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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	November 26, 2013
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-3975
Applicant Name:	GlaxoSmithKline
Date of Submission:	December 18, 2012
PDUFA Goal Date:	December 18, 2013
Proprietary Name:	Anoro Ellipta
Established Name:	Umeclidinium and vilanterol
Dosage form:	Inhalation Powder (inhaler contains 2 double-foil blister strips, each with 30 blisters containing powder for oral inhalation)
Strength:	Umeclidinium 62.5 mcg per blister and vilanterol 25 mcg per blister
Proposed Indications:	Maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD)
Action:	Approval

1. Introduction

GlaxoSmithKline (GSK) submitted this 505(b)(1) new drug application for use of Anoro Ellipta (umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is one inhalation (umeclidinium 62.5 mcg and vilanterol 25 mcg) once daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

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

Anoro Ellipta is a new inhalation product comprised of a long-acting anticholinergic umeclidinium and a long-acting beta-2 adrenergic agonist (LABA) vilanterol. Neither

component is currently approved for marketing in the US as a single-ingredient inhalation product. Vilanterol is approved as one of the two active ingredients in Breo Ellipta. Breo Ellipta is an inhalation product containing the ICS fluticasone furoate and the LABA vilanterol, which was approved in the US in May 2013 for use in COPD patients. Umeclidinium is a new molecular entity and not marketed for any indication in the US.

The Anoro Ellipta development program is distinctive in terms of the nature of the combination and the data available with the single active ingredients. While short-acting anticholinergics and short-acting beta-2 adrenergic agonists have been previously combined in inhalation dosage forms (such as ipratropium and albuterol in Combivent and in DuoNeb), Anoro Ellipta is comprised of the novel anticholinergic umeclidinium and the LABA vilanterol. The data available for the single ingredient umeclidinium and vilanterol were limited at the start of the Anoro Ellipta program. This was a departure from the historical development programs for inhalation combination products in the United States where the single ingredient products were developed first, followed by development of the combination product. The Anoro Ellipta development program was therefore large with dose ranging and dose frequency regimen studies for the single ingredient products and the pivotal COPD studies for the combination product folded into one development program.

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

Umeclidinium:

Umeclidinium is a new molecular entity that belongs to the anticholinergic class. Inhaled anticholinergics are widely available in the US and worldwide for the treatment of COPD. In the US, one short-acting anticholinergic, ipratropium bromide, and two long-acting anticholinergics, tiotropium bromide (Spiriva HandiHaler) and aclidinium bromide (Tudorza Pressair), are currently available. All of these products have anticholinergic adverse effects, such as dry mouth, constipation, and urinary retention. A meta-analysis of various studies suggested a concern regarding increased risk of stroke, cardiovascular death, and myocardial infarction associated with the use of short-acting and long-acting anticholinergics .[1] A pooled analysis of 29 studies conducted by Boehringer Ingelheim in 2007 (25 studies with Spiriva HandiHaler, and 4 studies with Spiriva Respimat) suggested an increased risk of stroke with tiotropium bromide.[2] In contrast, a 6,000 patient, 4-year study with Spiriva HandiHaler conducted by Boehringer Ingelheim in COPD patients (The UPLIFT Study – Understanding Potential Long-term Impacts on Function with Tiotropium) did not show increased mortality or cardiovascular safety risk

[1] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300:1439-50.
[2] FDA Early Communication about an Ongoing Safety Review of Tiotropium. Http://ww.fda.gov/cder/drug/early_comm/tiotropium.htm

with Spiriva HandiHaler.[3, 4] A more recent study conducted by Boehringer Ingelheim involving 17,135 COPD patients followed for 2.3 years (The TIOSPIR study – Tiotropium Safety and Performance in Respimat) showed comparable all-cause mortality between Spiriva Respimat and Spiriva HandiHaler.[5] These two large controlled studies, pending review of TIOSPIR study by the FDA, largely alleviate the concerns regarding excess mortality and cardiovascular safety risks with long-acting anticholinergic tiotropium. Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in COPD program to limit high systemic exposure and potential safety concerns. Dose ranging and dose regimen studies with inhaled anticholinergics are done in patients with COPD and not asthma because patients with asthma are usually not responsive to bronchodilation with anticholinergics.

