

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204275Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	May 10, 2013
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA #	204275
Supp #	
Applicant Name	GlaxoSmithKline
Proprietary / Established (USAN) Names	Breo Ellipta (Fluticasone furoate and vilanterol)
Dosage Forms / Strength	Inhaled powder (inhaler contains 2 double-foil blister strips, each with 30 blisters Fluticasone furoate 100 mcg and vilanterol 25 mcg per blister
Proposed Indication(s)	Chronic obstructive Pulmonary Disease
Action:	<i>Approval</i>

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding Breo Ellipta (BE) and the reader should review the action package for more detail. BE is a combination of vilanterol, a new molecular entity long-acting beta agonist (LABA) and fluticasone furoate, an inhaled corticosteroid (ICS) moiety that is already approved in the United States. GlaxoSmithKline (GSK) is seeking approval of BE 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.

Inhaled LABAs are widely used to provide bronchodilation in patients with COPD. LABAs currently marketed in the United States include salmeterol, formoterol, arformoterol and indacaterol. Some of the aforementioned LABAs are marketed as single ingredient products and others are marketed as combination products with ICS. Salmeterol, formoterol and arformoterol are dosed twice-daily and indacaterol is dosed once-daily as is being proposed for vilanterol. Other drug classes besides beta-2 adrenergic agonists (including short-acting) used to treat the symptoms of COPD include anticholinergic agents, combinations of LABAs and corticosteroids, combinations of LABAs and anticholinergics, phosphodiesterase-4 (PDE4) inhibitors and methylxanthines.

There are two unique aspects to this development program. The first is that inhaled beta-2 adrenergic agonists have a safety concern of severe asthma exacerbation, sometimes leading to death, in patients treating the symptoms of asthma.¹ However, this type of signal has not been shown with use of inhaled beta-2 agonists in patients with COPD. In the past, inhaled beta-2

¹ A higher dose of inhaled formoterol was not approved because of more severe asthma exacerbations compared to lower doses.

adrenergic agonist agents were developed for both asthma and COPD indications (usually in the asthma population first), but recently the trend has been for sponsors to submit applications for this class of drugs only for COPD indications. This is probably, at least partially, due to sponsors' concerns that the safety signal existing for this class of agents in asthma may lead to a perilous approval path. However, past experience with development programs for LABAs has for the most part informed us that the dose and dosing interval will probably be the same for both asthma and COPD. As such, a traditional development program would include dose-ranging trials performed in subjects with asthma due to their greater airway sensitivity response to adrenergic activation which is necessary to establish separation of dose responses. Once a dose was determined in subjects with asthma, that dose would be carried forward into COPD trials. As such it is important to perform at least some dose-selection trials in subjects with asthma.²

The second unique aspect of this application is that usually, the single ingredients are developed separately seeking approval, then are combined in a separate program and submitted for consideration. This application is seeking approval of the combination product for COPD (b) (4) each component has been studied separately which has resulted in this application being quite large. These issues are discussed in thorough detail in Dr. Chowdhury and Limb's reviews.

The Division believes that substantial evidence of efficacy and safety in line with other approved LABA + ICS combination products has been demonstrated that should allow for marketing of Breo Ellipta. I agree with this assessment and recommend an Approval action.

Efficacy

The efficacy program was developed to demonstrate efficacy of vilanterol (VI) and fluticasone furoate (FF) concurrently with the combination and also sought a bronchodilation claim as well as an exacerbation claim. Relevant trials are presented below in tables from Dr. Chowdhury's review (Page 9-11).

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 //
<i>Fluticasone furoate -- Dose-ranging and dose-regimen studies -- asthma patients</i>					
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

² Dose-ranging was performed in both asthma and COPD populations for this application and the agency agreed with the doses selected and carried forth in clinical trials. Dose-ranging trials included the same nominal dose given twice daily compared to once daily.

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Primary efficacy variables ¶	Regions and Countries //
109685 [2007-2008]	- 12 to 80 yr - Asthma - Parallel arm, DB - 8 weeks	FF 100 mcg QD PM FF 200 mcg 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 - 28 days	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
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
<p>* Study ID shown (top to bottom) as GSK's study number, and [year study started-completed]</p> <p>† DB=double blind, DD=double dummy</p> <p>‡ FF=fluticasone furoate in Ellipta device; FP=fluticasone propionate; VI=vilanterol in Ellipta device; Sal=salmeterol xinafoate;</p> <p>§ Intent to treat</p> <p>¶ 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).</p> <p>// 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</p>					

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 //
<i>Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients</i>					
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)
<i>Pivotal exacerbation efficacy and safety studies -- COPD patients</i>					
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)
<i>Supportive comparative efficacy and safety studies -- COPD patients and asthma patients</i>					
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 [2011-2011]	- ≥ 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	260 259	24-hour serial FEV ₁ trough on day 84	US, EU
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

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

Dose-ranging results for fluticasone furoate are presented below in the figure from Dr. Chowdhury's review (Page 14-15).

