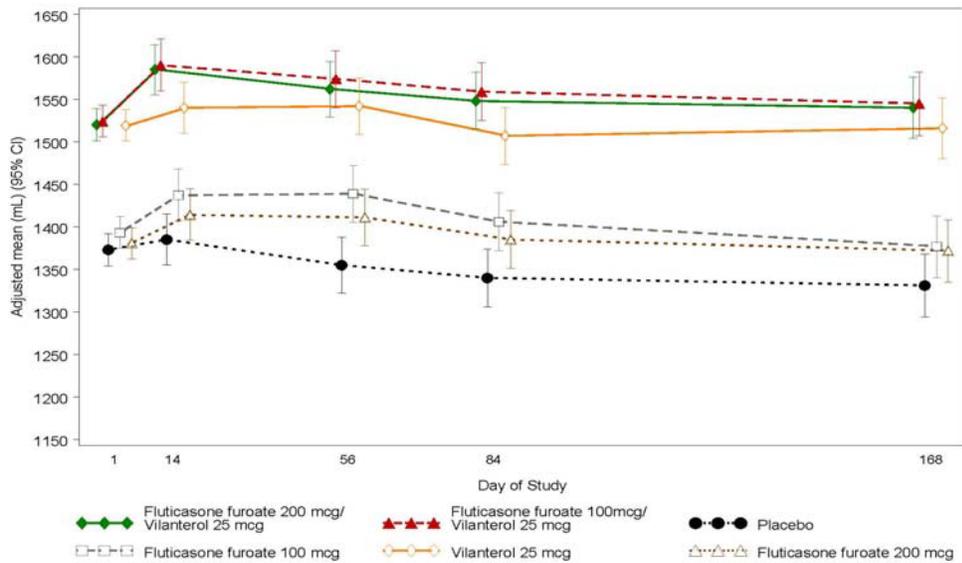
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AUC (0-4)				P=0.274	P<0.001	P<0.001	P=0.357	P<0.001	P<0.001
Source: CSR 112206 Tables 19 and 21 and CSR 112207 Tables 19 and 21									



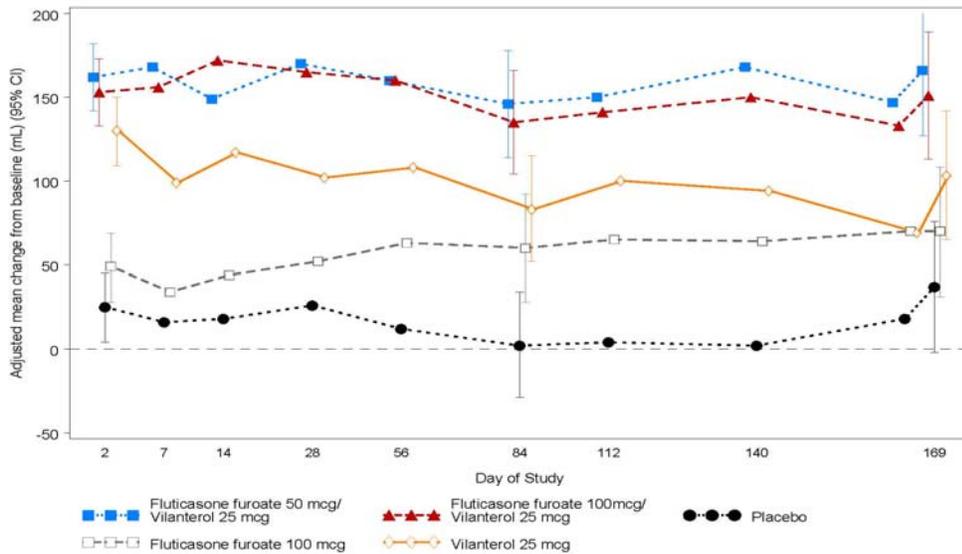
Weighted mean FEV1(0-4hr) ml for trial 112206

