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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	May 9, 2013
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-4275
Applicant Name:	GlaxoSmithKline
Date of Submission:	July 12, 2012
PDUFA Goal Date:	May 12, 2013
Proprietary Name:	Breo Ellipta
Established Name:	Fluticasone furoate and vilanterol
Dosage form:	Inhalation Powder (inhaler contains 2 double-foil blister strips, each with 30 blisters containing powder for oral inhalation)
Strength:	Fluticasone furoate 100 mcg per blister and vilanterol 25 mcg per blister
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

GlaxoSmithKline (GSK) submitted this 505(b)(1) new drug application for use of Breo Ellipta (fluticasone furoate 100 mcg and vilanterol 25 mg inhalation powder) for long-term once-daily maintenance treatment of airflow obstruction and the reduction of exacerbations in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is one inhalation (fluticasone furoate 100 mcg and vilanterol 25 mcg) once daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include short- and long-acting beta-2 adrenergic agonists (LABA), short- and long-acting anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents (both short-acting and long-acting), combination of long-acting beta-2 adrenergic agonists and corticosteroids, methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergic agents, combination products containing LABA and inhaled corticosteroids (ICS), and PDE inhibitors. With the exception of methyxanthines and PDE-4 inhibitors, all others are inhalation products.

Breo Ellipta is a new combination inhalation product comprised of an inhaled corticosteroid (ICS) and a long-acting beta-agonist (LABA). Neither component is currently marketed as a single-ingredient inhalation product in the United States. Fluticasone furoate, the ICS component, is marketed as an intranasal formulation for the treatment of allergic rhinitis. Vilanterol, the LABA component, is a new molecular entity and not marketed for any indication.

Development of ICS and LABAs in the United States has historically proceeded with the development of the individual components first, typically in asthma for both ICS and LABAs, and in COPD for LABAs. The combination products for ICS+LABA have historically been developed first in asthma and then in COPD. The dose and dosing frequency for both ICS and LABAs and ICS+LABA combination were characterized first in asthma and the same dose and dosing frequency were carried over to COPD. The recent concern with severe asthma exacerbation with LABAs (discussed below in this section) has changed this paradigm with pharmaceutical companies choosing to develop LABAs for COPD first, and not for asthma. Development of indacaterol and olodaterol are such examples where their sponsors have developed these products for marketing for COPD, but not asthma. GSK is following a similar paradigm, but with first priority for a combination product for COPD. GSK has conducted dose ranging and dose regimen studies with both the single ingredient products in asthma and COPD, pivotal studies with single ingredient vilanterol in COPD, and pivotal studies with the fluticasone furoate plus vilanterol combination product in patients with asthma. (b) (4) GSK is (b) (4) seeking approval for the fluticasone furoate plus vilanterol combination product for COPD. The development program was thus challenging and large because both the single components had to be studied individually to identify the appropriate dose and dosing frequency that would support the combination product.

In the subsequent sections of this review, the ICS component fluticasone furoate and the LABA component vilanterol are discussed, followed by a discussion of regulatory interaction between the Agency and GSK related to this application.

Fluticasone furoate:

Fluticasone furoate is not a new molecular entity as fluticasone furoate is marketed as a nasal formulation for the treatment of allergic rhinitis. Fluticasone propionate, another ester of fluticasone and propionic acid, is marketed for a variety of indications, including allergic rhinitis and asthma as a single ingredient product and as a combination product (Advair) with salmeterol, a LABA, for asthma and COPD. Corticosteroids have a variety of serious adverse effects that are well known. Although inhaled corticosteroids (ICS) do not usually have the typical serious systemic effects associated with corticosteroids because systemic absorption from the inhaled route is limited, ICS can have serious local adverse reactions in the lung in COPD patients. For example, Advair (fluticasone propionate plus salmeterol) is known to increase the risk of pneumonia in patients with

COPD, particularly at high doses. Also, ICS at high doses has systemic effects, such as changes in bone mineralization in COPD patients and an effect on linear growth in young growing patients with asthma. Identifying appropriate dosing frequency of ICS is also important because the same nominal dose given once daily can have substantially less efficacy compared to twice daily dosing, as was seen with fluticasone propionate and ciclesonide in patients with asthma. [1, 2] Therefore, it is important to select an appropriate dose and dosing frequency for any ICS. Dose selection for ICS in COPD is challenging given the lack of efficacy for ICS when used as a single agent in patients with COPD. Therefore, FDA has requested that sponsors conduct dose ranging and dose regimen trials for ICS products in patients with asthma, since patients with asthma are more steroid-responsive than COPD patients. This approach has limitations, as there may be fundamental differences in the pathophysiology that factor in the effect of ICS in COPD. In addition, spirometric endpoints like trough FEV1, which have been used traditionally to assess the effect of ICS in asthma, may not be sensitive in COPD, and trough FEV1 is a surrogate endpoint. Other efficacy variables, such as exacerbations, may be a more meaningful assessment of the added benefit of an ICS in an ICS+LABA combination in patients with COPD, but the design and conduct of an exacerbation trial for the purposes of dose selection are challenging. For this reason, FDA has recommended that sponsors consider carrying forward more than one dose of ICS into confirmatory trials for COPD.

Vilanterol:

Vilanterol is a new molecular entity that belongs to the class called long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, arformoterol, and indacaterol. Some of these are marketed as single ingredient products and others as combination products with inhaled corticosteroids. Salmeterol, formoterol, and arformoterol are dosed twice-daily and indacaterol is dosed once-daily. Vilanterol is proposed to be dosed once daily.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.[3, 4, 5, 6] More recently, inhaled LABAs have also been linked to severe asthma

[1] Purucker ME, Rosebraugh CJ, Zhou F, Meyer RJ. Inhaled fluticasone propionate by diskus in the treatment of asthma: A comparison of the efficacy of the same nominal dose given either once twice a day. Chest 2003; 124:1584-93.
[2] Chowdhury BA. Ciclesonide inhalation aerosol for persistent asthma. J Allergy Clin Immunol 2006; 117:1194-6. And, Alvesco (ciclesonide) Inhalation Aerosol, Package Insert, Product Label, Section 14.
[3] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[4] Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproteronol in spontaneous and induced asthma. N Eng J Med 1949; 240:45-51.
[5] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax 1991; 46:105-111.
[6] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. N Eng J Med 1992; 326:501-506.

exacerbations and asthma-related deaths.[7] This has been discussed at various FDA Advisory Committee meetings,[8] which has led to publications expressing concerns on safety,[9, 10, 11] and the establishment of a safe use strategy outlined by the FDA.[12] To further assess the safety of LABAs in asthma, the FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone.[13] The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.[14] Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for development of all LABAs, including vilanterol, which is proposed to be marketed for COPD. Most of the U.S.-marketed beta-adrenergic agonists carry both asthma and COPD indications, and the dose and dosing frequency in both indications are the same.

The indication claims of short-acting beta-adrenergic agonists, such as albuterol (Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, ProAir HFA Inhalation Aerosol, Proventil Inhalation solution) are for general bronchodilation ("treatment or prevention of bronchospasm with reversible obstructive airway disease"). The albuterol product labels do not mention a specific disease, such as asthma or COPD, in the indication section. Clinical studies supporting approval of these products were conducted in patients with asthma. Nevertheless, albuterol is used in patients with asthma and COPD. The indication claims of LABAs, such as salmeterol (Serevent Diskus, Serevent Inhalation Aerosol) and formoterol (Foradil Aerolizer), are also for general bronchodilation, but the product labels mention asthma and COPD as specific diseases in the indication section. Clinical trials supporting the dose and dosing frequency for these two long-acting beta agonists were also conducted in patients with asthma, and the same bronchodilatory dose was carried forward to studies in COPD. The regulatory precedence of performing dose ranging and dose regimen studies for

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[7] US Product Labels of salmeterol and formoterol containing products.
[8] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[9] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.
[10] Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. New Eng J Med 2009; 360:1952-1955.
[11] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[12] Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. New Eng J Med 2010; 362:1169-1171.
[13] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New Eng J Med 2011; 364:2473-2475.
[14] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:70-74.

bronchodilators in asthma patients has been established in order to demonstrate a large separation between doses, because the range of response is greatest in a bronchoresponsive population, such as patients with asthma. A COPD population, with some degree of fixed obstruction, has a smaller response range to a bronchodilator. The regulatory precedence of performing dose ranging and dose regimen studies in patients with asthma was followed in the development of indacaterol, a LABA that was approved for marketing in the United States in 2011 as a bronchodilator in patients with COPD. [15]

Regulatory interaction between the Agency and GSK:

The Division and GSK had typical milestone meetings on Breo Ellipta for its COPD program as well as its asthma program, in addition to meetings on the development of individual components fluticasone furoate and vilanterol. The following timeline highlights some major discussion that occurred during clinical development of these products.