Vilanterol:

Vilanterol is not a new molecular entity. It belongs to the class called long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol, arformoterol, indacaterol, and vilanterol. Some of these are marketed as single ingredient products and others as combination products with inhaled corticosteroids. Salmeterol, formoterol, and arformoterol are dosed twice-daily, and indacaterol and vilanterol are dosed once-daily.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.[6, 7, 8, 9] More recently, inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths.[10] This has been discussed at various FDA Advisory Committee meetings,[11] which has led to publications expressing concerns on safety,[12, 13, 14] and the establishment of a safe use strategy outlined by the FDA.[15] To

[3] Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359: 1543-54.
[4] Michele TM, Pinheiro S. Iyasu S. The safety of tiotropium – The FDA conclusions. N Eng J Med 2010; 363: 1097-99.
[5] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013; 369:1491-501.
[6] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[7] Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproteronol in spontaneous and induced asthma. N Eng J Med 1949; 240:45-51.
[8] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax 1991; 46:105-111.
[9] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. N Eng J Med 1992; 326:501-506.
[10] US Product Labels of salmeterol and formoterol containing products.
[11] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[12] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.

further assess the safety of LABAs in asthma, the FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone.[16] The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.[17] Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for development of all LABAs, including vilanterol. Most of the U.S.-marketed beta-adrenergic agonists carry both asthma and COPD indications. The dose and dosing frequency in both indications are the same. Dose ranging and dose regimen studies for beta-adrenergic agonists are usually done first in patients with asthma and then in COPD patients. Patients with asthma are generally more responsive and allow for larger separation of doses. Patients with COPD with some degree of fixed obstruction are likely to have a smaller response range to a bronchodilator. The regulatory precedence of performing dose ranging and dose regimen studies in patients with asthma was followed in the development of indacaterol, a LABA that was approved for marketing in the United States in 2011 as a bronchodilator in patients with COPD. [18]

Regulatory interaction between the Agency and GSK:

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

- Pre-IND meeting for vilanterol, January 31, 2007: The Division recommended that GSK characterize the vilanterol fully prior to development of Anoro.
- Pre-IND meeting for umeclidinium, June 4, 2009: The Division recommended evaluation of dose and dosing frequency for umeclidinium, and recommended that efficacy and safety of the individual component be demonstrated.

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[13] Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. New Eng J Med 2009; 360:1952-1955.
[14] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[15] Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. New Eng J Med 2010; 362:1169-1171.
[16] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New Eng J Med 2011; 364:2473-2475.
[17] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:70-74.
[18] Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. The risks and benefits of indacaterol – The FDA review. N Eng J Med 2011; 365:2247-2249.

- Type C teleconference meeting for asthma and COPD program, March 24, 2010: The Division stated that the proposed vilanterol 25 mcg once daily dose appeared reasonable for further evaluation in confirmatory studies.
- End-of-Phase 2 meeting for Anoro Ellipta, October 29, 2010: The Division did not confirm the proposed umeclidinium 125 mcg dose. The Division stated that demonstration of a dose response would be useful, particularly in light of ongoing safety concerns with inhaled anticholinergics in COPD.
- Pre-NDA meeting for Anoro Ellipta, January 18, 2012: The Division stated the need for replicate evidence of efficacy for the single ingredient products as well as the Anoro Ellipta combination product.
- Breo Ellipta for COPD approved on May 10, 2013.

3. Chemistry, Manufacturing, and Controls

The product Anoro Ellipta (umeclidinium 62.5 mcg and vilanterol 25 mcg inhalation powder) includes a dry powder inhaler device, the Ellipta inhaler, which contains 2 separate double-foil blister strips inside. Each blister on one strip contains micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg umeclidinium), magnesium stearate, and lactose monohydrate; and each blister on the other strip contains micronized vilanterol trifenatate (40 mcg equivalent to 25 mcg of vilanterol), magnesium stearate, and lactose monohydrate. The lactose monohydrate may contain trace amounts of milk proteins. The proposed commercial presentation of Anoro Ellipta has 30 blisters each of umeclidinium and vilanterol, which will be a one-month supply with a once daily dosing regimen. The device has a dose counter. The steps needed to use the product are simple and similar to some other dry powder inhaler devices. To deliver a dose, the patient will open the cover of the device. This action makes the powder from one blister containing umeclidinium and one blister containing vilanterol ready for inhalation at the airflow path inside the device. The patient will then inhale through the mouthpiece of the device. If a patient opens and closes the cover of the device without inhaling, the formulation powder will be held inside the device and will no longer be available to be inhaled. The Anoro Ellipta device has been tested for usability, reliability, and ruggedness through in vitro testing, human factor studies, and testing of devices used in the clinical program.

