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*APPLICATION NUMBER:*

**209482Orig1s000**

**SUMMARY REVIEW**

## SUMMARY REVIEW OF REGULATORY ACTION

Date: September 18, 2017

From: Lydia Gilbert-McClain, MD  
Deputy Director, Division of Pulmonary, Allergy, and  
Rheumatology Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 209482

Applicant Name: GlaxoSmithKline (GSK)

Date of Submission: November 18, 2016

PDUFA Goal Date: September 18, 2017

Proprietary Name: TRELEGY ELLIPTA

Established Name: fluticasone furoate, umeclidinium, and vilanterol

Dosage form: Inhalation powder

Strength: fluticasone furoate 100 mcg, umeclidinium 62.5 mcg, vilanterol 25 mcg

Proposed Indication: Long-term, once-daily, maintenance treatment of chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema

Action: Approval (with revised indication statement)

### 1. INTRODUCTION

GSK submitted a 505(b) (1) new Drug Application (NDA 209482) on November 18, 2016, for TRELEGY ELLIPTA (fluticasone furoate, umeclidinium, and vilanterol inhalation powder). Fluticasone furoate, umeclidinium, and vilanterol inhalation powder (hereafter referred to as FF/UMEC/VI) is a fixed dose triple combination comprised of 100 mcg of fluticasone furoate ([FF] an inhaled corticosteroid [ICS]), 62.5 mcg of umeclidinium ([UMEC] a long acting muscarinic receptor antagonist [LAMA]), and 25 mcg of vilanterol ([VI] a long acting beta<sub>2</sub> agonist [LABA]). All three active ingredients of TRELEGY ELLIPTA are already approved in three other ELLIPTA products for COPD indications. The proposed indication for FF/UMEC/VI is “maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and/or emphysema.” The Division Director summary memo will provide an overview of the application, and the Division’s rationale for the regulatory action. Notable in the review of this application is the disagreement by the biostatistics reviewer(s) regarding the sufficiency of the submitted data to support the approval of the NDA. The summary review will address the biostatistics reviewers’ comments and will articulate the Division’s assessment of the submitted data to support approval of this NDA.

## 2. BACKGROUND

### *COPD*

COPD is a chronic lung disease associated with inflammation in the respiratory tract and it is characterized clinically by persistent respiratory symptoms (chronic cough, wheezing, chronic sputum production, shortness of breath that is progressive over time) and airflow limitation that is demonstrated as obstructive physiology on spirometry. The persistent airflow limitation in COPD is due to airway and/or alveolar abnormalities as a result of the chronic inflammation which causes structural changes such as narrowing of the small airways and destruction of the lung parenchyma that ultimately leads to the loss of alveolar attachments to the small airways and decreases lung elastic recoil. The most common cause of COPD is significant exposure to noxious particles or gases.

The natural history of COPD is progressive lung function decline ultimately leading to respiratory failure and death. COPD is the third leading cause of death in the U.S.A and the fourth leading cause of death worldwide.<sup>1</sup> It is also the fourth leading cause of disability in the U.S.A and imposes an enormous burden on the nation's health care system.<sup>2</sup> Acute worsening of COPD symptoms (exacerbations) has significant impact on morbidity and mortality. Deteriorating airflow limitation is associated with an increasing prevalence of exacerbations, hospitalization, and risk of death. Hospitalization for a COPD exacerbation is associated with poor prognosis and increased risk of death.<sup>3</sup> Pharmacotherapy for COPD is geared towards reducing COPD symptoms, reducing the frequency and severity of exacerbations, and improving health status and exercise tolerance. Several treatment guidelines have been written regarding the management of COPD. The most comprehensive is found in the Global Initiative for Chronic Obstructive Disease (GOLD) guidelines, a document that was first published in 2001. Since then, there have been 6 updates to the document starting with the first update in 2011 to the current 2017 update. The GOLD guidelines classify COPD according to disease severity based on degree of airflow limitation (FEV<sub>1</sub>), symptom severity, and frequency of exacerbations.

### *Pharmacotherapy*

There are several classes of drugs approved for COPD; bronchodilators of the beta<sub>2</sub>-agonists and anticholinergic class, fixed dose combinations of bronchodilators of different pharmacological classes (beta<sub>2</sub>-agonists with anticholinergics) and combinations of inhaled corticosteroids (ICS) with long-acting beta agonists (LABAs). Roflumilast, a PDE4 inhibitor is approved to reduce the risk of COPD in patients with severe COPD associated with chronic bronchitis and a history of exacerbations. Of note, ICS are not approved as monotherapy for COPD.

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<sup>1</sup> <https://www.cdc.gov/copd/index.html> Accessed September 17, 2017

<sup>2</sup> <https://www.nhlbi.nih.gov/health-pro/resources/lung/copd-national-action-plan>  
Accessed September 17, 2017

<sup>3</sup> Soriano JB., et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. *The Lancet Respiratory Medicine* 2015; 3 (6): 443-50

COPD pharmacotherapy is tailored to individual patient needs depending on their disease severity and may include multiple medications as the disease progresses. It is standard of care to use different classes of bronchodilators concomitantly in select patients. Long-acting bronchodilators (LAMAs or LABAs) are preferred over short-acting agents except for patients with mild disease and infrequent symptoms. Patients may be started on single or dual long-acting bronchodilator therapy. ICS/LABA combination therapy is used in COPD for the anti-inflammatory component (ICS) which has been established in controlled clinical trials to reduce exacerbations in fixed dose combination with LABAs. The treatment goals for COPD are to reduce symptoms and reduce the morbidity risk associated with COPD by preventing and treating exacerbations, and preventing/reducing disease progression and mortality.<sup>4</sup>

The use of three-drug therapy (ICS, LABAs, and LAMAs) in the management of patients with moderate to severe COPD appears to be common practice.<sup>5</sup> A study in 126 patients showed that the combination of tiotropium plus fluticasone/salmeterol had significantly fewer exacerbations than either tiotropium or fluticasone/salmeterol over 12 months of follow up.<sup>6</sup> Recently, two clinical trials that evaluated fixed dose triple combination therapy vs. dual combination or open triple combination treatment were completed and one has been published.<sup>7</sup> The results from both trials which were presented at the 2016 European respiratory Society international Congress, demonstrated that triple therapy (ICS/LABA/LAMA) had better clinical outcomes than dual therapy (ICS/LABA).<sup>8</sup>

TRELEGY ELLIPTA will be the first fixed dose triple combination therapy to be approved for COPD. However, the Agency has already approved the use of the three active ingredients FF, VI, and UMEC in combination via two separate inhalers (i.e.

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<sup>4</sup> Global Initiative for Chronic Obstructive Lung Disease; Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2017 Report  
Available at: [www.goldcopd.org](http://www.goldcopd.org)

<sup>5</sup> “In the real world, COPD is usually discovered not when it’s mild, but when it’s moderate to severe”.... I can tell you from our clinical experience... that when we are asked to enroll patients with COPD who are only on two drugs, we can’t find them. It is a no-brainer that if you give these drugs together, rather than separately, there will likely be much greater adherence and probably better effects.” Eugene Bleecker, MD, Pulmonologist, Professor of Medicine, Co-Chief Division of Genetics, Genomics and Precision Medicine, University of Arizona Department of Medicine. Cited from commentary on triple therapy trials TRILOGY and TRINITY presented at the 2016 European Respiratory Society International Congress. Retrieved from: <http://www.medpagetoday.com/clinical-context/copd/60058?pop=0&ba=1&xid=tmd-md&hr=trendMD>  
Accessed August 24, 2017

<sup>6</sup> Agusti A, Calverley PM, Decramer M, Stockley RA, Wedzicha JA. Prevention of Exacerbations in Chronic obstructive pulmonary disease: Knowns and Unknowns. *J COPD F*. 2014; 1(2): 166-184. Doi: <http://dx.doi.org/10.15326/jcopdf.1.2.2014.0134>

<sup>7</sup> Dave Singh et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting  $\beta_2$ -agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomized controlled trial. *Lancet* 2016; **388**; 963 -73

<sup>8</sup> <http://www.medpagetoday.com/clinical-context/copd/60058?pop=0&ba=1&xid=tmd-md&hr=trendMD>  
accessed August 24, 2017

BREO ELLIPTA and INCRUSE ELLIPTA).<sup>9</sup> Nevertheless, the evidentiary standard for coadministration is different from the evidentiary standard for fixed dose combination products.