- Pre-IND meeting for vilanterol, January 31, 2007: The Division recommended that GSK characterize the vilanterol monocomponent fully prior to developing the Breo Ellipta combination product.
- Pre-IND meeting for Breo Ellipta, April 29, 2008: The Division stated that data will be needed to confirm once-daily dosing regimens for the individual components present in Breo Ellipta and recommended studies to compare once-daily dosing interval to twice-daily dosing interval. The Division also stated that the clinical program will need to demonstrate added benefit to justify multiple dose levels of the combination product.
- End-of-Phase-2 meeting for Breo Ellipta asthma program, March 31, 2009: The Division reiterated the need for confirmation of the dosing interval prior to initiating confirmatory studies.
- End-of-Phase-2 meeting for Breo Ellipta COPD program, June 17, 2009: The Division stated that the proposed doses of fluticasone furoate 50, 100, and 200 mcg once-daily appeared reasonable based on the Phase 2 results in asthma. The Division agreed that dosing interval studies in asthma could be extrapolated to COPD. The Division also stated that replicate clinical trials were expected to support a bronchodilator claim and an exacerbation claim.
- Type C teleconference meeting for asthma and COPD program, March 24, 2010: The Division stated that the proposed vilanterol 25 mcg once daily dose appeared reasonable for further evaluation in confirmatory studies.
- Second End-of-Phase 2 meeting for Breo Ellipta asthma program, June 30, 2010: The Division requested that relevant information from the asthma program, such as dose selection data for the fluticasone furoate and vilanterol monocomponents be included in the COPD NDA.
- Pre-NDA meeting for Breo Ellipta for COPD, July 13, 2011: The Division and GSK discussed the challenges of evaluating Breo Ellipta for COPD prior to evaluation in asthma and the established use of either the fluticasone furoate and vilanterol monocomponents, which differs from prior precedent. The Division also

[15] Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. The risks and benefits of indacaterol – The FDA review. N Eng J Med 2011; 365:2247-2249.

expressed concerns about the strength of the efficacy data based on preliminary review. In particular, the Division noted the lack of a consistent benefit for Breo Ellipta over vilanterol alone in terms of spirometry. Whether positive results from the ongoing exacerbation programs could help support a bronchodilation claim was deemed uncertain.

- Pre-NDA meeting for Breo Ellipta for asthma, October 12, 2011: The Division requested that an application for asthma be submitted concurrently with the COPD application, given the novelty of both the fluticasone furoate and vilanterol components. GSK stated that the recommendation would be taken under advisement. GSK noted that the strength of the bronchodilator efficacy data in asthma for Breo Ellipta over vilanterol has provided mixed results. [16]

3. Chemistry, Manufacturing, and Controls

The product Breo Ellipta (fluticasone furoate 100 mcg and vilanterol 25 mcg inhalation powder) includes a novel dry powder inhaler device, the Ellipta inhaler, which contains 2 separate double-foil blister strips inside. Each blister on one strip contains micronized fluticasone furoate (100 mcg) and lactose monohydrate; and each blister on the other strip contains micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate, and lactose monohydrate. The lactose monohydrate may contain trace amounts of milk proteins. The proposed commercial presentation of Breo Ellipta has 30 blisters each of fluticasone furoate and vilanterol, which will be a one-month supply with a once daily dosing regimen. The device has a dose counter. The steps needed to use the product are simple and similar to some other dry powder inhaler devices. To deliver a dose, the patient will open the cover of the device. This action makes the powder from one blister containing fluticasone furoate and one blister containing vilanterol ready for inhalation at the airflow path inside the device. The patient will then inhale through the mouthpiece of the device. If a patient opens and closes the cover of the device without inhaling, the formulation powder will be held inside the device and will no longer be available to be inhaled. The Breo Ellipta device has been tested for usability, reliability, and ruggedness through in vitro testing, human factor studies, and testing of devices used in the clinical program.

Breo Ellipta is packaged within a moisture-protecting foil tray with a desiccant packet. GSK submitted adequate stability data to support an expiry of 24 months for the product stored at room temperature inside the protective foil tray. Breo Ellipta should be discarded after all doses are used or 6 weeks after removal from the protective package, whichever comes first.

The drug substances are manufactured at a GSK facility in Jurong, Singapore and drug product including the Breo Ellipta device is assembled at a GSK facility in Ware, United Kingdom. The device components are fabricated (b) (4). All manufacturing and testing facilities associated with this drug product have acceptable

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

establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

The single ingredient products containing fluticasone furoate and vilanterol in the Ellipta device were used in clinical studies (described in section 7 below). The formulations of the single ingredient products in the device were the same as the combination product except the absence of one of the active ingredient. The single ingredient products (with placebo formulations in companion strips) were assessed for key attributes, such as delivered dose content uniformity, and aerodynamic particle size distribution to assure that these were sufficiently similar to the combination product and that there were no pharmaceutical differences that would hinder the interpretability of the clinical studies.

4. Nonclinical Pharmacology and Toxicology

GSK submitted results from a full preclinical program to the Agency. The program included studies in which animals were dosed with fluticasone furoate and vilanterol individually and in combination via inhalation. The studies assessed the general toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity of each compound and potential interactions between the compounds. In general, these studies showed that fluticasone furoate and vilanterol each possessed toxicity profiles typical of their respective pharmacological classes, and studies of the combination did not suggest any major interactions or synergistic effects between the two components.

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

The general toxicity of vilanterol was evaluated after the inhalation route of administration of the drug for up to 13, 26 and 39-weeks in mice, rats and dogs, respectively. These studies identified the upper airways, lung, heart, liver and testes as target organs of toxicity, and findings were typical of beta agonists. In terms of genetic testing, vilanterol tested negative in the Ames assay, UDS assay in vitro, and SHE cell assay in vitro, and rat bone marrow micronucleus assay in vivo; and equivocal in the mouse lymphoma assay. Two-year carcinogenicity studies in rodents showed a dose-related shortening of latency for pituitary neoplasms in both genders of the rat and increases in the incidence of leiomyomas in female rats. Female mice showed increases in the incidence of tubulostromal carcinomas in the ovaries. These findings were typical of beta agonists in rodents. A battery of reproductive and developmental studies evaluated the effects of vilanterol on male and female fertility in rats, the teratogenicity of vilanterol in rats and rabbits, and peri- and post-natal development of vilanterol in rats. Results showed that vilanterol was not teratogenic in rats or rabbits, but caused increases

in the incidence of skeletal variations at high doses in rabbit fetuses. Vilanterol had no effects on fertility in rats.

5. Clinical Pharmacology and Biopharmaceutics

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism and the pharmacokinetics after single and multiple inhaled doses of fluticasone furoate and vilanterol individually and in combination. The majority of studies were conducted in healthy volunteers, but several studies were done specifically to assess pharmacokinetics in COPD patients and the effect of renal and hepatic impairment. Fluticasone furoate and vilanterol have low oral bioavailability and systemic exposure for both components is primarily due to absorption of the inhaled portion. A study using four inhalations of fluticasone furoate 200 mcg and vilanterol 25 mcg administered as a combination by inhalation showed an approximate absolute bioavailability of 15% for fluticasone furoate and 27% for vilanterol. Given low oral bioavailability, systemic exposure for both components is primarily due to absorption of the inhaled portion. The estimated half-life for fluticasone furoate and vilanterol is 24 hours and 14-21 hours, respectively. Both fluticasone furoate and vilanerol are substrates of CYP3A4 and P-gp. The inhibition potential for both are low when administered by the inhaled route and no specific dose adjustments are recommended when the combination is administered with other drugs. No significant effects due to age, or renal impairment on pharmacokinetic parameters were observed, so no dose adjustment for age or renal function is recommended. Systemic exposure of fluticasone furoate is higher in hepatic impairment patients. In addition, a decrease in serum cortisol was noted in patients with moderate hepatic impairment. Therefore caution should be used in patients with moderate or severe hepatic impairment. A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval at the therapeutic dose.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1 and Table 2. As discussed in section 2 above, unlike previous development programs for ICS and LABA where individual components were developed before developing an ICS+LABA combination product (typically in asthma first, then COPD), GSK conducted a program for fluticasone furoate and vilanterol that was largely concurrent for the individual components and the combination product, with this first application for the combination product for COPD. Furthermore, the clinical program was conducted to support both a bronchodilation claim and an exacerbation claim. As a result the clinical program submitted with this application is extensive. Table 1 summarizes the main studies conducted in both COPD

and asthma to support dose selection and dosing frequency for the individual fluticasone furoate and vilanterol components with the to-be-marketed device. Table 2 summarizes the main studies conducted in COPD to support the combination product. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8. For brevity, the studies are referenced later in this review by the last four digits of the study number.