Source: Figure 1 proposed labeling



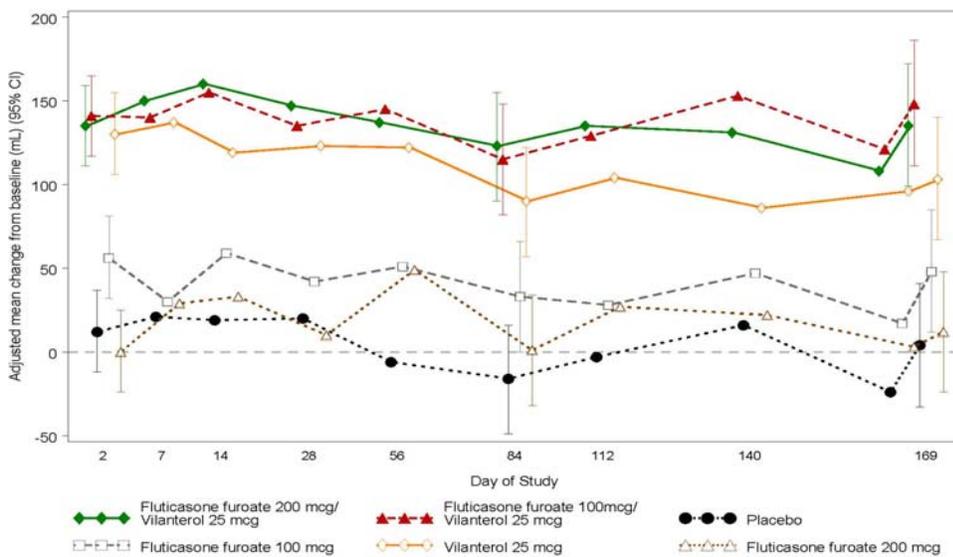
Weighted mean FEV1(0-4) ml for trial 112207

Source: Figure 3 proposed labeling



Trough FEV1 for trial 112206

Source: figure 3 proposed labeling



Trough FEV1 for trial 112207

Source: proposed labeling

**Preliminary exacerbation trial results**

Summary table of exacerbation data

	LS mean annual rate between ICS/VI & VI		
	50/25 FF/VI versus VI	100/25 FF/VI versus VI	200/25 FF/VI versus VI
<b>HZC102871</b>			
Ratio	0.87	0.66	0.85
P value	P=0.181	P<0.001	P=0.109

% reduction	13	34	15
95% CI	(-6, 34)	(19, 46)	(-4, 30)
HZC102970			
Ratio	0.81	0.79	0.69
P value	P=0.04	P = 0.024	P < 0.001
% reduction	19	21	31
95% CI	(1, 34)	(3, 36)	(15, 44)
Source: CSR HZC102871 and 102970 Table 13			

*Reviewer's comment:*

*Preliminary review of the pivotal phase 3 efficacy results demonstrates some inconsistencies in the data. For the bronchodilator trials, trial 2207 failed to show a statistically significant benefit for the high dose 200/25 FF/VI combination as well as the proposed 100/25 combination over VI alone for either of the co-primary endpoints. However the benefit of VI to the combination product was consistently demonstrated in both trials, as was the efficacy of the combination product compared to placebo. The exacerbation trial data is also not clean as trial 871 failed to demonstrate an improvement for the 200/10 mcg dose over placebo. Due to the hierarchical statistical testing procedure, a strict statistical interpretation means that while the 100/25 appears to demonstrate a benefit over VI monotherapy, the difference is not statistically significant. Again, as noted earlier, the efficacy of the ICS component in the combination product will be based on the totality of the data and will be a major point of review for this NDA application.*

**5. Safety Database**

Primary COPD Safety Database

	Placebo	FF/VI mcg once a day				VI mcg once a day							Total	
		50/25	100/25	200/25	400/25	3	6.25	12.5	25	50	100	200		
Intent-to-Treat Population, n														
All Studies	584	1060	1249	1047	40	99	101	101	1327	99	410	203	6225	
24 week studies														
HZC112206 + HZC112207	412	206	410	205	0	0	0	0	408	0	410	203	2254	
HZC112206	207	206	206	0	0	0	0	0	205	0	206	0	1030	
HZC112207	205	0	204	205	0	0	0	0	203	0	204	203	1224	
52 week studies														
HZC102871 + HZC102970	0	820	806	811	0	0	0	0	818	0	0	0	3255	
HZC102871	0	408	403	402	0	0	0	0	409	0	0	0	1622	
HZC102970	0	412	403	409	0	0	0	0	409	0	0	0	1633	
4 week studies														
B2C111045	101	0	0	0	0	99	101	101	101	99	0	0	602	
HZC110946	51	34	33	31	0	0	0	0	0	0	0	0	54	
HZC111348	20	0	0	0	40	0	0	0	0	0	0	0	60	
Source: clinical summary of safety Table														

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For its integrated summary of safety GSK has provided multiple groupings of the primary COPD safety data.