### ***Drug Development and Regulatory History for GSK ELLIPTA Products***

GSK began development of FF/ UMEC/VI under IND 114873 starting with a Pre-IND meeting held May 07, 2012. At the time of the Pre-IND meeting, drug development for the FF/VI and UMEC/VI dual combination programs, and UMEC monotherapy COPD programs were still ongoing. The Agency advised GSK at that time that the clinical program for a fixed-dose triple combination product is expected to identify a patient population that requires treatment with all three components and that in defining such a population, GSK should consider utilizing the criteria defined in the GOLD guidelines. The Agency agreed to a clinical program that was designed to evaluate the effect of FF/UMEC/VI compared to FF/VI, and UMEC/VI on COPD exacerbations as the primary endpoint.

The FF/VI (BREO ELLIPTA) clinical development program was designed to evaluate efficacy on lung function (2 pivotal trials) and exacerbations (2 pivotal trials). Prior to phase 3, GSK conducted adequate dose-ranging studies with the single ingredients FF, and VI to identify the doses to evaluate in the pivotal trials. The lung function trials were factorial in design and evaluated the contribution of vilanterol [VI] (mean FEV<sub>1</sub> 0-4hr) and fluticasone furoate [FF] (mean trough FEV<sub>1</sub>) on lung function. FF did not have a statistically significant improvement in trough FEV<sub>1</sub> in either trial. This was not altogether surprising because given the long duration of action of vilanterol with a prolonged effect on FEV<sub>1</sub> the effect of fluticasone furoate on trough FEV<sub>1</sub> may have been masked. The two exacerbation trials evaluated the contribution of FF over vilanterol on exacerbations [FF/VI vs. VI treatment arms]. The two exacerbation trials included 3,255 subjects with moderate to very severe COPD (range of FEV<sub>1</sub>/FVC 17% - 81%). Subjects treated with BREO ELLIPTA 100/25 had a lower annual rate of moderate/severe COPD exacerbations compared with vilanterol in both trials: ratio vs. vilanterol 25 mcg in the first trial = 0.79 (95% CI: 0.64, 97), ratio vs. vilanterol 25 mcg in the second trial = 0.66 (95% CI: 0.54, 81).

The UMEC (INCRUSE ELLIPTA) development program was designed to evaluate the effect of UMEC on bronchodilation using the mean trough FEV<sub>1</sub> to evaluate efficacy at the end of the dosing interval and serial spirometric evaluations to assess the effect of UMEC over the entire 24 hour dosing period.

The UMEC/VI (ANORO Ellipta) program evaluated the effect of both UMEC and VI on bronchodilation. Given that VI is a beta-agonist and UMEC is an anticholinergic drug the lung function endpoints chosen reflected the acute onset of bronchodilation provided by the VI component (FEV<sub>1</sub> AUC 0-4 hrs.) and the residual bronchodilator effect provided by the UMEC component (trough FEV<sub>1</sub>). The contribution of both UMEC and VI on

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<sup>9</sup> NDA 205382/S-002 approved February 24, 2016

bronchodilation was demonstrated in replicate full factorial designed studies. The efficacy of UMEC/VI on exacerbation rates was not evaluated in the UMEC/VI program. Time to first exacerbation was listed as one of multiple secondary endpoints.

GSK also completed four additional clinical trials to evaluate the additional benefit of bronchodilation when UMEC was added to their 2 fixed dose combination ICS/LABA products, i.e. BREO ELLIPTA (2 trials) and ADVAIR DISKUS (2 trials). All four trials demonstrated that the addition of INCRUSE provided statistically significant and clinically meaningful bronchodilation compared to BREO ELLIPTA alone or Advair Diskus alone. At the Pre-NDA meeting GSK asked about including these studies as part of the NDA for UMEC but the Division opined that the decision to put a patient on triple therapy falls under the practice of medicine and the Agency would be reluctant to place this type of information in the product label.<sup>10</sup>

Following the approval of INCRUSE ELLIPTA, GSK submitted a Type C meeting request on June 6, 2014 seeking advice from the Division and OPDP regarding the data from the INCRUSE ELLIPTA coadministration trials. GSK questioned whether the data could be used in promotion without the data from these trials being included in the current approved labeling. The Agency did not provide a definitive response at that time.<sup>11</sup> What followed was a lengthy internal assessment of GSK's proposal involving multiple discussions at many levels of the Agency including OND management, OPDP, Office of Chief Counsel, and Medical Policy. Ultimately, GSK was advised that since the trials were not in the labeling they could not promote.<sup>12</sup> The outcome was that GSK was asked to submit an efficacy supplement to support addition of the results from the coadministration trials with INCRUSE ELLIPTA and the two ICS/LABAs products in the Clinical Trials section (Section 14) of the INCRUSE ELLIPTA package insert. Of note, throughout these deliberations, the Division maintained its original position that the results from these trials did not need to be included in the label in order for GSK to promote but ultimately accepted the Agency's final determination of requiring inclusion of these trials in the label. GSK submitted an efficacy supplement to NDA 205382/S-002 on April 28, 2015 and the supplement was approved on February 24, 2016.

#### ***Revised FF/UMEC/VI program***

Following the approval of the INCRUSE efficacy supplement, GSK submitted a meeting request on March 3, 2016 to discuss a registration package to support a New Drug Application for FF/UMEC/VI for COPD. GSK proposed to use the completed UMEC+ FF/VI studies which they referred to as the "open" combination of FF/ UMEC/ VI to support the "closed" combination (i.e. the combination of all three ingredients in one Ellipta inhaler). GSK had previously provided Chemistry, Manufacturing, and Controls (CMC) data demonstrating the pharmaceutical sameness of the active ingredients of the Ellipta products given as single ingredients or in combination, and clinical pharmacology data showing no PK interaction between the ingredients, as part of their development program for their other combination Ellipta products. The Agency agreed that no

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<sup>10</sup> Meeting Minutes IND 106616 preNDA meeting January 18, 2012

<sup>11</sup> NDA 205382 Type C meeting Written Responses August 5, 2014

<sup>12</sup> Written communication to GSK January 14, 2015

additional CMC, pharmacology, or clinical data would be needed to support demonstration of a lung function benefit in the fixed dose triple combination product.

Based on review of CMC data that GSK had previously provided in support of the development programs for their other Ellipta products (dual and single combination products), the Agency agreed that GSK had provided sufficient data to support the pharmaceutical sameness or comparability of FF/UMEC/VI (closed) versus FF/VI + UMEC (open). GSK had previously provided full aerodynamic particle size distribution (APSD) profiles of FF, UMEC, and VI delivery at a flow rate of 60 L/min using the Next Generation Impactor (NGI). In prior communication with GSK<sup>13</sup> the Agency agreed that GSK had demonstrated pharmaceutical sameness or comparability of FF/UMEC/VI versus the FF/VI and UMEC/VI dual comparators. The same type of NGI comparison APSD data were provided in a meeting package<sup>14</sup> for another meeting and FF delivery from FF/UMEC/VI and FF/VI were deemed comparable, VI delivery from FF/UMEC/VI and FF/VI were deemed comparable, and VI delivery from FF/UMEC/VI, UMEC/VI, and FF/VI were all considered comparable. In all of these cases, comparability was considered to be attained if the in vitro mass deposition of any drug on the NGI stages 3-5 (defined as fine particle mass in a likely inhalable size range) did not differ by more than 10% from the mean of the existing product dataset for that particular drug. The CMC review also considered the overall comparability of the APSD distributions for all particle sizes captured by the impactor and accessory components.

Based on the completed coadministration clinical trials, and the CMC and clinical pharmacology data, the Agency agreed that no additional clinical trials were required to submit an NDA for the fixed-dose triple combination product.