Table 1. Relevant dose selection studies for fluticasone furoate, and vilanterol

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
Fluticasone furoate -- Dose-ranging and dose-regimen studies -- asthma patients					
109684 [2007-2008]	- 12 to 78 yr - Asthma - Parallel arm, DB - 8 weeks	FF 200 mg QD PM FF 400 mcg QD PM FF 600 QD PM FF 800 mcg QD PM FP 500 mcg BID Placebo	99 101 107 102 110 103	FEV_1 trough at week 8	US, Canada, Mexico, W Eur, E Eur, S Africa, Australia, Thailand
109685 [2007-2008]	- 12 to 80 yr - Asthma - Parallel arm, DB - 8 weeks	FF 100 mcg QD PM FF 200 mg QD PM FF 300 mcg QD PM FF 400 mcg QD PM FP 250 mcg BID Placebo	105 101 103 99 100 107	FEV_1 trough at week 8	US, Canada, Mexico, W Eur, E Eur, S Korea, Philippines
109687 [2007-2008]	- 12 to 78 yr - Asthma - Parallel arm, DB - 8 weeks	FF 25 mcg QD PM FF 50 mcg QD PM FF 100 mcg QD PM FF 200 mcg QD PM FP 10 mcg BID Placebo	97 100 110 95 102 94	FEV_1 trough at week 8	US, Canada, EU, EU, S Africa, Other
112202 [2007-2008]	- 12 to 76 yr - Asthma - Cross over, DB - 28 days	FF 200 mcg QD PM FF 100 mcg BID FP 200 mcg QD PM FP 100 mcg BID Placebo	140 142 42 43 187	FEV_1 trough at the end of 28-day treatment period	US
112059 [2010-2012]	- 12 to 84 yr - Asthma - Parallel arm, DB, DD - 24 week	FF 100 mcg QD PM FP 250 mcg BID Placebo	114 114 115	FEV_1 trough at week 24	US, EU
Vilanterol -- Dose-ranging and dose-regimen studies -- asthma patients					
109575 [2007-2008]	- 12 to 80 yr - Asthma - Parallel arm, DB - 28 days	VI 3 mcg QD PM VI 6.25 mcg QD PM VI 12.5 mcg QD PM VI 25 mcg QD PM VI 50 mcg QD PM Placebo	101 101 100 101 102 102	FEV_1 trough at day 28	US, EU, Canada, S Africa, Other
113310 [2009-2010]	- 18 to 71 yr - Asthma - Cross over, DB - 7 days	VI 6.25 mcg QD PM VI 6.25 mcg BID VI 12.5 mcg QD PM VI 25 mcg QD PM Placebo	75	FEV_1 trough at the end of 7-day treatment period	US
112060 [2010-2011]	- 12 to 79 yr - Asthma - Parallel arm, DB, DD	VI 25 mcg QD PM Sal 50 mcg BID Placebo	115 116 116	FEV_1 (0-24h) at end of 12 week treatment period	US, EU, Other

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
	- 28 days				
Vilanterol -- Dose-ranging study -- COPD patients					
111045 [2008-2009]	- ≥ 40 yr - COPD - Parallel arm, DB - 28 days	VI 3 mcg QD AM VI 6.25 mcg QD AM VI 12.5 mcg QD AM VI 25 mcg QD AM VI 50 mcg QD AM Placebo	99 101 101 101 99 101	FEV_1 trough at day 29	US, EU, Canada, Other

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

Table 2. Relevant clinical studies with Breo Ellipta (fluticasone furoate and vilanterol inhalation powder) in patients with COPD

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries //**
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
112206 Trial 2 [2009-2011]	- ≥ 40 yr - COPD by ATS criteria - Parallel arm, DB - 24 weeks	FF/VI 50/25 mcg QD AM FF/VI 100/25 mcg QD AM FF 100 mcg QD AM VI 25 mcg QD AM Placebo	206 206 206 205 207	1^o: FEV_1 0-4 hr on day 168 ΔFEV_1 trough baseline to day 169	US, EU, Other (39% US)
112207 Trial 2 [2009-2011]	- ≥ 40 yr - COPD by ATS criteria - Parallel arm, DB - 24 weeks	FF/VI 100/25 mcg QD AM FF/VI 200/25 mcg QD AM FF 100 mcg QD AM FF 200 mcg QD AM VI 25 mcg QD AM Placebo	204 205 204 203 203 205	1^o: FEV_1 0-4 hr on day 168 ΔFEV_1 trough baseline to day 169	US, EU, Other (25% US)
Pivotal exacerbation efficacy and safety studies -- COPD patients					
102871 Trial 3 [2009-2011]	- ≥ 40 yr - COPD by ATS criteria - Parallel arm, DB - 52 weeks	FF/VI 50/25 mcg QD AM FF/VI 100/25 mcg QD AM FF/VI 200/25 mcg QD AM VI 25 mcg QD AM	408 403 402 409	Annual rate of moderate to severe exacerbation **	US, EU, Canada, S Africa, Australia, Other (33% US)
102970 Trial 4 [2009-2011]	- ≥ 40 yr - COPD by ATS criteria - Parallel arm, DB - 52 weeks	FF/VI 50/25 mcg QD AM FF/VI 100/25 mcg QD AM FF/VI 200/25 mcg QD AM VI 25 mcg QD	412 403 409 409	Annual rate of moderate to severe exacerbation **	US, EU, Canada, S Africa, Australia, Other (36% US)
Supportive comparative efficacy and safety studies -- COPD patients and asthma patients					
113107 [2011-2011]	- ≥ 40 yr - COPD by ATS criteria - Parallel arm, DB, DD - 12 weeks	FF/VI 100/25 mcg QD AM FP/Sal 500/50 mcg BID	266 262	24-hour serial FEV_1 trough on day 84	EU, Other
113109 [2011-	- ≥ 40 yr - COPD by ATS criteria	FF/VI 100/25 mcg QD AM FP/Sal 250/50 mcg BID	260 259	24-hour serial FEV_1 trough on	US, EU

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries //**
2011]	- Parallel arm, DB, DD - 12 weeks			day 84	
112352 [2011-2012]	- ≥ 40 yr - COPD by ATS criteria - Parallel arm, DB, DD - 12 weeks	FF/VI 100/25 mcg QD AM FP/Sal 250/50 mcg BID	259 252	24-hour serial FEV_1 trough on day 84	US, EU, S Africa, Other
113091 [2011-2012]	- 12 to 80 yr - Asthma - Parallel arm, DB, DD - 24 weeks	FF/VI 100/25 mcg QD PM FP/Sal 250/50 mcg BID	403 403	24-hour serial FEV_1 trough on day 168	US, EU, Other

* Study ID shown (top to bottom) as GSK's study number, as referenced in the proposed Breo Ellipta product label, and [year study started-completed]
† DB=double blind, DD=double dummy
‡ FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); FF=fluticasone furoate in Ellipta device; FP=fluticasone propionate; VI=vilanterol in Ellipta; FP/Sal = Advair Diskus (fluticasone propionate and salmeterol xinafoate inhalation powder)
§ Intent to treat (ITT)
¶ Primary efficacy variables for studies 112206 and 112207 were analyzed using mixed model for repeated measure (MMRM) in the ITT population. Primary efficacy variable for studies 102871 and 102970 was analyzed using a general linear model assuming the negative binomial distribution in the ITT population.
// EU included UK, Germany, Italy, Netherlands, Sweden, Denmark, Spain, Estonia, Poland, Czech Republic, Romania; Other included Chile, Argentina, Peru, Mexico, Philippines, Thailand, Japan, S Korea, Russia, Ukraine
** COPD exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered to be of moderate severity if treatment with systemic corticosteroids and/or antibiotics were required and were considered to be severe if hospitalization were required.

b. Design and conduct of the studies

Fluticasone furoate dose ranging (9684, 9685, 9787) and dose regimen (2202, 2059) studies in asthma:

These studies were conducted in patients with persistent asthma with varying severity commensurate to the dose of fluticasone that were used in these studies: study 9684 enrolled patients who were symptomatic on moderate-dose ICS, study 9685 enrolled patients who were symptomatic on low-dose ICS, study 9687 enrolled patients who were symptomatic on SABA, and studies 2202 and 2059 enrolled patients with persistent asthma. Study treatment arms and primary efficacy variable are shown in Table 1. The primary analysis for studies 9684, 9685, and 9687 was linear trend in dose response in trough FEV1 at week 8. The primary analysis of study 2202 was non-inferiority of fluticasone furoate 200 mg QD to fluticasone furoate 100 mg BID trough FEV1 at week 8. Safety assessments included adverse event recording, vital signs, physical examination including oropharyngeal examination, clinical laboratory and hematology measures, and 24-hour urinary cortisol excretion.

Vilanterol dose ranging (9575), dose regimen (3310) and comparative (2060) studies in asthma:

These studies were conducted in patients with persistent asthma. Study treatment arms and primary efficacy variable are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, and ECGs.

Vilanterol dose ranging (1045) study in COPD:

This study was conducted in patients with COPD. Study treatment arms and primary efficacy variable are shown in Table 1. The primary analysis for study 9575 was linear trend in dose response in trough FEV1 at day 28. Safety assessments included adverse event recording, vital signs, physical examination, ECGs, and incidence of asthma exacerbation.