- 6 month trial data: Trials 112206 + 112207
- 52 week data: Trials 102871 + 102970
- Full integration: Trials 112206 + 112207 + 102871 + 102970 + 1405 + 110946 + 11348

Summary of SAEs and AE of special interest for 6 month trials: 112206 + 112207

	FF/VI mcg QD			VI QD	FF mcg BID		Placebo N=412
	50/25 N=206	100/25 N=410	200/25 N=205	25 mcg N=408	100 N=400	200 N=203	
Death <sup>1</sup>	2(<1)	2(<1)	1(<1)	3(<1)	1(<1)	0	2(<1)
SAE by SOC							
Total	6(3)	23(6)	15(7)	31(8)	22(5)	10(5)	21(5)
Resp d/o	0	9(2)	5(2)	11(3)	2(<1)	2(<1)	8(2)
PNA	1(<1)	1(<1)	3(1)	5(1)	2(<1)	2(<1)	1(<1)
Cardiac d/o	1(<1)	2(<1)	2(<1)	2(<1)	2(<1)	2(<1)	3(<1)
AE of interest <sup>2</sup>							
PNA	3(1)	6(1)	4(2)	7(2)	6(1)	3(1)	3 (<1)
Fatal PNA	0	0	0	0	0	0	0
PNA + LRTI <sup>3</sup>	3(1)	10(2)	2(<1)	11(3)	15(4)	6(3)	16(4)
Cardiac							
HTN	5(2)	4(<1)	1(<1)	3(<1)	8(2)	7(3)	10(2)
Arrhythmia	8(4)	21(5)	8(4)	19(5)	20(5)	14(7)	27(7)
ischemia	9(2)	3(1)	5(1)	2(<1)	2(<1)	8(2)	2(<1)
Failure	0	3(<1)	1(<1)	3(<1)	4(2)	3(<1)	2(<1)
Prolonged QT	0	1(<1)	0	0	0	0	0
Sudden death	0	0	0	1(<1)	0	0	0
Total <sup>4</sup>	22	32	15	28	34	32	41
Source ISS Table 41, 45, 57 and 67 SAE = serious adverse event; AE = adverse event; SOC = system organ class; PNA = pneumonia; LRTI = lower respiratory tract infection; HTN = hypertension							
<sup>1</sup> Death = on and post treatment death; SAE = on treatment							
<sup>2</sup> AE of special interest as categorized by GSK (Module 5.3.5.3 appendix 2)							
<sup>3</sup> LRTI excluding pneumonia							
<sup>4</sup> Total sum of above cardiac AE of interest							

Summary of SAEs and AE of special interest for 52 week exacerbation trials: HZC102871 & HZC102970

	50/25 N=820	100/25 N=806	200/25 N=811	VI 25 N=818
Death <sup>1</sup>	16(2)	10(1)	14(2)	13(2)

SAE by SOC				
Total	136(17)	123(15)	124(15)	126(15)
Resp d/o	59(7)	63(8)	59(7)	60(7)
PNA	22(3)	21(3)	21(3)	8(<1)
Cardiac d/o	14(2)	17(2)	10(1)	16(2)
AE of interest <sup>2</sup>				
PNA	48 (6)	51 (6)	55 (7)	27(3)
Fatal PNA	0	1 (<1)	6(<1)	0
Cardiac				
HTN	32(4)	36(4)	36(4)	25(3)
Arrhythmia	30(4)	27(3)	22(3)	31(4)
Ischemia	30(4)	19(2)	21(3)	26(3)
Failure	22(3)	26(3)	13(2)	33(4)
Prolonged QT	0	1(<1)	0	0
Sudden death	0	0	0	0
Total Cardiac <sup>4</sup>	112	109	92	115
Source: ISS Table 42, 47, 59 and 69				
<sup>4</sup> sum of cardiac events above				
SAE = serious adverse event; AE = adverse event; SOC = system organ class; PNA = pneumonia; LRTI = lower respiratory tract infection; HTN = hypertension				
<sup>1</sup> Death = on and post treatment death; SAE = on treatment				
<sup>2</sup> AE of special interest as categorized by GSK (Module 5.3.5.3 appendix 2)				
<sup>3</sup> LRTI excluding pneumonia				