### **3. CHEMISTRY, MANUFACTURING, AND CONTROLS**

The FF/UMEC/VI drug product is comprised of a plastic inhaler containing 2 foil blister strips each containing 30 blisters in the product intended for marketing [there is a 14-b blister strip physician sample product]. On one strip, each blister contains a white powder blend of micronized fluticasone furoate 100 mcg and lactose monohydrate 12.3 mg and on the other strip each blister contains a white powder blend of umeclidinium bromide 74.2 mcg (equivalent to 62.5 mcg umeclidinium), micronized vilanterol trifenate 40 mcg (equivalent to 25 mcg vilanterol), magnesium stearate 75 mcg and lactose monohydrate 12.3 mg. The container closure system including the double foil blister laminate, inhaler, desiccant, and tray for FF/UMEC/VI is the same as that in the other approved Ellipta products; with the exception of the color for the cover of the inhaler mouthpiece which is product specific. Information on the FF drug substance is provided in the approved NDA 204275 for FF/VI. Information on the UMEC drug substance is provided in DMF 026339 and information on the VI drug substance is provided in DMF 025906. There are no outstanding CMC or facilities inspection issues. The CMC recommendation is for approval.

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<sup>13</sup> Communication to GSK February 27, 2014 IND 114873

<sup>14</sup> Meeting package September 18, 2013 IND 114873

#### 4. NON CLINICAL PHARMACOLOGY/TOXICOLOGY

The Applicant submitted a 13-week triple combination inhalation toxicology study. There were no concerns with the study results. There were no novel toxicities attributable to the triple combination and no worsening or increase in the expected findings attributable to inhaled corticosteroids, beta<sub>2</sub> adrenergic agonists, and/or anticholinergics. See Dr. Dong Zhao's review for full details. The pharmacology/toxicology recommendation is for approval.

#### 5. CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS

GSK support this NDA submission with a cross reference to two clinical pharmacology studies (200587 and CTT116415) conducted with FF/UMEC/VI as a triple combination product ("closed triple" product; i.e. FF/UMEC/VI in one inhaler) that assessed the systemic exposure of FF/UMEC/VI compared to dual therapies FF/VI and UMEC/VI. Both studies were previously reviewed as part of the supplemental NDA 205382/S-002 for INCRUSE ELLIPTA. The Applicant also collected sparse (n=64) and serial PK samples (n = 10) in a subset of COPD patients from an active controlled study (CTT116853) conducted in Europe.

The following are the major findings from the clinical pharmacology review:

- 1) Data from study 200587 demonstrate that following single dose administration of four inhalations of FF/UMEC/VI (100/62.5/25 mcg) from the closed triple product, the C<sub>max</sub> and AUC<sub>0-4</sub> of FF were approximately 5% and 3% lower respectively, compared to single dose administration of four inhalations of FF/VI (100/25 mcg). In the same study, following single dose administration of four inhalations of FF/UMEC/VI (100/62.5/25 mcg) the C<sub>max</sub> and AUC<sub>0-2</sub> of UMEC were approximately 2% lower and 0.4% higher, respectively, compared to single dose administration of four inhalations of UMEC/VI (62.5/25 mcg). The C<sub>max</sub> and AUC<sub>0-6</sub> of VI were approximately 6% higher and 1% lower, respectively, compared to single dose administration of four inhalations of FF/VI (100/25 mcg) and were 20% and 9% higher, respectively compared to single dose administration of four inhalations of UMEC/VI (62.5/25). Based on these findings, there is no drug interaction between FF, UMEC, and VI when administered as closed triple product (FF/UMEC/VI) vs. dual combination products (FF/VI and UMEC/VI).
- 2) Following once daily administration of the closed triple product, FF/UMEC/VI in COPD patients, the observed systemic concentrations of FF, UEMC, and VI were within the range observed for dual and mono products, FF/VI, UMEC/VI, FF, and UMEC in COPD patients (data from study CTT116853).

The clinical pharmacology reviewers concluded that the clinical pharmacology data are acceptable.

## 6. CLINICAL MICROBIOLOGY

There are no clinical microbiology issues

## 7. CLINICAL AND STATISTICAL – EFFICACY

### *a. Overview of the clinical program*

The efficacy data to support this NDA comes from two replicate well-controlled trials (trial 200109 and 200110), and the previously established efficacy of FF/VI for the maintenance treatment of airflow obstruction and reducing exacerbations in COPD. The two trials were previously reviewed under NDA 205382/S-002 (INCRUSE ELLIPTA) submitted April 28, 2015 and approved February 24, 2016. The efficacy results are included in section 14 of the INCRUSE ELLIPTA package insert under the heading “**Combination with an ICS/LABA.**” GSK also submitted efficacy and safety data for FF/UMEC/VI obtained from a phase 3 study (CTT116853), which was primarily conducted to support an initial marketing authorization application for FF/UMEC/VI in the European Union. This study compares FF/UMEC/VI with a budesonide/formoterol combination active control in 1,810 subjects with COPD. The clinical data from this study are not being considered in the evaluation of FF/UMEC/VI.

### *b. Confirmatory Trials 200109 and 200110*

Trials 200109 and 200110 were randomized, double-blind, placebo-controlled trials with treatment duration of 12 weeks designed to evaluate the safety and efficacy of UMEC + FF/VI 100/25 mcg compared with placebo + FF/VI 100/25 mcg in patients with COPD. Subjects received a fixed dose of UMEC (62.5 mcg or 125 mcg) or placebo in combination with the approved FF/VI product administered once daily. The primary efficacy endpoint was trough FEV<sub>1</sub> at day 85 and the studies were powered (90% power) to detect a treatment difference of 80 mL in trough FEV<sub>1</sub>. Secondary endpoints included post-dose weighted mean FEV<sub>1 (0-6hr)</sub> on day 84, rescue medication use, and clinical outcome assessments using the St. Georges Respiratory Questionnaire (SGRQ).

### *Patient population*

Trials 200109 (n = 604) and 200110 (n = 620) enrolled adult male and female subjects ≥ 40 years of age with a clinical diagnosis of moderate to very severe COPD according to the GOLD guidelines. The baseline demographics of the patient population were similar for both trials across all the treatment groups and the majority of patients had moderate to severe COPD (GOLD stage 3 or 4).<sup>15</sup> In trial 200109, 98% of subjects were Caucasian and 66% were male. Similarly, in trial 200110, 86% were Caucasian and 63% were male. The age, gender and race distribution of the study subjects is consistent with

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<sup>15</sup> Prior to 2016 GOLD guidelines included lung function impairment (FEV<sub>1</sub> criteria) and exacerbation history in the disease severity classification. As of 2016, GOLD guidelines use a combination of letters (A, B, C, and D) and numbers (0 to 4) to denote exacerbation history/tendency and degree of lung function impairment respectively.

the demographic characteristics of a COPD population. The majority of subjects (84-87%) had not had an exacerbation requiring systemic steroids and/or antibiotics in the prior year. However, all subjects had to be symptomatic (defined by an mMRC<sup>16</sup> > 2) to be eligible for enrollment in the trial. The key baseline characteristics of the trial subjects are outlined in Table 1 below.

**Table1: Baseline Demographic Characteristics**

	Study 200109	Study 200110
Mean age (years)	64	63
Post-bronchodilator FEV <sub>1</sub> ( mean % predicted) [range]	45.3% [13% - 76%]	47.2 [ 12% - 70%]
Mean Post-bronchodilator FEV <sub>1</sub> /FVC [range]	0.48 [0.22 – 0.70]	0.47 [0.22 -0.69]
Reversibility to salbutamol (% of subjects)	28%	29 %
GOLD stage II	40%	48%
GOLD stage III	46%	41%
GOLD stage IV	14%	11%
<b>Prior COPD maintenance therapy prior to screening</b>		
ICS (monotherapy or in combination with ICS/LABA) prior to screening	63%	46%
LABA (monotherapy or as component of ICS/LABA)	61%	62%
LAMA	22%	46%

## **Results**

### Disposition

Most patients (93%) completed both trials and mean treatment compliance was high (98%). Across both trials, the main reasons for premature discontinuations were lack of efficacy (1 – 5%); COPD exacerbations (1-5%), and adverse effects (< 1-4%)

Results from the primary efficacy analysis from both trials showed statistically significant differences between UMEC and FF/VI vs. placebo + FF/VI for both UMEC 125 mcg and 62.5 mcg doses. There was no incremental benefit with the higher UMEC 125 mcg dose over the UMEC 62.5 mcg dose. The lower (62.5 mcg) dose is the approved dose for treatment of COPD in the UMEC monotherapy (INCRUSE) and FF/VI (ANORO) dual combination product. Rescue medication use was lower in subjects in the UMEC treatment arms compared to subjects treated with placebo + FF/VI over Weeks 1 to 12. Responder analysis of the SGRQ showed numerical differences in favor of the

<sup>16</sup> mMRC = Modified Medical Research Council Dyspnea Scale; 2 = walks slower than people of the same age because of dyspnea or has to stop for breath when walking at own pace; 3 = stops for breath when walking 100 yards (91 m) or after a few minutes; 4 = too dyspneic to leave house or breathless when dressing

UMEC treatment groups but these differences were not statistically significant. The primary efficacy results are shown in Table 2.