Pivotal bronchodilator (or lung function) studies (2206, 2207) in COPD:

These studies were identical in design except for the doses of study treatments (Table 2). Patients eligible for the studies were required to have a diagnosis of COPD as defined by ATS/ERS criteria, [17] with post-bronchodilator FEV1 of ≤70% predicted, a post-bronchodilator FEV1/FVC ratio of ≤0.70, and a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC). Eligible patients entered a 2-week single-blind placebo run-in period, and the patients who remained eligible entered the 24-week double-blind treatment period. These studies allowed ipratropium bromide at a constant dose, mucolytics, oxygen therapy ≤12 hours/day, and albuterol for rescue use. Prohibited medications included systemic or inhaled corticosteroids, LABAs, other combination products containing ICS+LABA, long-acting anticholinergics, combination product containing ipratropium+albuterol, and theophylline. The use of a placebo control for up to 24 weeks was considered ethically acceptable given the availability of rescue SABA and other medications in conjunction with close clinical monitoring for exacerbation symptoms. Patients were withdrawn from the study if they experienced an exacerbation. Study treatment arms and primary efficacy variables are shown in Table 1. To account for multiplicity across treatment comparisons, a step-down procedure was used with testing for high dose combination first, followed by low dose combination, and then other variables. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, 24-hour Holter monitoring, and 24-hour urinary cortisol excretion.

Pivotal exacerbation studies (2871, 2970) in COPD:

These studies were identical in design (Table 2). Eligibility criteria were similar to studies 2206 and 2207, with an additional requirement for a documented history of at least one COPD exacerbation that required antibiotics and/or systemic steroids or hospitalization in the past year. Eligible patients entered a 4-week open-label Advair

[17] Celli BR, MacNee W. Standards of the diagnosis and treatment of patients with COPD: A summary of the ATS/ERS position paper. Eur Respir J 2004; 23:932-946.

Diskus 250/50 twice daily treatment followed by 52-week double-blind treatment period. Permitted concomitant treatments were same as study 2206 and 2207, as well as use of oral corticosteroids and antibiotics for 14 days or less for the short term treatment of COPD exacerbations. Study treatment arms and the primary efficacy variables are shown in Table 1. To account for multiplicity across treatment comparison a step-down procedure was used with testing for high dose combination first, followed by low dose combination, and then other variables. COPD exacerbations were defined as worsening of 2 or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any 1 major symptom together with any 1 of the following minor symptoms: sore throat, colds (nasal discharge and/or nasal congestion), fever without other cause, and increased cough or wheeze for at least 2 consecutive days. COPD exacerbations were considered to be of moderate severity if treatment with systemic corticosteroids and/or antibiotics were required and were considered to be severe if hospitalization were required. Safety assessments included adverse event recording, vital signs, physical examination, assessment for pneumonia (all moderation to severe COPD pneumonia were assessed by chest x-ray), assessment for bone mineral density markers (study 2871 only), clinical laboratory and hematology measures, and ECGs.

Supportive comparative studies (3107, 3109, 2352) in COPD:

These studies were identical in design except for the doses of study treatments (Table 2). Study treatment arms and the primary efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, assessment for pneumonia, COPD exacerbation, and urine cortisol measurements (study 3109 only).

Supportive comparative study (3091) in asthma:

This study was conducted in patients with persistent asthma. Study treatment arms and the primary efficacy variable are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, asthma exacerbations, and urine cortisol measurements.

c. Efficacy findings and conclusions

The clinical program is adequate to support efficacy of Breo Ellipta 100/25 mcg (fluticasone furoate 100 mcg and vilanterol 25 mcg) for bronchodilation and reducing exacerbations in patients with COPD. The efficacy demonstration of Breo Ellipta builds on the selection of an appropriate dose and dosing regimen for fluticasone furoate and vilanterol, and then demonstrates the benefit for Breo Ellipta for the two claimed benefits of bronchodilation and reducing exacerbation over the single ingredient of fluticasone furoate and vilanterol.

Fluticasone furoate dose ranging and dose regimen in asthma:

As discussed in section 2 above, selection of an appropriate dose and dosing regimen is an important consideration for the development of ICSs, and these studies need to be conducted in patients with asthma because the effect of ICS in patients with COPD cannot be reliably assessed in COPD studies using lung function parameters. GSK conducted adequate exploration of dose ranges in 3 studies in patients with asthma and dose regimen in 1 study in patients with asthma (Table 1).

In dose ranging studies, trough FEV1 responses showed efficacy of fluticasone furoate 100 mcg once daily near the maximal efficacy with fluticasone furoate 200 mcg once daily (Figure 1). Efficacy was also demonstrated with fluticasone furoate 50 mcg once daily, but the difference compared to placebo and compared to other doses was less. With increasing doses of fluticasone furoate, the trough FEV1 response reached a plateau as expected, but also seemed to numerically decrease at the very high end of doses (Figure 1). Based on these data, GSK selected the nominal dose of fluticasone furoate 50, 100, and 200 mcg in combination with vilanterol for confirmatory COPD studies. This was reasonable and acceptable to the Agency. Additional support for the selected doses was later generated from study 2059 (Table 1), where fluticasone furoate 100 mcg once daily demonstrated a statistically significant increase in trough FEV1 from baseline.

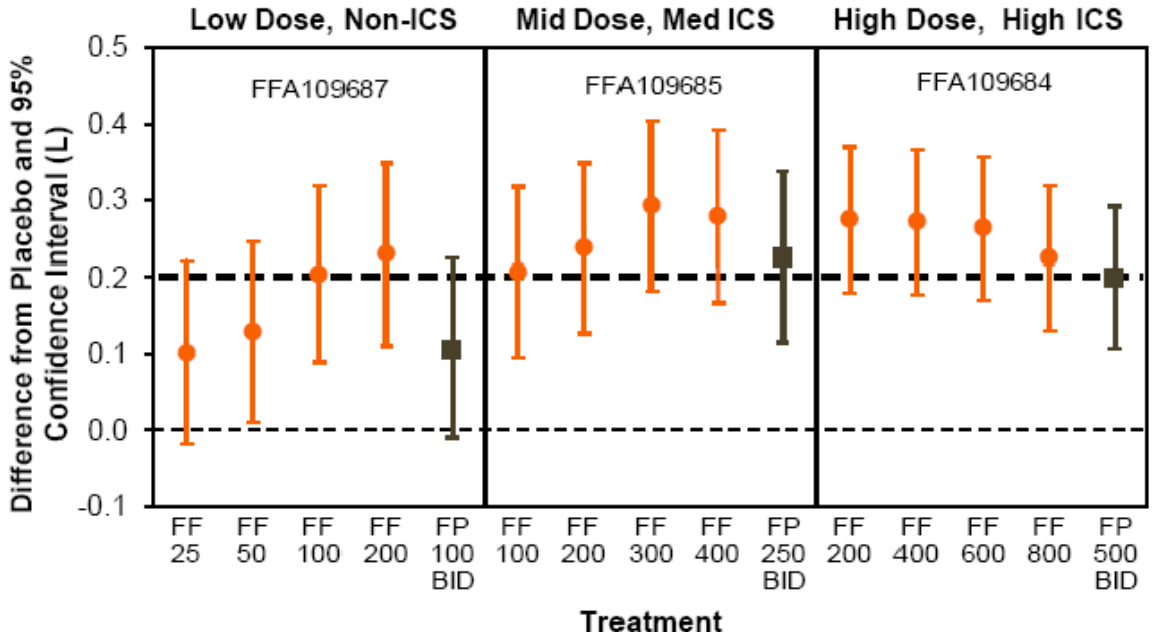

Figure 1. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at week 8 from three dose ranging studies in asthma (FF=fluticasone furoate, FP=fluticasone propionate).

Results of the dose regimen study showed numerically similar changes in trough FEV1 from baseline compared to placebo for fluticasone furoate 200 mcg once daily and fluticasone furoate 100 mcg twice daily, which support a once-daily dosing regimen for fluticasone furoate. The study had sensitivity to detect a difference between once- and twice-daily ICS dosing, since a numerically superior improvement in FEV1 compared to placebo was seen for the true twice-daily comparator, fluticasone propionate (Figure 2).