*Reviewer's comment: The safety database is sufficiently large, and of sufficient duration, to allow review of the application. In addition to the COPD database, GSK has also provided a separate integrated summary of safety for the use of FF/VI in asthma. This is important, as historically, extension of ICS/LABA combination products into COPD have followed approval in asthma and these COPD programs have been able to rely on the previous safety experience.*

*The safety review for this NDA will rely primarily on the separate integration of the 24 week trial data and 52 week data. Interpretation of the larger, fully integrated data set is limited by the trial design differences including the comparator arms, study population severity, and duration. In addition, the asthma safety database will be reviewed for LABA-related AE to help confirm the appropriateness of the dose selection. Particular attention will be paid to the components of the asthma composite endpoint including asthma-related death, intubations and hospitalizations.*

*Both ICS and LABAs are well characterized drug entities with known side effect profiles. Therefore, in addition to the typical, general overview of the safety database, the review will also contain an analysis of adverse events of special interest.*

*GSK has identified the following AEs of special interest as:*

- *Bone disorders*

- *Cardiovascular effects*
- *Effects on potassium*
- *Effects on glucose*
- *Hypersensitivity*
- *Local corticosteroid effects*
- *Ocular effects*
- *LRTI excluding pneumonia*
- *Pneumonia*
- *Systemic corticosteroid effects*
- *Tremor*

*A review of the selected terms defining these AE of special interest reveals a comprehensive list of selected preferred terms defining each of these events. In addition, these events are consistent with the known side effect profiles identified for these drugs. For COPD, an assessment of pneumonia risk will help determine the risk benefit of the chosen ICS dose. In addition, the cardiovascular effects of bronchodilators, including LABAs, have been recent areas of interest in COPD.*

*For pneumonia, the 6 month airflow obstruction studies captured pneumonia as an adverse event where x-rays were encouraged but not required (27 of 32 pneumonia events had xray confirmation). In addition, any subject who developed pneumonia was withdrawn from the study. The clearest assessment of pneumonia risk will be from the one-year exacerbation trials. In these trials, to a pneumonia diagnosis was required to be CXR confirmed, and any subject meeting the study definition of moderate or severe exacerbation was required to have a CXR to evaluate for the presence of pneumonia.*

*For the cardiovascular risk, GSK's analysis differs from other, more recent, COPD bronchodilator programs<sup>23</sup> which analyzed for composite MACE (major adverse cardiac events) endpoint which have included cardiovascular death, non fatal cardiac ischemia and non fatal stroke. However, GSK has provided a detailed analysis of the following cardiovascular effects which appears to be sufficient:*

- *cardiac arrhythmia*
- *hypertension*
- *ischemia*
- *cardiac failure*
- *acquired long QT*
- *sudden death*

*In addition to the AEs of special interest, GSK conducted post-hoc standardized MedDRA queries (SMQs) to assess for cardiac arrhythmias, anaphylactic reaction, angioedema, ischemic heart disease and cardiac failure.*

*To better focus the review, different safety databases will be utilized depending on the limitations of the included studies. At this time, the following plan will be used, acknowledging that this may change depending on any findings during the review.*

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<sup>2</sup> *Aclidinium, NDA 202-450 approved May 25, 2012*

<sup>3</sup>  (b) (4)

- *Integrated data for 12 month exacerbation trials: focus on respiratory related events, including pneumonia and other time-sensitive steroid-related AEs. Given that the comparator arm was a LABA, analysis of any LABA related safety events is limited.*
- *Integrated data for 6 months trials: as studies included ICS, LABA, and placebo comparator arms, the review can focus on LABA related and ICS related events. However analysis for pneumonia and other more rare cardiovascular events will be limited by the shorter duration of the trials.*
- *Supplemental safety data from active control studies can provide any additional safety information particularly for short term cardiovascular events compared to a currently approved product.*