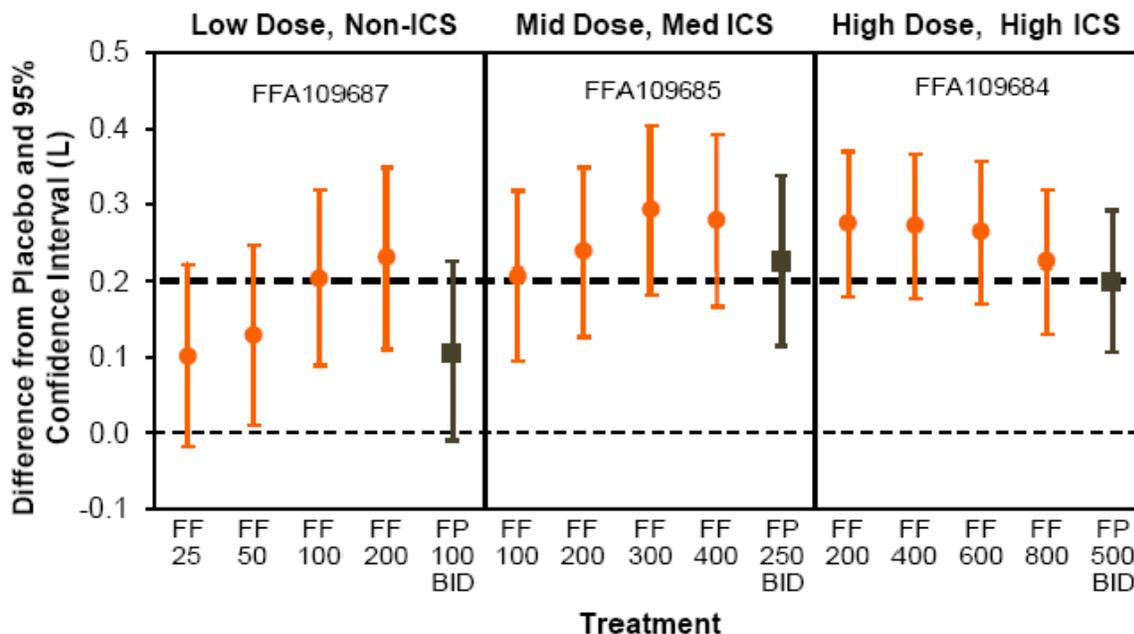


Figure 1. Adjusted treatment difference from placebo for change from baseline in trough FEV1 in liters at week 8 from three dose ranging studies in asthma (FF=fluticasone furoate, FP=fluticasone propionate).

These data demonstrated that FF 100 mcg appeared as effective as higher doses. It is interesting to note a tapering off of effectiveness at doses of FF 600 mcg and 800 mcg. The same nominal dose of FF given either twice a day, or once a day was also compared and found to support once daily dosing (data not shown here). Based on these results the sponsor chose FF 50, 100 and 200 mcg nominal doses to combine with vilanterol for confirmatory COPD trials.

The results for vilanterol dose-ranging are presented in the figures below from Dr. Chowdhury's review (Page 16).

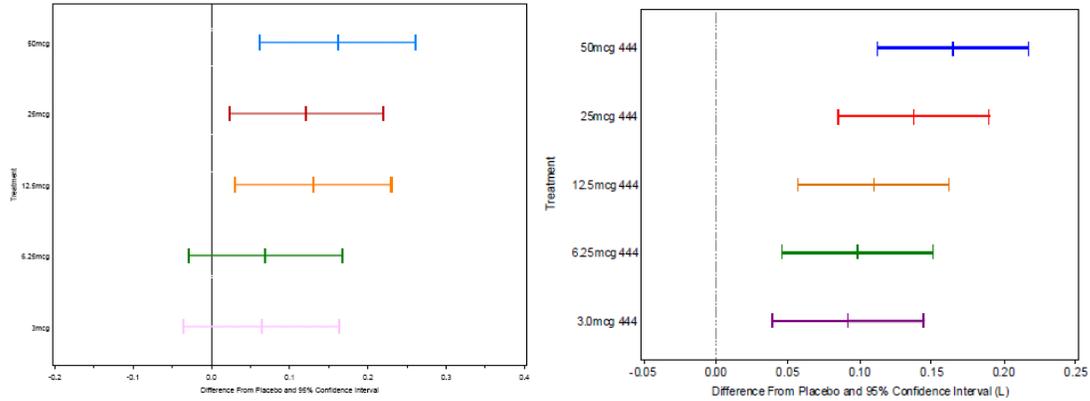


Figure 2. Adjusted treatment difference from placebo change from baseline in trough FEV1 in liters at day 29 in patients with asthma (study 9575, left panel) and COPD (study 1045, right panel).