**Table 2. Primary Efficacy Results: LS Mean Difference in Change from Baseline (CFB) in Trough FEV<sub>1</sub> (L) at Day 85 (ITT) – Trials 200109 and 200110**

Study Treatment	CFB in Trough FEV <sub>1</sub> LS Mean (SE)	Treatment Difference		
		LS Mean Vs. Placebo	95% CI	p-value
<b>Trial 200109</b>				
UMEC 62.5 + FF/VI N=206	1.338 (0.0110)	0.124	(0.093, 0.154)	<0.001
UMEC 125 + FF/VI N=207	1.343 (0.0111)	0.128	(0.098, 0.159)	<0.001
Placebo + FF/VI N=206	1.215 (0.0111)	-	-	-
<b>Trial 200110</b>				
UMEC 62.5 + FF/VI N=206	1.476 (0.0107)	0.122	(0.091, 0.152)	<0.001
UMEC 125 + FF/VI N=207	1.466 (0.0106)	0.111	(0.081, 0.141)	0.001
Placebo + F/VI N=206	1.355 (0.0110)	-	-	-

Source: Module 2 Clinical Overview Table 3 page 23. Data source NDA 205382/S-002 m2.7.3. in-text table 12

Serial FEV<sub>1</sub> measurements on Day 84 support maintenance of bronchodilator effect of UMEC (data not shown). Subgroup analyses on the primary endpoints were conducted by gender, age, race, and region and COPD GOLD stage. In general, the subgroup analyses were consistent with the primary results from the overall population. The St. George’s Respiratory Questionnaire (SGRQ) was assessed as a secondary endpoint in both trials. In trial 200109, the SGRQ responder rate for the UMEC 62.5 mcg+ FF/VI treatment arm was 40% compared to 35% for placebo [Odds Ratio: 1.2; 95% CI: 0.8, 1.8]. In trial 200110, the SGRQ responder rate for the UMEC 62.5 mcg + FF/VI treatment arm was 35% compared to 21% for placebo [Odds Ratio: 2.0; 95% CI: 1.3, 3.1].

#### Efficacy Conclusions

GSK has provided adequate support for the efficacy of UMEC 62.5 mcg in coadministration with FF/VI for the maintenance treatment of COPD by demonstrating a statistically significant and clinically meaningful improvement in lung function in terms of change from baseline in trough FEV<sub>1</sub> compared to placebo in two well-controlled replicate 12-week treatment trials. The efficacy of UMEC 62.5 mcg in coadministration with FF/VI was also supported by other measures of lung function, decrease in rescue medication use and health-related quality of life (SGRQ).

Indirect evidence from the FF/VI and UMEC/VI development programs supports the contribution of VI and FF in the triple combination product. That said the statistical reviewers are not in agreement that the data provided are adequate to support the

approval of FF/UMEC/VI and have recommended a Complete Response action for the NDA. In his review Dr. Gregory Levin cites the lack of a comparison of FF/UMEC/VI with UMEC/VI as a key deficiency. The division disagrees with the statistical team's overall assessment of the data in support of this NDA and with their recommendation for a complete response action. I will address the main areas of disagreement throughout the remaining sections of the Division Director Summary review below.

***c. Interpretation of the Combination Rule***

FF/UMEC/VI by virtue of its presentation in a single inhaler is a new fixed dose combination product. The regulatory evidentiary standard for the approval of coadministration of two or more products is different from the standard to support approval of a fixed dose combination product. Consequently, despite the approval of NDA 205382/S-002, which allowed for the concomitant use of FF/VI and UMEC via separate inhalers, the Combination Rule set forth in 21CFR 300.50 which states that “two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects and the dosage of each component (amount, frequency, duration) is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug” is applicable to the evaluation of FF/UMEC/VI.

In its interpretation of the Combination Rule, the Agency has often (but not always) relied on factorial designed clinical studies to evaluate the contribution of each component in the combination. A full factorial design for a triple combination product ABC would require studies with the following comparisons: ABC vs. AB, vs. AC, vs CB. GSK does not have a clinical program that includes all of these comparisons.

In the initial discussion with the Division (Pre-IND meeting May 7, 2012) regarding the development program for FF/UMEC/VI, the Division had advised GSK to conduct a partial factorial design study comparing FF/UMEC/VI to FF/VI and UMEC/VI. At the time of that advice, GSK were developing the dual fixed combinations of FF/VI, and UMEC/VI. At that time, there were no fixed-dose LABA/LAMA products approved but there was a short-acting beta<sub>2</sub>-agonist and anti-cholinergic product on the market (ipratropium/albuterol) for COPD. The Division did not require a comparison of FF/UMEC/VI to UMEC/FF and the meeting minutes reflect that the Division stated that GSK “*would be expected to provide data that justifies (sic) the use of the combination product over the individual components and the 2-component combination products that are relevant in the treatment of COPD, i.e. fluticasone/vilanterol (FF/VI) and umeclidinium/vilanterol (UMEC/VI).*” It is unclear what was actually meant by the choice of the words “relevant in the treatment of COPD” because while there are no fixed dose combination ICS/LAMA products, the combination of LAMAs and steroids are used in the treatment of COPD. In a comparative healthcare resource utilization study using healthcare claims data between January 2004 and December 2008, (b) (4) et.al from (b) (4) reported the use of LAMAs as 41.9%, corticosteroids

(oral and inhaled) 41.7% and LABAs 42.1% among single and multiple-inhaler users.<sup>17</sup> Furthermore, the LAMA, tiotropium, approved in 2004 has occupied a central role in the management of COPD for the last decade<sup>18</sup> and it is reasonable to conclude that in the practice of medicine tiotropium would be used in combination with ICS either in monotherapy or in a ICS/LABA fixed dose combination product. It is possible, that the Division's statement was a reflection of the drug development landscape at the time in which there were no approved ICS/LAMAs fixed- dose combination products under development for COPD.

Trial CTT116855 (the IMPACT study) was designed to address the Agency's original recommendation and was ongoing at the time of the NDA submission but has been recently completed.<sup>19</sup> Subsequent to the 2012 Pre-IND meeting, the Agency approved the fixed dose combinations of FF/VI (BREO ELLIPTA), UMEC/VI (ANORO ELLIPTA), and the monotherapy UMEC (INCRUSE ELLIPTA) as safe and effective therapies for the treatment of COPD. Both INCRUSE and ANORO ELLIPTA are approved with bronchodilator claims (maintenance treatment of airflow obstruction) whereas, BREO ELLIPTA is approved for both airflow obstruction and reducing exacerbations.

With the clinical, CMC, clinical pharmacology, and preclinical data now in hand, a re-evaluation of the initial recommendations made at the 2012 Pre-IND meeting to determine whether the partial factorial design requested is necessary to support the regulatory requirements of the combination rule to support the triple combination product is appropriate. It is the Division's position that there is adequate evidence from the submitted data, and the already established safety and efficacy of the previously approved Ellipta products to support the approval of TRELEGY ELLIPTA.

Given that triple therapy should be not used as initial therapy for COPD but should be for patients who require additional treatment because of ongoing symptoms and or exacerbations in spite of treatment with dual therapies,<sup>20</sup> a modification to GSK's proposed indication statement is appropriate. Taking the narrowest approach, the indication will be restricted to patients already on FF/VI (for treatment of airflow obstruction and reducing exacerbations) who require additional treatment of airflow obstruction, OR for patients who are currently taking umeclidinium and FF/VI via separate inhalers. This is a very narrow indication but it speaks directly to the actual clinical trials submitted with the application. Furthermore, this modification to the indication statement is consistent with the already approved labeling in the Clinical Trial section of the INCRUSE ELLIPTA label. The modification to the indication statement

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<sup>17</sup> Andrew P. Yu et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. *Respiratory Medicine* (2011) **105**, 1861-1871

<sup>18</sup> Joshua S Cohen, Matthew C miles, James F Donohue and Jill A Ohar. Dual therapy strategies for COPD: the scientific rationale for LAMA + LABA. *International Journal of COPD* 2016: **11** 785-797

<sup>19</sup> In email communication to the Division on August 21, 2017 the Applicant advised that they are anticipating the public release of headline results (a subset of key efficacy and safety results in advance of full statistical analysis on all endpoints) on all endpoints) on September 20, 2017. The full analysis is anticipated to be available by October 19, 2017, and the clinical study report by January 2018.