*From a preliminary review of the safety data, FF/VI appears to be associated with the class related increase in pneumonia seen with ICS/LABA products in COPD. In addition, on preliminary review, no apparent cardiovascular signal has been identified. Finally, GSK has identified an increase in long bone fractures not typically associated with osteoporosis induced fractures. As discussed in Section 9 below, it appears from the submission (Module 1.6 Section 4.2.5) that GSK is planning for a post marketing study to further evaluate the risk of osteoporosis and fracture.*

## **6. Labeling Highlights and potential review issues**

### Highlights of prescribing information:

- box warning information has been condensed with removal of standard class language
- relevant warning and precautions included (growth effect in children not included)

### Section 1: Indications and Usage

- airflow obstruction
- reduce exacerbation
- NOT indicated for acute bronchospasm or asthma

### Section 2 Dosage and Administration

- Includes onset of action claim

○

(b) (4)

### Section 4

- Contraindicated in milk protein allergy, or hypersensitivity of FF, VI or excipients

### Section 5

- 5.11 Hypersensitivity reactions references hypersensitivity reports from other powder products containing lactose, but not FF/VI specifically
- 5.12 does not have CNS effects of excessive beta adrenergic stimulation outlined

### Section 6

- Adverse event table displayed as integrated data from 6 months studies; 12 month studies data provided as written supplement

### Section 14

- 4 pivotal trials are presented grouped into lung function and exacerbation trials
- Lung function: figures 1 and 2 display graphical representations of weighted mean FEEV(0-4) over the course of the study for each trial; figures 3 and 4 display changes in trough FEV1. Data for onset of action provided.
- Exacerbation: no tables or figures just written language
- 14.3 information for duration of action, figure for 24 hour spirometric data provided

*Reviewer's comment: Neither of the approved ICS/LABA combination products for COPD, Advair or Symbicort, carry onset of action claims in the product label. The applicability of a time of onset claim for a chronically administered product with a warning statement that the drug is not indicated for acute bronchospasm relief will be a review issue. However it is notable that the product labels for both formoterol and salmeterol contain onset of action information in both an asthma and COPD population.*

## **7. OSI review/audit**

The statistical reviewer determined that conducting a center effect analysis would not be helpful in identifying possible sites for an Office of Scientific Investigations (OSI) audit. This was due to the fact that the trials were comprised of many individual centers enrolling only a small number of subjects. This ultimately resulted in many centers failing to enroll subjects in each treatment group.

One site, center 189089, had two sub-investigators who are listed as current or former employees of GSK. This center enrolled 25.9% (7 of 27 subjects) in trial HZA11326. GSK ran an internal impact analysis that determined that the removal of data from this site decreased the FF/VI treatment, but remained statistically superior to placebo. Removal of this trial on the early asthmatic response retained a numeric positive treatment effect of FF/VI but statistical significance was lost.

*Reviewer's Comment: Given the results of GSK's internal analysis and more importantly, that these asthmatic data only provide supplement evidence of efficacy for the sponsor's proposed COPD indication, no OSI audit of this site will be requested.*

GSK provided financial disclosure information for trials with study sites in the United States. None of the investigators had a proprietary interest in the product, but one investigator (b) (6) reported significant equity interest.

- (b) (6) principal investigator for site (b) (6), recruited (b) (6) subjects in trial (b) (6) and reported an equity interest in GSK that peaked at \$72,000.

GSK failed to obtain follow-up financial information on 3 additional investigators, one investigator retired and was not available for follow up, another investigator died, and the third failed to fully complete the form.

Of note, GSK has identified a disproportionate number of fatal cases of pneumonias from a single site in the Philippines with four of the seven fatal cases from that trial occurring from this

site. In addition, trial 102871 had a disproportionate number of fatal pneumonia cases with all but one of the cases occurring in this study.