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

The drug substances are manufactured at a GSK facility in Jurong, Singapore and drug product including the Anoro Ellipta device is assembled at a GSK facility in Ware, United Kingdom. The device components are fabricated by (b) (4). All manufacturing and testing facilities associated with this drug product have acceptable establishment evaluation status. All DMFs associated with this application were also found to be acceptable.

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

4. Nonclinical Pharmacology and Toxicology

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

The general toxicity of umeclidinium was evaluated after the inhalation route of administration of the drug for up to 13, 26, and 39-weeks in mice, rates, and dogs, respectively. These studies identified the lungs, tracheal bifurcation, larynx, nasal turbinates, and heart as target organ of toxicity. There were adequate margins of safety between these findings in animals and human doses. In terms of genetic testing, umeclidinium tested negative in the Ames assay, rat bone marrow micronucleus assay in vivo, and the mouse lymphoma assay in vitro. Two-year carcinogenicity studies in rodents showed no evidence of tumorigenicity. Reproductive and developmental studies showed that umeclidinium had no effects on fertility or reproductive performance in rats and was not teratogenic in rats or rabbits. Umeclidinium caused a skeletal variation in rats in a dose-dependent manner. Umeclidinium did not have any effects on pre- or post-natal development in rats.

The general toxicity of vilanterol was evaluated after the inhalation route of administration of the drug for up to 13, 26, and 39-weeks in mice, rats and dogs, respectively. These studies identified the upper airways, lung, heart, liver and testes as target organs of toxicity, and findings were typical of beta agonists. In terms of genetic testing, vilanterol tested negative in the Ames assay, UDS assay in vitro, and SHE cell assay in vitro, and rat bone marrow micronucleus assay in vivo, and equivocal in the mouse lymphoma assay. Two-year carcinogenicity studies in rodents showed a dose-related shortening of latency for pituitary neoplasms in both genders of the rat and increases in the incidence of leiomyomas in female rats. Female mice showed increases in the incidence of tubulostromal carcinomas in the ovaries. These findings were typical of beta agonists in rodents. A battery of reproductive and developmental studies evaluated the effects of vilanterol on male and female fertility in rats, the teratogenicity of vilanterol in rats and rabbits, and peri- and post-natal development of vilanterol in rats.

Results showed that vilanterol was not teratogenic in rats or rabbits, but caused increases in the incidence of skeletal variations at high doses in rabbit fetuses. Vilanterol had no effects on fertility in rats.

5. Clinical Pharmacology and Biopharmaceutics

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism and the pharmacokinetics after single and multiple inhaled doses of umeclidinium and vilanterol individually and in combination. The majority of studies were conducted in healthy volunteers, but several studies were done specifically to assess pharmacokinetics in COPD patients and the effect of renal and hepatic impairment. Umeclidinium and vilanterol have low oral bioavailability and systemic exposure for both components is primarily due to absorption of the inhaled portion. Following inhaled administration, Cmax of both umeclidinium and vilanterol occurred at 5 to 15 minutes. The primary metabolic pathway for umeclidinium is CYP2D6 and that of vilanterol is CYP3A4. No clinically meaningful difference in systemic exposure to umeclidinium was observed following repeat daily inhaled dosing in CYP2D6 normal and poor metabolizer subjects. The inhibition potential for both metabolic pathways is low when administered by the inhaled route and no specific dose adjustments are recommended when the combination is administered with other drugs. No significant effects due to age, hepatic or renal impairment on pharmacokinetic parameters were observed, so no dose adjustment for age, hepatic or renal function is recommended. A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval at the therapeutic dose.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1 and Table 2. As discussed in section 2 above, GSK conducted a program for umeclidinium and vilanterol that was largely concurrent for the individual components and the combination product. As a result the clinical program submitted with this application is large. Table 1 summarizes the main studies conducted in both COPD and asthma to support dose selection and dosing frequency for the individual umeclidinium and vilanterol components with the to-be-marketed device. Table 2 summarizes the main studies conducted in COPD to support the combination product. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8. For brevity, the studies are referenced later in this review by the last four digits of the study number.