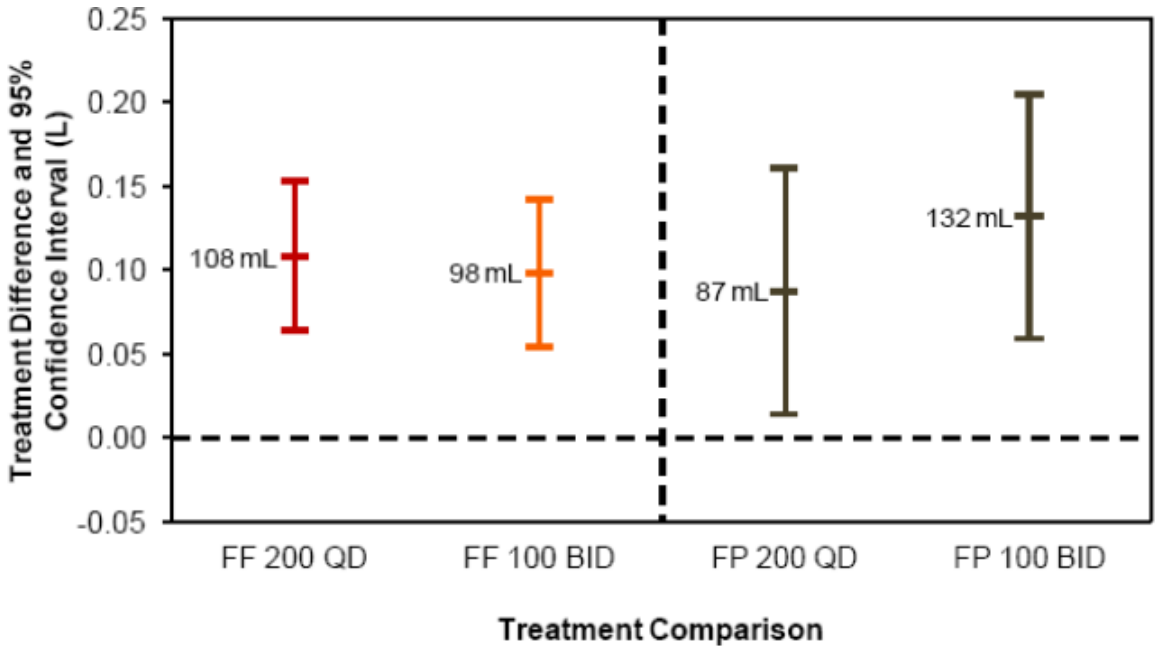

Figure 2. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at day 28 from dose regimen study in asthma (FF=fluticasone furoate, FP=fluticasone propionate).

Vilanterol dose ranging and dose regimen in asthma and COPD:

As discussed in section 2 above, the selection of an appropriate dose and dosing regimen is an important consideration for development of LABAs, and these studies need to be conducted in patients with asthma in addition to COPD because the bronchodilator response is greater in bronchoresponsive patients, such as patients with asthma who can show larger separation between doses. GSK conducted adequate exploration of dose ranges and dose regimens in patients with asthma and COPD (Table 1).

In the asthma dose ranging study (9575), vilanterol 3 mcg and 6.25 mcg once daily were not statistically significantly different from placebo for the primary endpoint of trough FEV1; vilanterol 12.5 mcg, 25 mcg, and 50 mcg once daily resulted in similar level of improvement in the primary endpoint of trough FEV1 that were all statistically significantly greater than that observed with placebo (Figure 3). In the COPD dose ranging study (1045), all doses of vilanterol were statistically significantly different from placebo for the primary endpoint of trough FEV1 with a numerical increasing trend with

increasing dose (Figure 3). Based on the results of these two studies, GSK selected vilanterol 25 mcg nominal dose in combination with fluticasone furoate 50, 100, and 200 mcg once daily doses for confirmatory COPD studies. This was reasonable and acceptable to the Agency.

Lack of an active comparator was a limitation in these dose-ranging studies. GSK has conducted a study (2060) that compared vilanterol 25 mcg once daily to salmeterol 50 mg twice daily (approved dose of salmeterol) in patients with asthma. The study showed a larger increase in trough FEV1 with vilanterol compared to salmeterol (359 mL vs 283 mL), but neither of the treatment groups were statistically significantly different to placebo, because placebo unexpectedly also increased trough FEV1 (289 mL). This study was therefore not helpful. Comparative efficacy studies conducted later with combination product (studies 3107, 3109, 2352, and 3091) showed comparable FEV1 time response curves after the first dose and also at later time points (Figure 4 shows two representative curves after the first done). The first dose bronchodilator response allowed comparison between vilanterol 25 mcg and salmeterol 50 mcg that was relatively unaffected by the ICS component. These results further supported the vilanterol 25 mcg dose.

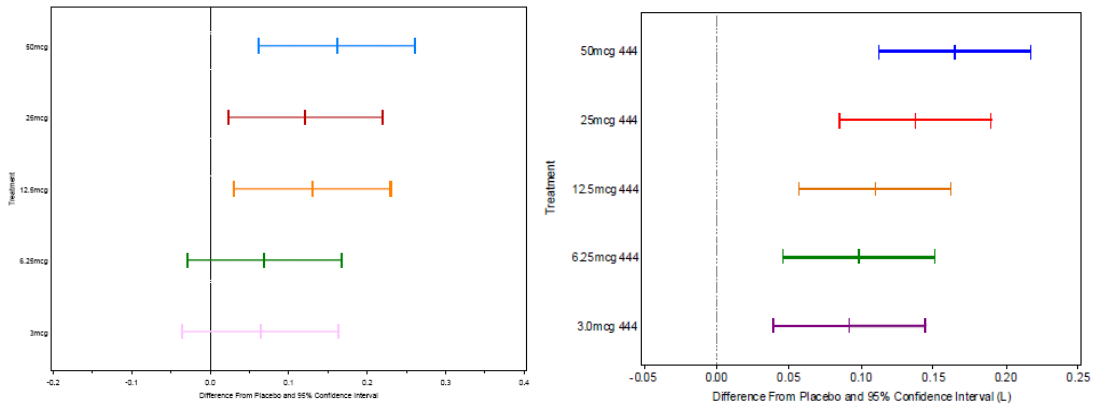

Figure 3. Adjusted treatment difference from placebo change from baseline in trough FEV1 in liters at day 29 in patients with asthma (study 9575, left panel) and COPD (study 1045, right panel).

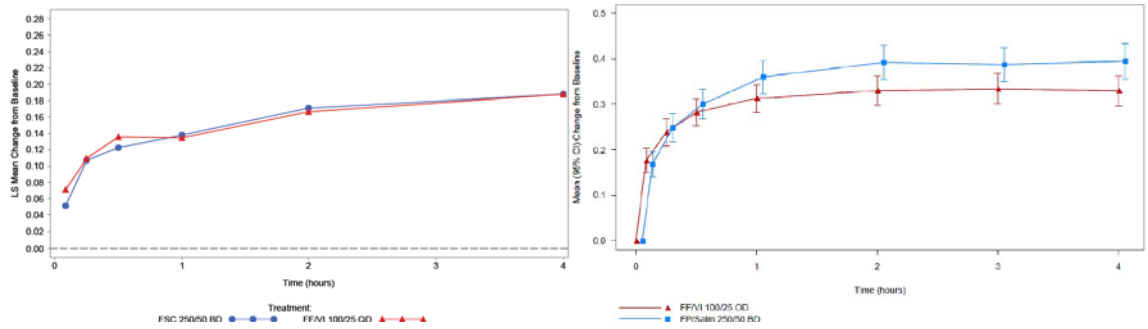

Figure 4. Mean change in FEV1 over time after the first done from COPD study 2352 (left panel) and asthma study 3091 (right panel).

Vilanterol dose regimen was investigated in study 3310 that compared once- and twice-daily dosing in patients with asthma (Table 1). The dose selected for comparison was 12.5 mcg (12.5 mcg once daily compared to 6.25 mcg twice daily), which is expected to be at the steep part of the dose-response curve, where differences between dose regimens would be easier to detect. Mean change in trough FEV1 on day 7 is shown on Figure 5. The trough FEV1 measure at day 7 suggests that vilanterol twice-daily provides a numerically better response than once-daily. The trough FEV1 with vilanterol 6.25 mcg twice daily was numerically comparable to vilanterol 25 mg once daily (Figure 5 left panel). GSK contended that weighted mean FEV1 time response curve (measures efficacy over 24 hours rather than at trough) is a better way to compare the doses. Using the weighted mean FEV1 time response, vilanterol 6.25 mcg twice daily and vilanterol 12.5 mcg once daily was similar with LS mean difference from placebo of 166 mL and 168 mL, respectively (time response curve shown in Figure 5 right panel). As an additional analysis, the Agency's Clinical Pharmacology team generated the FEV1 time response curve for day 7 using raw FEV1 (Figure 6). The FEV1 time response curves (using either repeated measures or raw FEV1) show higher FEV1 response with higher nominal doses in the first 12 hours of dosing interval, and the curve for the 6.25 mcg twice-daily shifts upwards with the evening dose and is comparable to the 25 mcg and 12.5 mcg once-daily doses for the second 12 hours of the 24-hour interval. These results support a once-daily dosing frequency for vilanterol and support GSK's decision to select vilanterol 25 mcg nominal once-daily dose in combination with fluticasone furoate 50, 100, and 200 mcg once-daily doses for confirmatory COPD studies.