Largest center enrollment for pivotal trials in the United States

Site #	Contact Information	Protocol Number	Number of Subjects
068982	Martinez	102871	29 out of 1622 (1.79%)
065190	Dunn	102970	24 out of 1633 (1.47%)
069133	Kerwin	112206	28 out of 1030 (2.71%)
069206	Cullen	112207	24 out of 1224 (1.96%)

Source: CSR 112206 and 112207 table 5.09 and 102871 and 102970 table 5.08

*Reviewer's Comment: Given that (b) (6) site recruited only (b) (6) the study participants, any potential conflict of interest would not impact the overall interpretation of the study results. Multiple additional investigators had financial disclosures to report; however, all of the investigators enrolled fewer than 2% of the study participants. Again, any potential misconduct would not impact the study results. In addition, the failed reporting from these investigators is unlikely to impact the overall interpretation of the studies.*

*While an audit of the Philippines site with the disproportionate number of fatal pneumonia cases may be informative in determining that cause of the imbalance, the data from this site is unlikely to impact the interpretation of efficacy and the safety signal works against the product.*

*Based on this information, the clinical team will recommend an OSI review of the two US centers that enrolled the highest number of subjects in the pivotal trials.*

- Site 069133, Dr. Kerwin, for trial 112206 (airflow obstruction trials)
- Site 068982, Dr. Martinez for trial 102871 (exacerbation trials)

## 8. Proposed REMS and Pharmacovigilance Plan

GSK's proposed REMS has the following objectives:

- Inform on the appropriate use of the product for the approved COPD indication
- Increased risk of asthma related death and serious outcomes with LABA, including FF/VI, when used to treat asthma
- Inform providers of increased risk of pneumonia, including those resulting in hospitalization, in patients with COPD who take FF/VI

To accomplish this, GSK proposes a communication plan including

- Dear healthcare provider letter outlining safety information on
  - Increased risk of asthma-related death in patients taking LABA
  - Increased risk of pneumonia resulting in hospitalization or death in patients with COPD
  - New prescribing guidelines that FF/VI is not indicated for the treatment of acute bronchospasm or for asthma
- Dear medical society letter
- Printed or web based information

GSK will assess physician understanding within 6 months following dissemination of educational materials. In addition, an annual analysis of SAE narratives for pneumonia fatalities, asthma-related death narratives, and drug utilization patterns will be performed. GSK will annually report on any completed assessments as well as provide a status report of on-going assessments.

NDA 204275, Breo Ellipta (fluticasone furoate/vilanterol) for COPD, GSK

GSK plans to combine communication about REMS assessments across its LABA containing products which include Serevent and Advair. This date falls on November 18.

In addition to the proposed REMS, GSK has submitted a pharmacovigilance plan that further characterizes the pneumonia and cardiovascular risk through a large on-going COPD mortality study. The plan also includes a potential post-approval bone mineral density study to evaluate the effects of FF/VI (HZC102972) on the development of osteoporosis.

### 9. Pediatric Development Program

As COPD is a condition specific to adults, the sponsor is requesting a Pediatric waiver. Traditionally, these have been granted for medications proposed for COPD. Thus the requested waiver appears reasonable.

### 10. Recommendation

This NDA application is recommended as fileable.

### 11. Comments to Sponsor

The following comments are to be conveyed to the Applicant in the 74-day filing letter:

1. We note inconsistencies in your pivotal phase 3 trial results, particularly as they relate to the benefit of the combination product over VI alone. Whether the data sufficiently support the benefit of the combination product over VI alone will be a review issue.

### 12. Filing Checklist

**NDA Number: 204-275**

**Applicant:**

**Stamp Date:**

**Drug Name: fluticasone furoate + NDA/BLA Type: NDA  
vilanterol**

**July 11, 2201**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	Electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			Module 2.7

	Content Parameter	Yes	No	NA	Comment
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			Module 1.14.1
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries ( <i>i.e.</i> , Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			5.3.5.3 ISS COPD 5.3.5.3 ISS asthma
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			5.3.5.3 ISE COPD
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Module 2.5 section 6
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)1
<b>DOSE</b>					
13.	<p>If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i>, appropriately designed dose-ranging studies)?</p> <p><b>Asthma FF dose ranging</b></p> <p>1. Study Number: FFA 109684 (high dose)  Sample Size: 622      Arms: FF QD 200, 400, 600, 800  FP 500 BID  Placebo  Location in submission: 5.3.5.4 ffa109684</p> <p>2. Study Number: FFA 109685 (med dose)  Sample Size: 615      Arms: FF QD 100, 200, 300, 400  FP 250 BID  Placebo  Location in submission: 5.3.5.4 ffa109685</p> <p>3. Study Number: FFA 109687 (low dose)  Sample Size: 622      Arms: FF QD 25, 50, 100, 200  FP 100 BID  Placebo  Location in submission: 5.3.5.4 ffa109687</p> <p><b>VI Asthma dose ranging</b></p> <p>1. Study Number: b2c 109575  Sample Size: 607      Arms: VI QD 3, 6.25, 12.5, 25, 50  Placebo  Location in submission: 5.3.5.4 b2c109575</p> <p><b>VI COPD dose ranging</b></p> <p>1. Study Number: b2c 111045  Sample Size: 602      Arms: VI QD 3, 6.25, 12.5, 25, 50  Placebo  Location in submission: 5.3.5.1 b2c111045</p>	X			<p>a. FF dose ranging in asthma</p> <p>b. VI dose ranging in asthma + COPD</p> <p>c. FF dose regimen in asthma</p> <p>d. FF am vs pm dose in asthma</p> <p>e. FF/VI dose ranging (3 strength FF + 25 VI) performed in phase 3 COPD program</p>