Table 1. Relevant dose selection studies for umeclidinium, and vilanterol

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
Umeclidinium -- Dose-ranging and dose-regimen studies -- COPD patients					
113073 [Oct 2009 – Mar 2010]	- ≥ 40 yr - COPD - XO, active controlled - 14 days	Umec 1000 mcg QD Umec 500 mcg QD Umec 250 mcg QD Umec 125 mcg QD Umec 62.5 mcg QD Umec 250 mcg BID Umec 125 mcg BID Umec 62.5 mcg BID Tiotropium 18 mcg QD Placebo	32 38 38 34 35 38 37 34 35 158	FEV_1 trough at day 15	US (55%), Germany
113589 [Dec 2009 - Jul 2010]	- ≥ 40 yr - COPD - PG, placebo controlled - 28 days	Umec 500 mcg QD Umec 250 mcg QD Umec 125 mcg QD Placebo	71 72 71 71	FEV_1 trough at day 29	US (42%), W Europe, E Europe
115321 [July 2011 - Oct 2011]	- ≥ 40 yr - COPD - XO, active controlled - 7 days	Umec 125 mcg QD Umec 62.5 mcg QD Umec 31.25 mcg QD Umec 15.6 mcg QD Umec 31.25 mcg BID Umec 15.6 mcg BID Tiotropium 18 mcg QD Placebo	60 59 58 57 56 60 56 60	FEV_1 trough at day 8	US (100%)
115408 [July 2011 - Feb 2012]	- ≥ 40 yr - COPD - PG, placebo controlled - 12 weeks	Umec 125 mcg QD Umec 62.5 mcg QD Placebo	69 69 68	FEV_1 trough at day 85	US (23%), Germany, Japan
Vilanterol -- Dose-ranging and dose-regimen studies -- asthma patients					
109575 [Dec 2007- Sep 2008]	- 12 to 80 yr - Asthma - PG, placebo controlled - 28 days	VI 3 mcg QD VI 6.25 mcg QD VI 12.5 mcg QD VI 25 mcg QD VI 50 mcg QD Placebo	101 101 100 101 102 102	FEV_1 trough at day 28	US (36%), E Europe, W Europe, Canada, S Africa, Other
113310 [Sep 2009 - Jan 2010]	- 18 to 71 yr - Asthma - XO, placebo controlled - 7 days	VI 6.25 mcg QD VI 6.25 mcg BID VI 12.5 mcg QD VI 25 mcg QD Placebo	75	FEV_1 trough at the end of 7-day treatment period	US (100%)
112060 [Sep 2010 – Aug 2011]	- 12 to 79 yr - Asthma - PG, placebo controlled - 28 days	VI 25 mcg QD Sal 50 mcg BID Placebo	115 116 116	FEV_1 (0-24h) at end of 12 week treatment period	US (20%), E Europe, W Europe, Other
Vilanterol -- Dose-ranging study -- COPD patients					
111045 [Feb 2008 – Oct 2009]	- ≥ 40 yr - COPD - PG, placebo controlled - 28 days	VI 3 mcg QD VI 6.25 mcg QD VI 12.5 mcg QD VI 25 mcg QD VI 50 mcg QD Placebo	99 101 101 101 99 101	FEV_1 trough at day 29	US (50%), E Europe, W Europe, Canada, Other

* Study ID shown (top to bottom) as GSK's study number, and [month year study started-completed]
† XO=cross over, PG=parallel group
‡ Umec=umeclidinium in Ellipta device; VI=vilanterol in Ellipta device; Sal=salmeterol xinafoate;

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
§ Intent to treat ¶ Primary efficacy variables and selected secondary efficacy variables are shown. The efficacy analysis for the pivotal studies were performed using analysis of covariance (ANCOVA). // Europe and other included: Argentina, Belgium, Chile, Denmark, Estonia, France, Mexico, Netherlands, Peru, Philippines, Poland, Romania, Russian Federation, S Korea, Slovakia, Sweden, Thailand, Ukraine					

Table 2. Relevant clinical studies with Anoro Ellipta (umeclidinium and vilanterol inhalation powder) in patients with COPD