As shown in the figures, the evaluation of once-daily doses of vilanterol (3, 6.25, 12.5, 25, and 50 mcg) demonstrated a relative dose-response from 6.25 mcg to 50 mcg in both COPD and asthma. The same nominal dose of vilanterol given either twice a day or once a day supported once-daily dosing (data not shown here). Based on these results, the sponsor chose a nominal dose of 25 mcg of vilanterol to combine with FF for confirmatory COPD trials.

Studies 2206 and 2207 were the two primary studies designed to support the lung function effect for Breo. These trials were factorial in design with the concept that bronchodilation soon after dosing (FEV1 0-4 hours) will be due primarily to vilanterol whereas end-of-interval dosing improvement in lung function (trough FEV1) will be due to FF. Another measure of FF effect would be decreases in exacerbations. The bronchodilator effect for Breo is demonstrated below (Page 19, Dr. Chowdhury’s review).

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

Treatment *	N	Change (L)	Diff from Placebo (95% CI)	P value	Diff from FF (95% CI)	P value
lower doses.						

Breo demonstrated efficacy on FEV1 0-4 hours over FF and placebo, demonstrating the contribution of vilanterol.

The table below demonstrates the mean change in trough FEV1, which would evaluate the contribution of FF to Breo (Dr. Limb's review, page 22-23).

Table 4 Trials 2206 and 2207: Mean change from baseline in trough FEV1 at Day 169 (ITT population)							
Treatment	N	LS mean (L)	LS mean change	Difference from placebo (95% CI)	P	Difference from VI [95% CI]	P
2206							
FF/VI 100/25	206	1.364	0.151	0.115 (0.060, 0.169)	<0.001	0.048 (-0.006, 0.102)	0.082
FF/VI 50/25	206	1.378	0.166	0.129 (0.074, 0.184)	<0.001	0.062 (0.008, 0.117)	0.025*
VI 25	205	1.316	0.103	0.067 (0.012, 0.121)	0.017	-	-
FF 100	206	1.282	0.070	0.033 (-0.022, 0.088)	0.241	-	-
Placebo	207	1.249	0.037	-	-	-	-
2207							
FF/VI 200/25	205	1.479	0.135	0.131 (0.08, 0.183)	<0.001	0.032 (-0.019, 0.083)	0.224
FF/VI 100/25	204	1.492	0.148	0.144 (0.091, 0.197)	<0.001	0.045 (-0.008, 0.097)	0.093*
VI 25	203	1.447	0.103	0.100 (0.048, 0.151)	<0.001	-	-
FF 100	204	1.392	0.048	0.044 (-0.008, 0.097)	<0.095	-	-
FF 200	203	1.356	0.012	0.008 (-0.044, 0.060)	<0.756)	-	-
Placebo	205	1.347	0.004	-	-	-	-

* Nominal p-values. 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..

These results demonstrate efficacy of Breo over placebo. However, while there is numerical improvement of Breo over vilanterol (32 to 62 ml), there is not statistical improvement. Below are the results of studies 2871 and 2970 which demonstrate efficacy in improvement of exacerbations, which would be due to FF use (Page 21-22, Dr. Chowdhury's review).

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
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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	-	-
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.				

Breo demonstrated efficacy over vilanterol in study 2970 for all three Breo doses, and in study 2871 for the Breo 100/25 mcg dose. Other examinations such as time to first moderate or severe exacerbation or exacerbations requiring systemic corticosteroids are informative. These endpoints, some of which demonstrate dose-related effects, all are supportive of a treatment effect for Breo over vilanterol alone.

Although the hierarchical prespecified statistical analysis plan would make 2871 technically a failed study for exacerbation, the p-value for the Breo 100/25 mcg dose was small, the steroid effect is probably at a plateau, and when all data are considered the preponderance of evidence demonstrates substantial evidence of efficacy for FF on this endpoint.