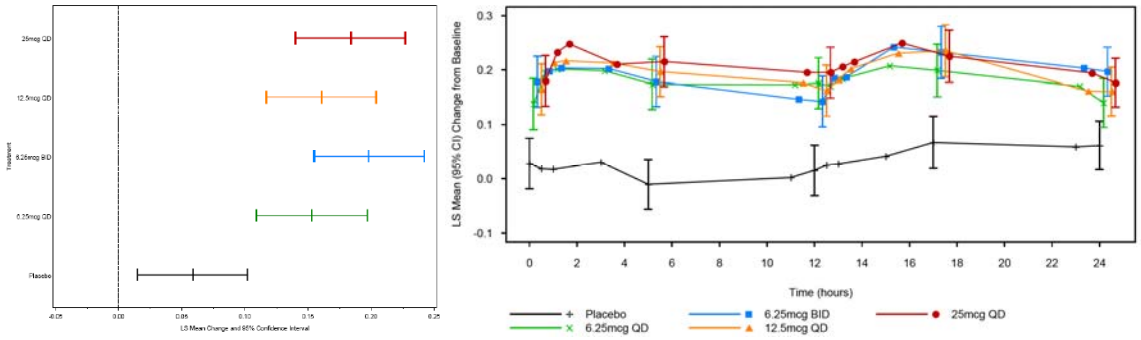

Figure 5. LS mean change in trough FEV1 on day 7 (left panel) and repeated measure adjusted mean change without placebo correction (right panel) on day 7 in patients with asthma, (vilatererol dose regimen study 3310 in asthma).

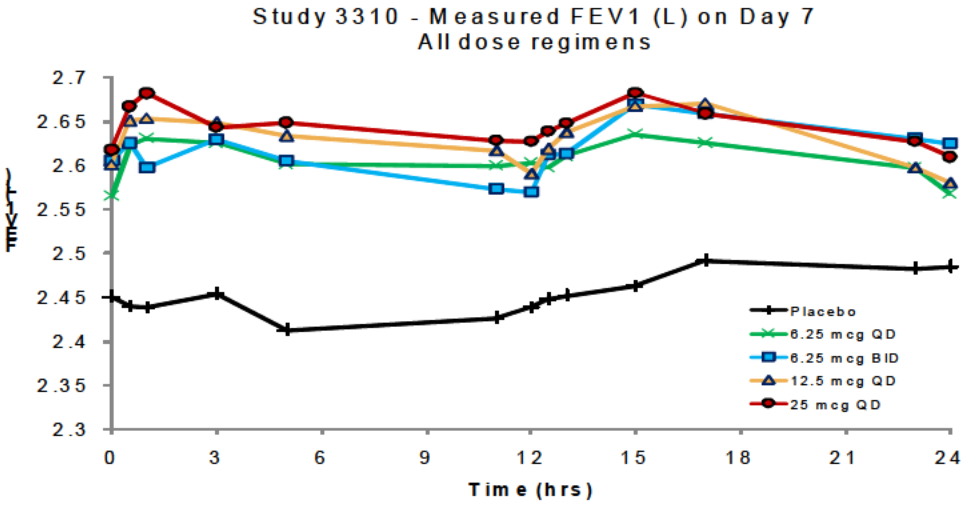

Figure 6. FEV1 time profile for 24 hours on day 7 using raw FEV1 values (vilanterol dose regimen study 3310 in asthma).

Breo Ellipta, bronchodilator effects:

Studies 2206 and 2207 are the two primary studies designed to support the bronchodilator claim for Breo Ellipta (fluticasone furoate plus vilanterol). In both the studies approximately 25% of the patients discontinued during treatment. The primary reasons for discontinuations were adverse events and lack of efficacy. Despite the dropouts, the pre-specified primary analysis remains valid because the dropout rates and the reasons for discontinuations were well balanced across treatment arms, and various sensitivity analyses (that applied different missing data assumptions) were consistent in the magnitude and direction to the results with primary analysis (applying mixed-model repeated measures method).

Studies conducted to support combination products typically compare the combination to each active component to show the contribution of each component present in the combination, and also to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination to justify the use of the combination product by patients. Studies 2206 and 2207 compared Breo to fluticasone furoate and to vilanterol and also compared multiple doses of Breo. For a combination product such as Breo, the bronchodilation benefit will be primarily from vilanterol.

The primary efficacy variable of FEV1 0-4 hours is intended to show the benefit of Breo over fluticasone furoate alone (show contribution of vilanterol in the combination). Results from the analysis of this primary efficacy variable showed a statistically significant difference between Breo 100/25 mcg and fluticasone furoate in both the studies but no separation between the Breo doses at the time point of day 168 (Table 3), and at various other time points (data not shown in this review). The submitted data are adequate to show the benefit of Breo over fluticasone furoate (contribution of vilanterol).

Table 3. Bronchodilator studies 2206 and 2207; Mean change from baseline in weighted mean FEV1 0-4 hour on day 168 (ITT population)

Treatment *	N	Change (L)	Diff from Placebo (95% CI)	P value	Diff from FF (95% CI)	P value
Study 2206						
FF/VI 100/25	206	0.20	0.17 (0.12, 0.22)	<0.001	0.12 (0.07, 0.17)	<0.001
FF/VI 50/25	206	0.22	0.19 (0.14, 0.24)	<0.001	-	-
VI 25	205	0.13	0.10 (0.05, 0.15)	<0.001	-	-
FF 100	206	0.08	0.05 (0.00, 0.10)	0.040	-	-
Placebo	207	0.03	-	-	-	-
Study 2207						
FF/VI 200/25	205	0.20	0.21 (0.16, 0.26)	<0.001	0.17 (0.12, 0.22)	<0.001
FF/VI 100/25	204	0.20	0.21 (0.16, 0.27)	<0.001	0.17 (0.12, 0.22)	<0.001†
VI 25	203	0.17	0.19 (0.13, 0.24)	<0.001	-	-
FF 100	204	0.03	0.05 (-0.01, 0.10)	0.085	-	-
FF 200	203	0.03	0.04 (-0.01, 0.09)	0.123	-	-
Placebo	205	-0.01	-	-	-	-

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

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

The primary efficacy variable of change in trough FEV1 is intended to show the benefit of Breo over vilanterol alone (show contribution of fluticasone furoate in the combination). Results of this primary efficacy variable failed to show a statistically significant difference between Breo and vilanterol at any of the doses in either of the studies at the time point of day 169 (Table 4), and at various other time points assessed (data not shown in this review). These FEV1 data alone are not adequate to show the benefit of Breo over vilanterol. However, other studies, such as the exacerbation studies (2871, 2970), provide data that demonstrate the benefit of Breo over vilanterol (discussed below under COPD exacerbation). Furthermore, comparative efficacy studies show a comparable FEV1 time profile response for Breo compared to Advair 250/50, which has bronchodilator and exacerbation claims (a representative curve is shown in Figure 7).

Table 4. Bronchodilator studies 2206 and 2207; Mean change from baseline in trough FEV1 on day 169 (ITT population)

Treatment *	N	Change (L)	Diff from Placebo (95% CI)	P value	Diff from vilanterol (95% CI)	P value
Study 2206						
FF/VI 100/25	206	0.15	0.12 (0.06, 0.17)	<0.001	0.05 (-0.01, 0.10)	0.082
FF/VI 50/25	206	0.17	0.13 (0.07, 0.18)	<0.001	0.06 (0.01, 0.12)	0.025†
VI 25	205	0.10	0.07 (0.01, 0.12)	0.017	-	-
FF 100	206	0.07	0.03 (-0.02, 0.09)	0.241	-	-
Placebo	207	0.04	-	-	-	-
Study 2207						

Treatment *	N	Change (L)	Diff from Placebo (95% CI)	P value	Diff from vilanterol (95% CI)	P value
FF/VI 200/25	205	0.14	0.13 (0.08, 0.18)	<0.001	0.03 (-0.02, 0.08)	0.224
FF/VI 100/25	204	0.15	0.14 (0.09, 0.20)	<0.001	0.05 (-0.01, 0.10)	0.093†
VI 25	203	0.10	0.10 (0.05, 0.15)	<0.001	-	-
FF 100	204	0.05	0.04 (-0.01, 0.10)	<0.095	-	-
FF 200	203	0.01	0.01 (-0.04, 0.06)	<0.756	-	-
Placebo	205	0.00	-	-	-	-

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

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

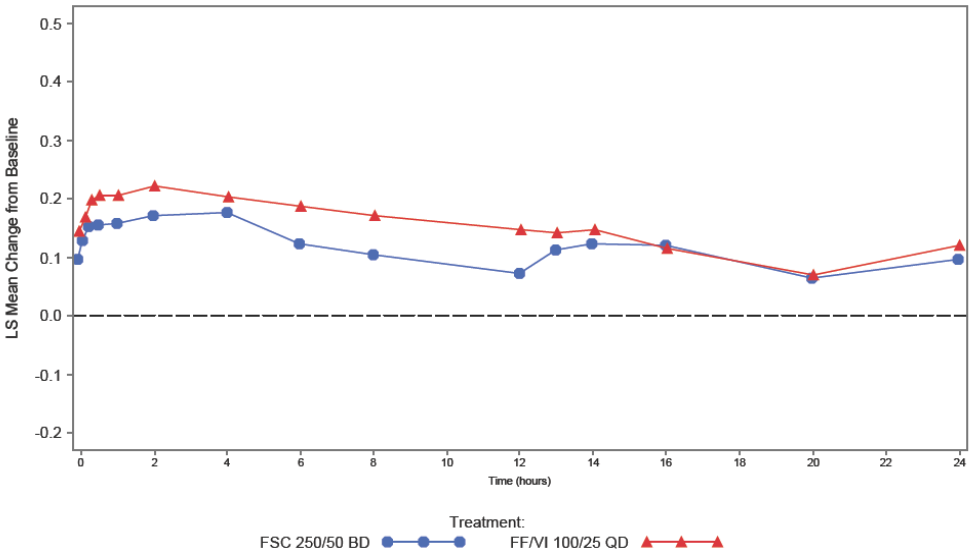

Figure 7. FEV1 time profile over 24 hours for Breo 100/25 and Advair 25/50 using LS mean change from baseline in FEV1 at day 84 (comparative study2352).