	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	1 endpoint: AR mod/sev exac. FF/VI 100/25 FF/VI 200/25 VI 25 Qam Location in submission: 5.3.5.1 hzc102871  Pivotal Study #2 hzc102970 Sample Size: 1560 Arms: FF/VI 50/25 1 endpoint: AR mod/sev exac. FF/VI 100/25 FF/VI 200/25 VI 25 Qam Location in submission: 5.3.5.1 hzc 102970				
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			No formal agreements  Airflow obstructive trials: • Trough FEV1 Exacerbation • Mod/sev exacerb
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				For ISE: 2.7.3 ISE Section 3.3.5
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (e.g., QT interval studies, if needed)?				FF/VI: HZA102936
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>4</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			<b>Asthma + COPD total # exposed</b> • FF/VI 100/25: 3904 • FF/VI 200/25: 1502 • FF/VI 400/25 40  <b>7 COPD trials FF/VI</b> ISS Table 2 pg 54

<sup>4</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
					<p><i>Total exposed:</i> (required &gt; 1500) Total ≥ 100/25: 2296</p> <ul style="list-style-type: none"> <li>• FF/VI 100/25: 1249</li> <li>• FF/VI 200/25: 1047</li> <li>• FF/VI 400/25 40</li> </ul> <p><i>6 months</i> (required 300-600) Total ≥ 100/25: 230</p> <ul style="list-style-type: none"> <li>• FF/VI 100/25: 140</li> <li>• FF/VI 200/25: 90</li> </ul> <p><i>48-52 weeks:</i> (required &gt; 100) Total ≥ 100/25: 777</p> <ul style="list-style-type: none"> <li>• FF/VI 100/25: 395</li> <li>• FF/VI 200/25: 382</li> </ul> <p><i>&gt; 52 weeks:</i> Total ≥ 100/25: 457</p> <ul style="list-style-type: none"> <li>• FF/VI 100/25: 222</li> <li>• FF/VI 200/25: 235</li> </ul> <p><b>Adequate size and exposure for safety database</b></p>
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>5</sup> used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			<p>5.3.5.3.28 ISS Section 2.1.4.2 pg 175</p> <ul style="list-style-type: none"> <li>• Bone disorders</li> <li>• Cardiovascular</li> <li>• potassium</li> <li>• glucose</li> <li>• Hypersensitivity</li> <li>• Local CS effects</li> <li>• Ocular effects</li> <li>• LRTI exclude PNA</li> <li>• Pneumonia (PNA)</li> <li>• Systemic CS effects</li> <li>• Tremor</li> </ul>

<sup>5</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			Table of links to all narratives for all CSR ISS Table 72 Pg 223  CSR 112206 11.2. Pg 260  CSR 112207 11.2 Pg 244  CSR HZC102871 attach. 1.2.1 Pg 1357 = fatal  CSR HZC 102970 attach. 1 (no TOC) Pg 1372 = fatal Pg 1401 = non fatal
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Pediatric waiver requested for COPD indication
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			5.3.5.3.28 ISS Section 5.6 Drug Abuse  No indication for abuse for combination or components
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			US vs Non US subgroup analysis performed in the individual CSR
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			Within individual CSR
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?				Module 1.3.4 Narrative page 1-12
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?				Mod 2.5 Section 1.4.1 Page 10 And individual CSR

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_YES\_**

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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SOFIA S CHAUDHRY  
09/04/2012

SUSAN L LIMB  
09/04/2012