I agree with Dr. Chowdhury's assessment that efficacy for the combination drug has been demonstrated. The data supporting the contribution of vilanterol from Breo in lung function is clear, while the data supporting the contribution of FF in lung function are not as robust. The surrogate measure of efficacy of trough FEV1 is numerically greater and consistent but is not statistically significant. However these results when combined with the clear exacerbation benefit demonstrates the contribution of FF to the combination product. It needs to also be considered that FF is not a bronchodilator and with a long duration of action provided by vilanterol on FEV1, the effect of FF on trough FEV1 may not be apparent.

Safety

Main safety issues with LABA/ICS combination products used for COPD include increased risks of pneumonia and bone fractures, thought due to the ICS component. These are well-recognized complications. These two safety issues are presented in the tables and figure below from Dr. Chowdhury's review (Page 24).

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

	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

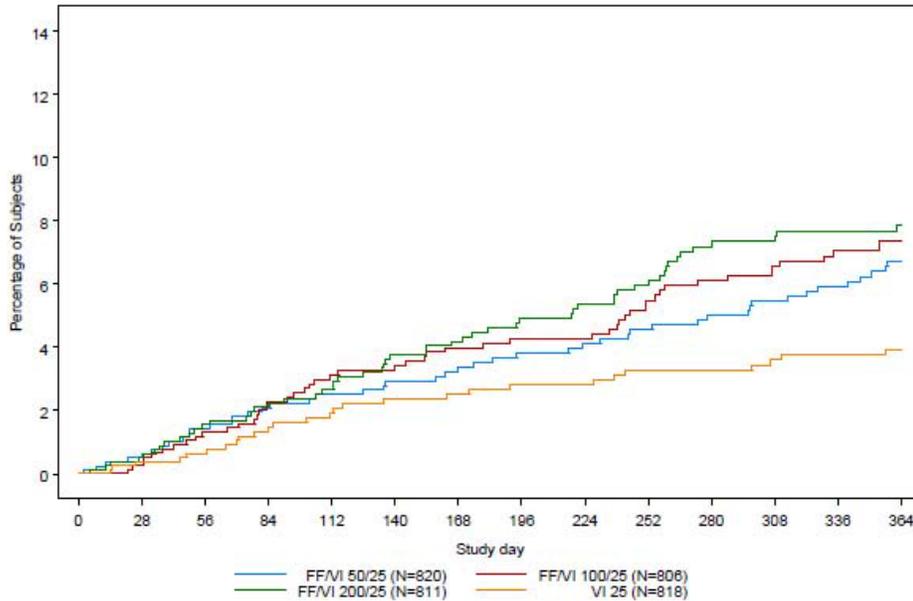


Figure 9. Time to first on-treatment pneumonia in exacerbation studies 2871 and 2970

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

As can be seen above, pneumonia occurred more frequently in all Breo doses compared to vilanterol. Some (but not all) of the components evaluated for pneumonia suggest dose-ordering. Pneumonia is a known risk of ICS therapy and has been seen in other LABA/ICS development programs as discussed by Dr. Chowdhury.

Breo demonstrated an increase numerical risk of fracture compared to vilanterol. There did not appear to be dose-ordering, but there were few events. As discussed by Dr. Chowdhury, decrease in bone mineral density and fractures are also a known risk of ICS therapy and have been demonstrated in previous LABA/ICS combination programs.

There were no indications of a cardiovascular signal or adrenal axis inhibition signal.

Breo did not have any indication of a safety concern that was different from any other LABA/ICS combination product.

Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on April 17, 2013. Major issues for discussion were if each component contributed to efficacy and adequacy of safety data and appropriateness of safety findings for COPD. The committee voted 9-yes, 4-no, 0-abstain in favor of approval for airflow obstruction in COPD and 8-yes, 5-no, 0-abstain in favor of granting an indication for reduction of COPD exacerbation.

Conclusions and Recommendations

GSK has submitted a novel program in that a combination product was developed for treatment of aspects of COPD without first developing each individual component. They also did not submit Breo for treatment of asthma, although they have extensive data. As such, this NDA was large and detailed to include all the information that typically would have been developed in a step-wise fashion for each component over several programs.

Extensive dose-ranging was performed for each component, and the results are comforting that the sponsor has selected the appropriate dose of each component to bring forward for marketing. Safety concerns were identified that are shared by all combination LABA/ICS products and seemed of a frequency that is not unexpected. Efficacy results demonstrated the contribution of each component and were robust for the product in the indications requested.

The overall risk-benefit assessment is appropriate to support marketing of Breo for maintenance of airflow obstruction and reducing exacerbations in patients with COPD at the dose noted above. I recommend approval.

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/s/

CURTIS J ROSEBRAUGH
05/10/2013