Breo Ellipta, COPD exacerbation:

Studies 2871 and 2970 are the two primary studies designed to support the exacerbation claim for Breo Ellipta (fluticasone furoate plus vilanterol). As in the bronchodilator studies, in both of these exacerbation studies also approximately 25% of the patients discontinued during treatment. The discontinuation rates were slightly higher in the vilanterol group, but the reasons for discontinuations were generally well balanced. Impact of missing data was examined. However, the approaches used assume that there was no relationship between the response and the missing outcome, that is, the method assumes that the event rate after withdrawal from trial is the same as the event rate on trial treatment. This is often not the case particularly when the reason for missing data is treatment-related. It is difficult to predict the number of exacerbations one may have post-withdrawal except to collect the actual exacerbation data after patient withdraws

from the trial. Therefore, the applicant's reported rates are estimates based on the assumption that the same event rates occur between pre- and post-withdrawal.

As discussed under bronchodilator effects above, studies conducted to support a combination product typically compare the combination to each active component to show the contribution of each component present in the combination, and also to show that the combination provides clinically meaningful benefit over each single ingredient to justify the use of the combination product by patients. Studies 2871 and 2970 compared Breo to vilanterol to demonstrate the additional benefit of the fluticasone furoate component on COPD exacerbations. Multiple doses of Breo were studied to test for an incremental benefit with higher dose of fluticasone furoate.

The primary efficacy variable of annual rate of moderate to severe exacerbation showed the benefit of Breo over vilanterol in study 2970 for all three Breo doses, and in study 2871 for the Breo 100/25 mcg dose. Although the prespecified statistical analysis plan required statistical significance of the higher dose prior to testing the lower dose, in study 2871 (technically a failed study for exacerbation), the magnitude of effect for the Breo 100/25 mcg dose was consistent with study 2970. The time to first moderate or severe exacerbation showed a benefit of Breo over vilanterol in both studies (Figure 8 results for study 2970). There was no clear separation among the three Breo doses. The Breo 50/25 mcg dose seemed to provide consistently lesser benefit, and the Breo 100/25 mcg and 200/25 mcg doses seemed to be similar. Taking the two studies together, the submitted data are adequate to support an exacerbation claim for Breo Ellipta 100/25 mcg.

The exacerbation data helps to place the trough FEV1 data discussed above in context. As discussed above, Breo at any of the doses was not statistically significantly superior to vilanterol on trough FEV1 (Table 5). Trough FEV1 is considered to be a surrogate measure of efficacy, and probably reflects benefit on exacerbations. With the direct demonstration of an exacerbation benefit, a statistically significant difference between Breo and vilanterol on trough FEV1 is hard to justify as being necessary. Furthermore, fluticasone furoate is not a bronchodilator, and with the long duration of action of vilanterol with prolonged effect on FEV1, the effect of fluticasone furoate on trough FEV1 may be masked.

Table 5. Exacerbation studies 2871 and 2970; Annual rate of moderate to severe COPD exacerbations

Treatment *	N	LS Mean Annual Rate	Comparison to vilanterol Ratio (95% CI)	P value
Study 2871				
FF/VI 200/25	402	0.90	0.85 (0.70, 1.04)	0.109
FF/VI 100/25	403	0.70	0.66 (0.54, 0.81)	<0.001†
FF/VI 50/25	408	0.92	0.87 (0.72, 1.06)	0.181†
VI 25	409	1.05	-	-

Treatment *	N	LS Mean Annual Rate	Comparison to vilanterol Ratio (95% CI)	P value
Study 2970				
FF/VI 200/25	409	0.79	0.69 (0.56, 0.85)	<0.001
FF/VI 100/25	403	0.90	0.79 (0.64, 0.97)	0.024
FF/VI 50/25	412	0.92	0.81 (0.66, 0.99)	0.04
VI 25	409	1.14	-	-

* FF/VI = Breo Ellipta (fluticasone furoate and vilanterol inhalation powder); VI=vilanterol in Ellipta
† Nominal p-value. The p-values reported here do not take into account the testing hierarchy pre-specified in the statistical analysis plan, which required statistical significance for the higher dose prior to testing of lower doses.

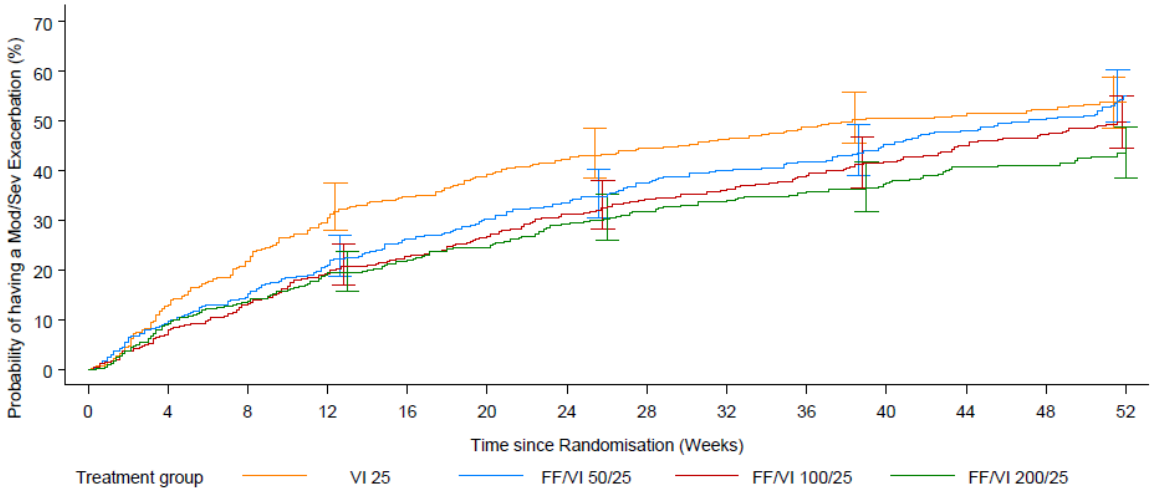

Figure 8. Kaplan-Meier plot of time to first moderate or severe exacerbation in study 2970.

8. Safety

a. Safety database

The safety assessment of Breo Ellipta is based on studies shown in Table 1 and Table 2 and various other studies. The primary COPD safety database for Breo is comprised of four pivotal COPD studies in 5509 patients (2254 patients in 24 week studies, and 3255 patients in 52 week studies). Additional safety data is available from 2342 patients in various other COPD studies, and 9379 patients in asthma studies. The safety database for Breo was large and adequate.

b. Safety findings and conclusion

The submitted data support the safety of Breo for use as maintenance treatment of airflow obstruction and reducing exacerbations in patients with COPD.

GSK conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[18]), common adverse events (AEs), assessment for pneumonia, assessment of bone disorder and fractures, assessment of cardiovascular effects (ECGs, Holter monitoring, thorough QT study), and assessment of adrenal function by 24-hour urinary cortisol excretion.

A total of 43 on-treatment deaths were reported in the 52-week COPD exacerbation studies and 8 on-treatment deaths were reported in the 24-week bronchodilation studies. These were balanced among the treatment groups. Common causes of deaths included COPD exacerbation, respiratory failure, and myocardial infarction, which are expected causes of death in older COPD patients. Reporting of SAEs was fairly common across treatment arms, as was discontinuation from the studies (some were defined in the protocol as discussion in section 7 above). These were also balanced among the treatment causes, and the events were typical and expected in COPD patients. The number of deaths and SAEs in other studies was also balanced and did not raise any concerns.

Two safety findings of interest identified in the program were pneumonia and bone fractures.

Pneumonia was observed in the Breo COPD program, most prominently in the 52-week exacerbation studies that were conducted in sicker COPD patients. Pneumonia was seen more frequently in all doses of Breo compared to vilanterol (Table 6). Time to first on-treatment pneumonia also showed a similar increase for all Breo doses compared to vilanterol with a dose-related trend for Breo (Figure 9). Pneumonia is a known risk of high dose inhaled steroids in patients with COPD and has been seen in previous LABA+ICS combination products. In two, replicate 52-week trials in 1579 patients; Advair Diskus (fluticasone propionate/salmeterol; FP/S) 250/50 mcg had a higher incidence of pneumonia (7%) compared to salmeterol (3%)[19]. Similar imbalances were seen in the 3-year mortality study (TORCH trial) comparing fluticasone propionate/salmeterol 500/50 to fluticasone propionate, salmeterol, and placebo. A total of 248 (16%) and 224 (14%) of fluticasone propionate/salmeterol and fluticasone propionate patients had a pneumonia event compared to 162 (11%) and 139 (9%) of patients in the salmeterol and placebo arms.[20]

[18] 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.