<sup>20</sup> Gold 2017 Report pg. 85

addresses the specific aspect of the Combination Rule which states.... .. “for a significant patient population requiring such concurrent therapy.”<sup>21</sup>

Support for satisfying the contribution of each component in the combination comes from the available body of clinical, clinical pharmacology, and CMC data, that in their totality provide support for the contribution of FF, UMEC, and VI in the combination. Data from the partial factorial design study CTT116855 (when available) will provide additional meaningful clinical information regarding the overall benefit of F/UMEC/VI in COPD, and depending on the results may allow for a broader indication statement but reliance on data from this study is not necessary to support an approval of the NDA for the restricted indication.

### ***Contribution of each component in the combination***

The fixed dose combination FF/UMEC/VI is comprised of an inhaled corticosteroid (FF), an anticholinergic (UMEC) and a long-acting beta<sub>2</sub>-adrenergic agonist (VI). Each of these components contributes to the treatment of COPD via different mechanisms. The 3 drug classes (ICS, LABAs, and LAMAs) are well established drug classes in the treatment of COPD with well-known safety and efficacy profiles. Specifically, LABAs and LAMAs are bronchodilators that produce relaxation of airway smooth muscle via stimulation of β<sub>2</sub> adrenergic receptors (LABAs) or via blockade of acetylcholine activity at the muscarinic receptors (LAMAs).

Bronchodilators (LAMAs and LABAs) have been evaluated in registration trials using FEV<sub>1</sub> (lung function) endpoints. However, bronchodilators have been shown to have clinical effects beyond improvement in lung function and some of these outcomes are also reflected in approved labeling. Other demonstrated beneficial effects of bronchodilators (both LABAs and LAMAs) include improvement in patient reported outcomes (typically using the SGRQ), symptoms, reducing exacerbations, and specifically in the case of LABAs reduction of hyper dynamic inflation during exercise.

ICS are anti-inflammatory agents that work to reduce inflammation in COPD (in combination with LABAs). Corticosteroids have a wide range of actions on multiple cell types involved in inflammation. The anti-inflammatory benefit of ICS (in combination with LABAs) has been demonstrated in registration trials by showing reduction in COPD exacerbations. ICS not only reduces the frequency of exacerbations but have been shown to reduce the severity, the time to first exacerbations, and hospitalizations due to COPD exacerbations.

Based on the available clinical trial data with FF/VI, UMEC/VI, and UMEC + FF/VI) and the unique mechanistic pharmacologic effect of each component, the division concludes that there is adequate data to support the contribution of each ingredient in the fixed dose combination. The Agency has not always relied on factorial studies to satisfy the Combination Rule to support approval of combination products for COPD. Examples include: Combivent Respimat (the fixed dose combination of albuterol and ipratropium)

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<sup>21</sup> 21CFR 300.30

for bronchodilator indications, and the ICS/LABA dual combination products for exacerbation indications. As written, the Combination Rule does not specifically state that factorial studies must be conducted. It is DPARP's position that for this application, full factorial studies are not necessary given the well-understood mechanistic effects of the three drug classes and the available clinical, CMC, and clinical pharmacology data.

In the Federal Register (FR) notice for the proposed revisions to the Combination Rule the FR notice states "the amount and type of data and information needed may vary depending on a number of factors, including the therapeutic intent of the combination..... [Finally], it is important to note that it is not always a requirement that a fixed-combination formulation be used in a factorial study. The data from a factorial study in which the individual active ingredients are administered separately can be relied upon to support an application for a fixed-combination drug *if the study data is linked to a fixed-combination formulation by a bioavailability study*<sup>22</sup> (emphasis supplied)." This statement in the FR notice is particularly relevant to this application because GSK have provided a satisfactory CMC and clinical pharmacology link that provides sufficient reassurance that the systemic exposure (which addresses systemic safety) and the delivered dose of all the components of FF/UMEC/VI are comparable when administered as FF/UMEC/VI via a single inhaler or from separate Ellipta inhalers. These data provide sufficient reassurance that the clinical data obtained from the other Ellipta products can be used as indirect evidence (extrapolation) to support the contribution of the individual components of the triple combination product, and that the safety profile of the fixed-dose triple combination product would be similar to that of the safety profile of the other Ellipta products.

***Contribution of UMEC (airflow obstruction):*** There is direct clinical evidence provided by the data from clinical trials 200109 and 200110. The statistical team is in agreement with the contribution of UMEC in the combination.

***Contribution of VI (airflow obstruction):*** There is indirect evidence provided by prior clinical data from the UMEC/VI clinical program. In this program, both UMEC, and VI independently contributed to a lung function benefit in full factorial design studies. A full factorial design was necessary for the UMEC/VI fixed dose combination because the effect being measured (i.e. airway smooth muscle relaxation via FEV<sub>1</sub>) was the *same* for each of the ingredients (albeit via different pharmacologic mechanisms).<sup>23</sup> Given the lack of pharmaceutical interactions between any of the ingredients in FF/UMEC/VI, the contribution of VI in the triple combination can be assured without additional clinical trial data. There is no need for a comparison of FF/UMEC/VI vs. FF/UMEC to evaluate the contribution of VI because the bronchodilatory effect of VI is not going to be blunted

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<sup>22</sup> Federal Register/Vol.80, No.246/Wednesday, December 23, 2015/Proposed Rules

<sup>23</sup> The same principle was applied for the approved triple combination products Anturnide (aliskirin hemifumarate, amlodipine besylate, hydrochlorothiazide), Tribenzor (amlodipine besylate, hydrochlorothiazide, olmesartan medoxil), and Exforge HCT (amlodipine besylate, hydrochlorothiazide, valsartan) for hypertension where the effect of each ingredient in the combination (i.e. blood pressure lowering) was the same. Also for the fixed dose triple product Tri-Luma (fluocinolone acetonide, hydroquinone, tretinoin) a full factorial design was required because the effect being evaluated (improved skin outcome measure – melasma severity) was the same.

if given on a background of FF. The findings from the already completed FF/VI program support this conclusion.

***Contribution of FF (reduction of COPD exacerbations):*** There is direct mechanistic evidence to support the contribution of FF in the combination and indirect clinical evidence can be extrapolated from the FF/VI program given the lack of pharmaceutical interaction with the individual ingredients. There is no scientific data to suggest that FF would cease to have an anti-inflammatory effect in the presence of UMEC and VI. In fact, there is molecular evidence suggesting that there are complementary interactions between corticosteroids and LABAs and between corticosteroids and LAMAs. Available data suggest that the effect of corticosteroids on muscarinic receptors may be species specific and tissue/cell specific. Most of the evidence comes from animal experimental models and there have been few reports using human airways. Nevertheless, if the experimental findings thus far can be replicated in humans then corticosteroids may enhance the effects of anticholinergics by influencing the differential expression of M<sub>2</sub> and M<sub>3</sub>-receptors.<sup>24</sup> Corticosteroids can modulate  $\beta_2$ -receptors and their function by several mechanisms which may have clinical relevance in preventing the development of tolerance to  $\beta_2$  agonists in patients with COPD who are on chronic therapy. Other studies have shown that translocation of the glucocorticoid receptor from the cell cytosol to the nucleus, a fundamental step in the anti-inflammatory activity of corticosteroids, is increased by the addition of a LABA.<sup>25</sup>

Dr. Gregory Levin in his statistical review raises concerns regarding persistence of the benefits of FF added to UMEC/VI and postulate that patients may reach a therapeutic plateau where benefits of FF may become diminished or absent because of the addition of UMEC/VI.<sup>26</sup> We agree that both UMEC and VI in addition to their bronchodilatory effects may also have a beneficial effect on COPD exacerbations. That said given the unique anti-inflammatory effect of FF and the distinct pharmacologic mechanisms of UMEC and VI there is no plausible scientific basis to consider that the anti-inflammatory effect of FF would be attenuated or extinguished in the presence of UMEC.