[19] Advair Diskus; NDA 21-077; Prescribing Information

[20] Calverley et al; Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease; N Engl J Med 2007; 256:775-89.

Table 6. Pneumonia shown as number of patients in COPD exacerbation studies 2871 and 2970

	Breo 50/25 N=820	Breo 100/25 N=806	Breo 200/25 N=811	Vilanterol 25 N=818
Pneumonia as a cause of death	0	1	6	0
Pneumonia reported as SAE	24	25	23	8
Pneumonia leading to discontinuation	3	5	8	3
Total number of pneumonia	54	58	65	28
Patients with pneumonia	48	51	55	27
Patients with >1 pneumonia	5	7	6	1

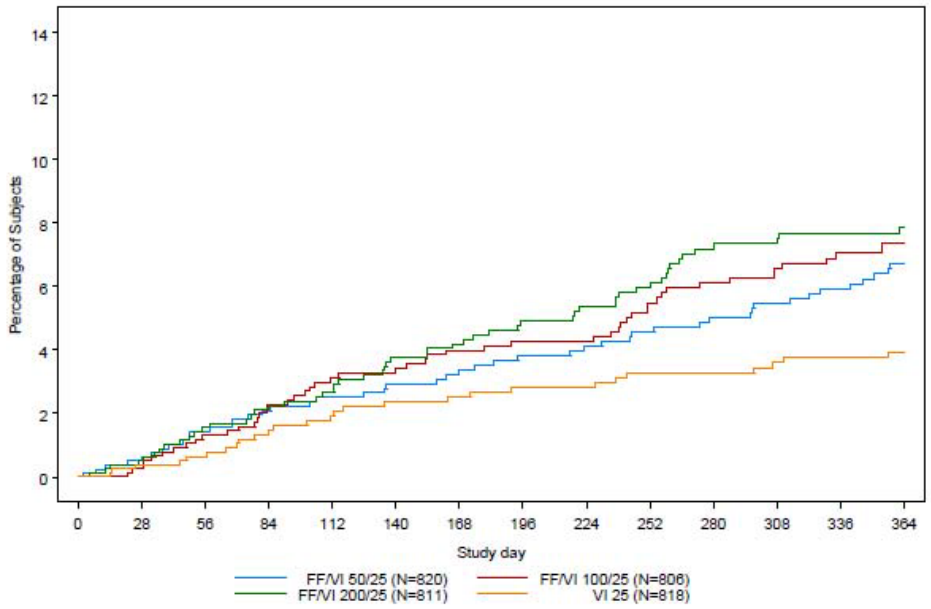

Figure 9. Time to first on-treatment pneumonia in exacerbation studies 2871 and 2970

An increased risk of fractures was seen with Breo compared to vilanterol (Table 7). Similar to pneumonia, a decrease in bone mineral density and increased fractures are also known risk factors for inhaled doses of ICS and have been seen in previous LABA+ICS combination product development programs for COPD. Bone disorder data was assessed in the 3-year COPD mortality trial (TORCH) evaluating Advair 500/50 mcg versus salmeterol and placebo. The Advair 500/50 mcg arm had a rate of 22.4 fractures per 1000 treatment-years compared to 18.6 for placebo, 20.4 for salmeterol and 20.3 for 500 mcg of fluticasone propionate. [21]

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

Table 7. Fractures shown as number of patients in COPD exacerbation studies 2871 and 2970

	Breo 50/25 N=820	Breo 100/25 N=806	Breo 200/25 N=811	Vilanterol 25 N=818
Fractures	14	19	14	8

Other safety assessments, such as assessments of cardiovascular function and adrenal axis did not show any safety signals. Analysis of common adverse events and laboratory parameters and common adverse events also did not show any specific findings of concern.

Asthma exacerbation and asthma-related deaths with LABA are safety concerns for patients with asthma. While a similar safety concern has not been seen in COPD, the clinical experience with vilanterol in asthma is of interest as secondary safety information and as confirmation of the selection of appropriate dose. GSK provided a summary of safety data from the asthma development program for FF/VI, which includes data from approximately 9000 patients, of which over 2500 have received Breo. The summary included an analysis of a composite safety endpoint for asthma-related hospitalizations, intubations, and deaths, which did not suggest an increased risk of severe asthma-related adverse events associated with vilanterol alone or in combination with fluticasone furoate.

c. REMS/RiskMAP

GSK submitted a REMS for Breo Ellipta consisting of a Medication Guide and a communication plan regarding LABA safety of asthma related death. The communication plans included a Health Care Professional Letter, information posted on a website, and notification of professional societies.

Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. The information regarding LABA safety and asthma-related death has been widely distributed to health care providers with demonstrated uptake of the information into clinical practice; the communication plan REMS requirements for other LABAs are currently being removed. Thus, while a Medication Guide is required to communicate the potential risks of vilanterol, a Medication Guide as part of REMS is not necessary.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on April 17, 2013, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indications of airflow obstruction and COPD exacerbation, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for Breo Ellipta 100/25 mcg once daily for the proposed indications. In general, the panel members concluded that there

were sufficient data to support the efficacy of Breo for both the proposed indications of airflow obstruction and COPD exacerbation. On voting questions, the Committee voted favorably regarding whether there was substantial evidence of efficacy for airflow obstruction in COPD (12 yes, 1 no, 0 abstain), for reduction of COPD exacerbations (8 yes, 5 no, and 0 abstain), and whether the safety of Breo had been adequately demonstrated (10 yes, 3 no, and 0 abstain). Regarding the approvability question, which is essentially the sum of the demonstration of efficacy and safety, the results were in favor of approval for airflow obstruction in COPD (9 yes, 4 no, 0 abstain[22]), and for reduction of COPD exacerbation (8 yes, 5 no, and 0 abstain). Overall, members felt that GSK had conducted an extensive, rigorous, and well-designed program.

10. Pediatric

GSK is requesting a claim for Breo for COPD only and is not requesting a claim for asthma. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required related to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two clinic representative sites in the pivotal COPD studies 112206 (bronchodilator study) and 102871 (exacerbation study) in the United States. The clinical and statistical review teams recommended the sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. One investigator had significant financial interest in GSK. The number of subjects enrolled in the investigator site was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

[22] Official vote 9 yes, 4 no, 0 abstain. One committee member noted during the discussion that he had inadvertently voted "Yes" but meant to Vote "No" The vote count in the text accounts for this change.

12. Labeling

a. Proprietary Name

GSK submitted Breo Ellipta as the proposed proprietary name, which was accepted by the DMEPA.

b. Physician Labeling

GSK submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. Asthma-related safety warnings are described in the label, including in a Boxed Warning, which are present in all LABAs. The Division and GSK have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Breo Ellipta will carry an asthma-related safety warning that will be part of the Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

GSK has submitted adequate data to support approval of Breo Ellipta (fluticasone furoate 100 mcg and vilanterol 25 mg inhalation powder) for long-term once-daily maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, at the dose of one inhalation (fluticasone furoate 100 mcg and vilanterol 25 mcg) once daily. The recommended regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Breo Ellipta inhalation powder at a dose of one inhalation (fluticasone furoate 100 mcg and vilanterol 25 mcg) once daily for long-term once-daily maintenance bronchodilator treatment of airflow obstruction and reducing exacerbations in patients with COPD, including bronchitis and emphysema.

A major safety concern with vilanterol is linked to the selection of an appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators. GSK conducted a comprehensive program, including dose ranging through pivotal confirmatory studies, to select the 25 mcg once daily dose

for the Breo combination product. The safety concerns with fluticasone furoate, similar to other ICS, are the risk of pneumonia in COPD patients, and systemic effects at high doses. GKS conducted adequate dose ranging studies early in the program, and carried multiple doses of ICS into the pivotal studies to select the 100 mcg once daily dose for the Breo combination product. The safety of profile of Breo 100/25 mcg was acceptable. The major safety findings were apparent increased risks of pneumonia and fractures, which seemed to occur at frequencies comparable to other IC/LABA products approved for COPD. The efficacy data submitted were adequate to support the indications of maintenance of airflow obstruction and reduction of exacerbation in COPD patients. Breo showed benefit over fluticasone furoate alone in FEV1 0-4 hours, and a benefit over vilanterol alone in COPD exacerbations. The efficacy data showed contribution of each component present in Breo, and also showed that Breo provides a clinically meaningful benefit over each single ingredient present in the combination.

c. Post-marketing Risk Management Activities

Breo will carry an asthma-related safety warning that will be part of the Medication Guide. No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
05/09/2013