In its discussion on triple therapy the GOLD 2017 report mentions that adding a LAMA to existing LABA/ICS improves lung function and patient reported outcomes, in particular exacerbation risk. However, the GOLD Report goes on to say that “*a RCT did not demonstrate any benefit of adding ICS to LABA plus LAMA on exacerbations. Altogether, more evidence is needed to draw conclusions on the benefits of triple therapy LABA/LAMA/ICS compared to LABA/LAMA.*”<sup>27</sup> The cited clinical trial<sup>28</sup> evaluated

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<sup>24</sup> Malcolm Johnson. Corticosteroids: Potential  $\beta_2$ -agonist and anticholinergic interactions in chronic obstructive pulmonary disease. Proc AM Thorac Soc Vol 2 2005 pp. 320-325

<sup>25</sup> Ibid

<sup>26</sup> Statistical review page 6

<sup>27</sup> Global Initiative for Chronic Obstructive Lung Disease; Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2017 Report pg 55  
Available at: [www.goldcopd.org](http://www.goldcopd.org)

<sup>28</sup> Aaron, s. et al. Tiotropium in Combination with Placebo, Salmeterol, or Fluticasone-Salmeterol for Treatment of Chronic Obstructive Pulmonary Disease, A Randomized Trial,” Ann of Intern Med. 2007; 146:545-555

whether combining tiotropium (LAMA) with salmeterol (LABA) or fluticasone-salmeterol (ICS/LABA) improves clinical outcomes in adults with moderate to severe COPD compared with tiotropium alone. From a regulatory standpoint it is important to point out that the definition of exacerbation for the primary endpoint used in that trial – “a sustained worsening of the patient’s respiratory condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication” is not the definition of exacerbation that we accept in COPD exacerbation trials. Because there is no defined objective measure for an exacerbation (e.g. imaging modality, spirometric measure, etc.), and there is invariably some measure of clinical judgement in defining exacerbations, the division has always relied on specific clinical criteria to define COPD exacerbations for the purposes of registration clinical trials (i.e., worsening of two or more major symptoms (dyspnea, sputum volume, and sputum purulence) or worsening of any one major symptom together with any one 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 two consecutive days). COPD exacerbations are considered moderate if treated with antibiotics and/or systemic corticosteroids and are considered to be severe if hospitalization (for the exacerbation) is required.

Aside from how the primary endpoint was defined in the study, although the proportion of patients who experienced at least one COPD exacerbation during the trial did not differ significantly across all the treatment groups, the referenced article reported that patients treated with tiotropium plus fluticasone-salmeterol had lower rates of severe exacerbations of COPD (i.e., COPD exacerbations requiring hospitalizations) than did patients treated with tiotropium. All-cause hospitalizations were also reduced in patients treated with tiotropium plus fluticasone-salmeterol compared with patients treated with tiotropium. Additionally tiotropium plus fluticasone-salmeterol improved the FEV<sub>1</sub> more than did tiotropium. The referenced article did not provide data on the comparison between tiotropium plus fluticasone-salmeterol (triple therapy) and the LAMA/LABA therapy (tiotropium plus salmeterol) for these endpoints so there is insufficient information to state that the RCT did not demonstrate *any* benefit of adding ICS to LABA plus LAMA on exacerbation. In the same trial, health-related quality of life, as measured by the St. George’s Respiratory Questionnaire (SGRQ), showed that treatment with tiotropium plus fluticasone-salmeterol improved quality of life with improvement in SGRQ score of 8.6 points that was clinically meaningful (>4 points is the clinically meaningful cut off for this outcome instrument) compared to tiotropium alone (4.5 points) or tiotropium plus salmeterol alone (6.3 points).

From a clinical perspective, a reduction in COPD exacerbations requiring hospitalizations is of tremendous clinical significance for the COPD population, because long-term prognosis following hospitalization for COPD exacerbation is poor, with a five-year mortality rate of about 50%.<sup>29</sup> In summary, despite the primary endpoint (which is not an objective and FDA standard endpoint) not showing statistical significance, improvements in a range of other clinically relevant endpoints suggest that triple therapy may be a beneficial therapeutic approach in COPD.

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<sup>29</sup> Hoogendoorn M, et al “Case fatality of COPD exacerbations: a meta-analysis and statistical modelling approach.” Eur Respir J 2011; 37 (3): 508-15

## 8. SAFETY

### *a. Safety database*

The safety assessment of TRELEGY ELLIPTA is based on the two coadministration trials and on the long-term ( $\geq 12$  months) safety data from the fixed-dose combination of fluticasone furoate/vilanterol, umeclidinium/vilanterol, and the umeclidinium monotherapy programs. The lack of pharmaceutical interactions, comparable in vitro characteristics, and the comparable systemic exposure of the components of TRELEGY Ellipta from single or multiple inhalers provide sufficient reassurance that the data from the other Ellipta programs can be used to support the safety of TRELEGY ELLIPTA.

### *b. Safety findings and conclusion*

The submitted data along with the totality of the data from the BREO ELLIPTA, ANORO ELLIPTA, and INCRUSE ELLIPTA development programs support the safety of TRELEGY ELLIPTA for the treatment of COPD. A total of 824 subjects with COPD were evaluated in the two 12-week coadministration trials and the safety profile was similar to that seen in the long-term trials with the other Ellipta products. Discontinuations due to adverse events were low ( $< 1 - 4\%$ ) across both coadministration trials. The incidence of pneumonia was  $< 1\%$  in both treatment arms and fatal pneumonia was reported in one subject receiving placebo + fluticasone furoate/vilanterol (Trial 200110). The case narrative for the fatal pneumonia stated that the diagnosis was not confirmed because r/o<sup>30</sup> pneumonia was judged by the ER staff as the cause of death without any diagnostic tests. The subject had been brought into the ER already deceased. The risk of pneumonia (in COPD) with ICS has been well documented and is known to be dose-related. GSK conducted adequate dose ranging studies early in the BREO ELLIPTA development program, and carried two doses of ICS into the pivotal studies. The Agency selected the 100 mcg once daily dose (the lowest effect dose) for the COPD indication. All ICS combination products for COPD carry a Warning/Precaution for pneumonia and a similar same class Warning will be in the TRELEGY ELLIPTA label.

## 9. ADVISORY COMMITTEE MEETING

An Advisory committee (AC) meeting was not convened for this application. The three classes of products ICS, LAMAs, and LABAs for the treatment of COPD have been the topic of multiple ACs in the past. The statistical team raised the safety concerns with ICS in COPD as a major issue; however, the topic of ICS in COPD has been previously discussed at AC meetings.

Advair Diskus, the first ICS/LABA product for COPD was taken to an advisory committee (AC) meeting on January 17, 2002. In spite of the ICS safety concerns the Advisory committee voted in favor of approval. Another AC meeting was held on May 1, 2007 to discuss Advair Diskus 500/50 for COPD following the completion of the

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<sup>30</sup> r/o = rule out

TORCH trial. Although Advair Diskus 500/50 showed significant benefit on exacerbations, the Agency did not approve the higher strength product. The Agency has always approved the lowest effective dose of ICS for COPD indications and only the lower strength 250/50 Advair Diskus product has been approved for COPD.

BREO ELLIPTA (FF/VI) was discussed at an Advisory Committee meeting on April 17, 2013. The Agency did not have any unique ICS safety issues for discussion at the AC meeting. Notably, the focus of the safety discussion [as reflected in the Agency’s safety discussion question] was on cardiovascular safety in light of the new LABA vilanterol.<sup>31</sup> The committee voted affirmatively (Yes = 10; No = 3) that the safety of FF/VI once daily had been adequately demonstrated for the proposed indications, and voted affirmatively (Yes = 9; no = 4) that the efficacy and safety data provide substantial evidence to support approval of FF/VI once daily for the long-term maintenance treatment of airflow obstruction (separate question) and reduction in exacerbations (separate question).<sup>32</sup>

Prior to the approval of BREO ELLIPTA, GSK initiated a large event-driven mortality trial in over 16,000 patients with moderate COPD and increased cardiovascular risk. The trial known as SUMMIT was a prospective double-blind, randomized, placebo-controlled trial conducted in 43 countries worldwide and at 1368 centers. The trial has been completed, the results published<sup>33</sup> and the Agency reviewed the data and updated the BREO ELLIPTA labeling on May 15, 2017.

In this prospectively designed randomized, full factorial trial there were no new safety signals, no increase in mortality with FF/VI nor single ingredient fluticasone furoate [Mortality per 100-patient-years was 3.1 for FF/VI, 3.5 for placebo, 3.2 for fluticasone furoate, and 3.4 for vilanterol], nor increase in pneumonia with FF/VI or FF compared to placebo. Furthermore, on-treatment deaths due to pneumonia were less than 0.2 per 100 patient-years for each treatment group.<sup>34</sup> That said, the label for all ICS/LABA products including BREO ELLIPTA already including a Warning/Precaution for pneumonia as class Warning for ICS-containing products for COPD.

The application was discussed at a Medical Policy Council (MPC) meeting on Wednesday July 26, 2017. The reason the NDA was taken to the MPC was because of the disagreement between the review division and the statistical review team regarding the regulatory action for the NDA. The council members generally accepted the division’s scientific arguments that the pharmacological mechanisms of the three ingredients were distinct and that there was a strong basis to expect that there would be greater benefit with the fixed-dose triple vs. any of the particular dual combinations. Since the clinical

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<sup>31</sup> See Agency’s final advisory committee questions for advisory committee meeting for BREO ELLIPTA available at: <https://wayback.archive-it.org/7993/20170403224205/https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm329187.htm>

<sup>32</sup> *ibid*

<sup>33</sup> Jergen Vestbo et al. “Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomized controlled trial. *Lancet* 2016; **387**: 1817-26.

<sup>34</sup> BREO Ellipta Package Insert

trial comparing the triple combination to the LABA/LAMA, and ICS/LABA dual combinations was nearing completion and expected to read out soon, the majority of the council members suggested waiting for the results of the ongoing clinical trial. The Division appreciates the advice from the MPC but maintains its position that the data from the IMPACT trial are not necessary to support approval of the NDA for a restricted indication. There is adequate mechanistic/pharmacologic data to support the contribution of each ingredient in the fixed dose combination product to satisfy the combination rule and the efficacy and safety results from the coadministration trials provide corroborative evidence to support this conclusion. Taken together, the data submitted, along with the clinical data from the other Ellipta programs, meet the regulatory evidentiary standard of safety and efficacy to support the approval of TRELEGY ELLIPTA for the restricted indication (i.e. patients already taking BREO ELLIPTA for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired, or patients already taking BREO ELLIPTA and INCRUSE ELLIPTA via separate inhalers).

Although TRELEGY ELLIPTA is a new fixed-dose combination product, it contains the *same* active ingredients administered in the *same* dosage (amount, frequency, duration), in the *same* formulation, and in the *same* device and is intended to be used in the *same* population for the *same* therapeutic intent for which the 2 products are already approved. Given the lack of pharmaceutical interactions and the similar pharmacokinetic profile, there is no scientific reason to suggest that there would be a unique safety concern with TRELEGY ELLIPTA that would warrant taking this application to an advisory committee meeting.

## **10. PEDIATRICS**

COPD including chronic bronchitis and emphysema is not a pediatric disease and PREA requirements are waived.

## **11. OTHER RELEVANT REGULATORY ISSUES**

### ***a. DSI Audits***

A DSI audit was not necessary for this application. The clinical trials submitted to support registration of the product were previously reviewed.

### ***b. Compliance with Good Clinical Practices***

The pivotal studies referenced in this NDA complied with good clinical practices

### ***c. Financial Disclosure***

Adequate financial disclosure information was provided by GSK with the submission of the trials in the sNDA 205382/S-002. No new financial disclosure information is required because there are no new clinical trials submitted.

*d. Other*

The statistical review cites several regulatory implications of approving this NDA without data from trial CTT116855 (the IMPACT trial). Based on the Agency’s prior precedent and approach to combination product development for COPD, the approval of TRELEGY ELLIPTA for a restricted indication without consideration of the IMPACT trial data does not in any way change the Agency’s current requirements for combination therapy development in COPD. I will address each of these regulatory implication concerns raised by the statistical review team below:

- I. In his statistical review Dr. Levin asserts that with approval of this NDA sponsors can propose the development of a fixed dose LABA/LAMA product without conducting factorial design studies.<sup>35</sup> As stated before, full factorial studies have been required for all LABA/LAMA products because the effect being measured (i.e. bronchodilation) is the *same* for each component of the combination. This principle was applied in requiring full factorial studies for the fixed-dose triple combinations of the anti-hypertensive drugs products Anturnide (aliskirn hemifumarate, amlodipine besylate, hydrochlorothizide), Tribenzor (amlodipine besylate, hydrochlorothiazide, olmesartan medoxil), and Exforge HCT (amlodipine besylate, hydrochlorothiazide, valsartan) where the contribution of each ingredient in the combination was being evaluated via the same effect (i.e. blood pressure lowering). That same principle was also applied for the fixed dose triple product Tri-Luma (fluocinolone acetonide, hydroquinone, tretinoin) where a full factorial design was required because the effect being evaluated was the same (melasma severity) for each component. The approval of TRELEGY ELLIPTA does not in any way negate that principle.
  
- II. The statistical review states that “*Alternatively, the sponsor could propose a fixed dose combination of the LABA with an ICS based on clinical trials comparing the ICS/LABA to the LABA monotherapy, along with extrapolation of the contribution of the LABA from the monotherapy studies. This approach would be in direct contrast to the current expectation that sponsors carry out a factorial design comparing the safety and effectiveness of ICS/LABA combination products to both the ICS and LABA monotherapies to support approval for treatment of COPD.*”<sup>36</sup> The Agency has never required a full factorial design for an exacerbation indication in COPD with fixed dose ICS/LABA products. The Agency has required a full factorial design for evaluation of the FEV<sub>1</sub> (airflow obstruction) contribution of each ingredient (ICS and LABA) followed by an active control comparison –i.e. ICS/LABA vs. LABA for exacerbation. The Agency has always taken the position that the anti-inflammatory effect of ICS is sufficiently distinct from that of bronchodilators that a full factorial program is not required for evaluation of an exacerbation claim for COPD for ICS/LABA fixed dose combination products. It should be noted that until very recently, single ingredient LABAs and LAMAs were approved for the treatment of *bronchospasm/bronchoconstriction* associated with COPD (e.g. salmeterol, formoterol, tiotropium, acclidinium). This terminology reflects the direct

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<sup>35</sup> Statistical review pg 7

<sup>36</sup> *ibid*

bronchodilatory effect on lung function attributable to the pharmacologic effect of the product. The indication statement ‘*maintenance treatment of airflow obstruction*’ was first introduced with the approval of Advair Diskus. The reason being that fluticasone propionate is not a bronchodilator and its primary mechanism in improving airflow is not via the mechanism of improvement in airway smooth muscle relaxation (i.e. a bronchodilatory effect) but rather via its anti-inflammatory properties of ameliorating airway inflammation and other inflammatory changes that lead to increased airway narrowing. Improvement in the trough FEV<sub>1</sub> measure with ICS is considered to be a surrogate measure of efficacy which to date has been demonstrated in registration trials by showing exacerbation benefit. With the more recent approvals of single ingredient LABAs and LAMAs the restricted term ‘bronchospasm’ in indication statements has been abandoned.

- III. Finally, although not discussed under “Regulatory Implications” there are statements in the statistical review regarding asthma development programs for ICS/LABA products that are not correct as they relate to satisfying the combination rule. It is important to clarify these statements. In his statistical review Dr. Levin states that:..... “*On the other hand, approval of ICS/LABA combination products such as Breo for treatment of asthma has been supported by (1) clinical trials comparing the ICS/LABA combination to the ICS monotherapy to establish the contribution of the LABA component to the effectiveness of the combination product; and (2) a conclusion that the ICS component contributes to the safety of the combination product, given known safety concerns (ICS/LABA products have a black box (sic) warning about asthma-related death) regarding the use of LABA without concomitant ICS in asthma—a clinical trial comparing the combination product to the LABA monotherapy is therefore not considered necessary or ethical.*”<sup>37</sup>

The Agency (and the academic community) acknowledge that LABA monotherapies are unsafe in asthma and should be used with an ICS or other controller medications.<sup>38</sup>

However, the above description of how the ICS component in ICS/LABA asthma programs satisfies the combination rule is incorrect. Unlike COPD, single ingredient ICS are safe and effective approved therapies for asthma. As such, with the appreciation of the LABA safety concerns, the Agency designed alternative strategies whereby the efficacy contribution of ICS in fixed-dose ICS/LABA products for asthma could be demonstrated. The most frequently used approach has been the evaluation of multiple doses of the ICS and demonstrating contribution of the higher dose(s) of the ICS compared to lower dose(es) on a background of the same dose of LABA. Other strategies have been discussed with sponsors developing fixed dose ICS/LABA products for asthma.<sup>39</sup> The Agency has not made definitive statements that ICS mitigate the risk of LABA. In order to establish this it would be necessary to compare ICS/LABA vs. LABA which we were unable to assess in the LABA safety trials that were mandated under FDAAA.<sup>40</sup> In the LABA safety trials the safety of ICS/LABA vs. ICS was

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<sup>37</sup> Statistical Review pg 4 -5

<sup>38</sup> FDA approved labeling for LABA containing products for asthma

<sup>39</sup> Pre-IND [REDACTED] (b) (4)

<sup>40</sup> FDAAA = Food and Drug Administration Amendments Act of 2007

assessed to evaluate whether adding a LABA to background ICS increased the risk of serious asthma outcomes.

## 12. LABELING

### *Proprietary Name*

The name TRELEGY ELLIPTA was reviewed and deemed provisionally acceptable by the Division of Medication Error Prevention and Analysis (DMEPA)

### *Carton and Immediate Container Labels*

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

### *Patient Labeling and Medication Guide*

The product contains a LABA and as such carries a Medication Guide. The Medication Guide was reviewed by the patient labeling team. GSK has revised the Medication Guide and addressed all the labeling comments.

### *Physician Labeling*

The full prescribing information (PI) has been discussed with GSK and labeling changes have been agreed upon. Of note the indication statement has been revised from the originally proposed indication statement which stated:

 (b) (4)

To:

“TRELEGY ELLIPTA is a combination inhaled corticosteroid/anticholinergic/long-acting beta<sub>2</sub>-adrenergic agonist indicated for the long-term, once-daily, maintenance treatment of patients with chronic obstructive pulmonary disease (COPD), who are on a fixed- dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients who are already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol.”

The modification to the indication statement restricts the population based on the clinical trial data submitted and is appropriate.

### **13. ACTION AND RISK BENEFIT ASSESSMENT**

#### ***a. Regulatory Action***

The regulatory action for this application is approval.

#### ***b. Risk/ Benefit Assessment***

TRELEGY ELLIPTA has a favorable risk/benefit profile. The safety and efficacy of the components of TRELEGY ELLIPTA have been previously evaluated in monotherapy (INCRUSE ELLIPTA) and dual combination (BREO ELLIPTA and ANORO ELLIPTA) programs and were all found to have a favorable risk benefit profile.

In his statistical review Dr. Levin states that in the BREO ELLIPTA program the exacerbation benefit with FF translates to roughly 25 exacerbations prevented for every 100 patients treated for one year and the risk of pneumonia is roughly 3 pneumonias caused for every 100 patients treated for one year.<sup>41</sup> The prevention of 25 COPD exacerbations/100 patients /year is a very meaningful public health benefit. COPD exacerbations have significant impact on patients including reducing health status, increasing airway inflammation and disease progression, worsening peripheral muscle weakness, and reducing daily activities. Patients with frequent exacerbations and those with severe exacerbations are most at risk from the effects of the exacerbation.<sup>42</sup> Furthermore, the healthcare utilization cost of COPD exacerbations (while not a factor in regulatory decision making for drug approvals) is very high and exacerbations of COPD lead to significant increases in resource utilization and cost to the health care system.<sup>43</sup> Therefore, therapies that can reduce COPD exacerbation frequency would be a significant public health benefit and justify the known risk of pneumonia with the ICS component.

In acknowledging the known risks of ICS, and the fact that the risks are dose-related, the Agency has only approved the lowest effective dose of ICS in combination products for COPD in order to mitigate the risk. The statistical review noted that in the long-term mortality trial with BREO ELLIPTA with over 16,000 patients the magnitudes of benefit and risk were smaller than in the previous phase 3 trials (i.e. roughly 6 exacerbations prevented and 1.1 pneumonias caused for every 100 patients treated for one year with FF/VI instead of VI).<sup>44</sup> In considering the smaller magnitude of benefit, is important to note that the patient population in the mortality trial had less severe disease (moderate COPD) than the patients in the BREO ELLIPTA phase 3 trials. That said, all-cause mortality was not increased and on-treatment deaths due to pneumonia was less than 0.2 per 100 patient-years for each treatment arm in the trial.<sup>45</sup>

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<sup>41</sup> Statistical review pg 6

<sup>42</sup> Jadwiga A., Wedzicha and Tom Wilkinson. Impact of Chronic Obstructive Pulmonary Disease exacerbations on patients and payers. Pro Am Throac Soc Vol 3 pp 218-221, 2006

<sup>43</sup> Margaret K Pasquale et al. Impact of exacerbations on health care cost and resource utilization in chronic obstructive pulmonary disease patients with chronic bronchitis from a predominantly Medicare population. International Journal of COPD 2012; 7 757-764

<sup>44</sup> Statistical review pg 6- 7

<sup>45</sup> Breo Ellipta Package Insert

The incremental benefit of improved airflow obstruction afforded by the addition of umeclidinium to the FF/VI component of TRELEGY ELLIPTA has significant public health benefits because deteriorating airflow limitation is associated with an increasing prevalence of exacerbations, hospitalization, and the risk of death.<sup>46</sup>

From the standpoint of patient convenience, reducing the number of inhalers used by the COPD population has the potential to improve adherence. Poor adherence in chronic disease states is not a trivial matter and is of such significant public health concern that in 2003 the World Health Organization (WHO) issued a Call for Action Statement to address this problem.<sup>47</sup> Simplifying treatment regimens such as reducing the number of inhalers could have a positive impact on patient adherence and clinical outcomes. Andrew P Yu et al<sup>48</sup> reported on the clinical and economic outcomes of using multiple versus single long-acting inhalers in COPD treatment. They compared healthcare resource utilization and healthcare costs between COPD patients who used multiple long-acting inhalers versus those who used a single long-acting inhaler. After controlling for a number of potentially confounding factors, multiple- inhaler users experienced significantly more exacerbations, a higher risk of exacerbations, more inpatient days, more urgent care visits and other medical services than single-inhaler users, resulting in significantly higher all-cause health care costs.<sup>49</sup>

In conclusion, the risk/benefit of TRELEGY ELLIPTA for the treatment of COPD is quite favorable and has the potential to have significant benefit from a public health perspective for a disease that is currently the third leading cause of death in the U.S. In May 2017 the National Institutes of Health released the COPD National Action Plan – a patient-centered roadmap for addressing one of the most urgent health concerns facing Americans. The plan was developed at the request of Congress with input from the broad COPD community and was guided by the National Heart, Lung, and Blood Institute.<sup>50</sup> The action plan has five goals one of which is to improve the diagnosis, prevention, treatment, and management of COPD by improving the quality of care delivered across the health care continuum. The Agency can play a critical role in helping to achieve this goal by facilitating drug development in COPD.

### ***c. Recommendation for Postmarketing Risk Management Activities***

None

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<sup>46</sup> Soriano JB., et al. Mortality prediction in chronic obstructive pulmonary disease comparing the GOLD 2007 and 2011 staging systems: a pooled analysis of individual patient data. *The Lancet Respiratory Medicine* 2015; **3** (6): 443-50

<sup>47</sup> [www.who.int/chp/knowledge/publications/adherence\\_report/en/](http://www.who.int/chp/knowledge/publications/adherence_report/en/)

Accessed August 24, 2017

<sup>48</sup> Andrew P. Yu et al. Clinical and economic outcomes of multiple versus single long-acting inhalers in COPD. *Respiratory Medicine* (2011) 105, 1861-1871

<sup>49</sup> *ibid*

<sup>50</sup> <https://www.nhlbi.nih.gov/health-pro/resources/lung/copd-national-action-plan>

Accessed September 17, 2017

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/s/  
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LYDIA I GILBERT MCCLAIN  
09/18/2017