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries //**
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
113373 Trial 1 [Mar 2011 - Apr 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, placebo controlled - 24 weeks	Umec/VI 62.5/25 QD Umec 62.5 QD VI 25 QD Placebo	413 418 421 280	ΔFEV_1 trough baseline to wk 24	US (28%), E Europe, W Europe, Other
113361 Trial 2 [Mar 2011 - Sep 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, placebo controlled - 24 weeks	Umec/VI 125/25 QD Umec 125 QD VI 25 QD Placebo	403 407 404 275	ΔFEV_1 trough baseline to wk 24	US (21%) E Europe, W Europe, Other
113360 Trial 3 [Mar 2011 - Apr 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, active comparator - 24 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD VI 25 QD Tiotropiium 18 QD	214 212 209 208	ΔFEV_1 trough baseline to wk 24	US (27%), E Europe, W Europe, Other
113374 Trial 4 [2009-2011]	- ≥ 40 yr - COPD by ATS criteria - PG, active comparator - 24 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD Umec 125 QD Tiotropium 18 QD	215 217 222 215	ΔFEV_1 trough baseline to wk 24	US (26%), E Europe, W Europe, Other
Exercise endurance efficacy and safety studies -- COPD patients					
114417 [Mar 2011 - Jun 2012]	- ≥ 40 yr - COPD by ATS criteria - XO, placebo controlled - 12 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD Umec 125 QD Umec 62.5 QD VI 25 QD Placebo	144 152 50 49 76 170	ΔETT baseline to week 12 ΔFEV_1 trough baseline to wk 12	US (56%), E Europe, W Europe
114418 [Mar 2011 - July 2012]	- ≥ 40 yr - COPD by ATS criteria - XO, placebo controlled - 12 weeks	Umec/VI 125/25 QD Umec/VI 62.5/25 QD Umec 125 QD Umec 62.5 QD VI 25 QD Placebo	128 130 41 40 64 151	ΔETT baseline to week 12 FEV_1 trough at week 12	US (45%), E Europe, W Europe, S Africa, Canada
Safety study -- COPD patients					
113359 [Jan 2011 - July 2012]	- ≥ 40 yr - COPD by ATS criteria - PG, placebo controlled - 52 weeks	Umec/VI 125/25 QD Umec 125 QD Placebo	226 227 109		US (28%), E Europe, Chile, S Africa
* Study ID shown (top to bottom) as GSK's study number, as referenced in the proposed Anoro Ellipta product label, and [month and year study started-completed] † XO=cross over, PG=parallel group ‡ Umec=umeclidinium in Ellipta device; VI=vilanterol in Ellipta device					

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries //**
§ Intent to treat (ITT) ¶ FEV1 trough is mean values 23 and 24 hours after dosing on day 168. Primary efficacy variables for the four bronchodilator studies were analyzed using mixed model for repeated measure (MMRM) in the ITT population. // Europe and other included: Argentina, Australia, Belgium, Bulgaria, Chile, Czech Republic, Denmark, Estonia, France, Germany, Greece, Hungary, Italy, Japan, Mexico, Netherlands, Norway, Peru, Philippines, Poland, Romania, Russia, Slovakia, Spain, South Korea, Sweden, Thailand, UK, Ukraine.					

b. Design and conduct of the studies

Umeclidinium dose ranging (3073, 3589, 5321, 5408) and dose regimen (3073, 5321) studies in COPD:

These studies were conducted in patients with COPD. The study treatment arms and primary efficacy variable are shown in Table 1. The primary analysis was the linear trend in dose response in trough FEV1 at day 8. Safety assessments included adverse event recording, vital signs, physical examination, and clinical laboratory and hematology measures.

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

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

Vilanterol dose ranging (1045) study in COPD:

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

Pivotal bronchodilator (or lung function) studies (placebo-controlled studies 3373 and 3361; active-controlled studies 3360 and 3373) in COPD:

These studies were identical in design except for the doses of study treatments and comparators (Table 2). Patients eligible for the studies were required to have a diagnosis of moderate-to-severe COPD as defined by ATS/ERS criteria, [19] with post-

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

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

Exercise endurance studies (4417, 4418) in COPD:

These studies were identical in design (Table 2). Eligibility criteria were similar to pivotal bronchodilator studies with a demonstrated ability to perform exercise shuttle walk test. Eligible patients entered a 12-21 day run in period, followed by 12-week treatment periods separated by 14-day washout period. The crossover study treatment arms and the primary efficacy variables are shown in Table 2. Safety assessments were similar to the pivotal bronchodilator studies.

Long-term safety study (3359) in COPD:

This study enrolled more stable COPD patients than those enrolled in the pivotal bronchodilator studies (there were no mMRC criteria, and the FEV1 criteria was ≥35% to ≤70%). A wide range of concomitant medications was allowed that justifies using a placebo arm. Safety assessments were similar to the pivotal bronchodilator studies.

c. Efficacy findings and conclusions

The clinical program is adequate to support the efficacy of Anoro Ellipta 62.5/25 mcg (umeclidinium 62.5 mcg and vilanterol 25 mcg) for bronchodilation in patients with COPD. The efficacy demonstration of Anoro Ellipta builds on the selection of an appropriate dose and dosing regimen for umeclidinium and vilanterol, and then demonstrates the benefit for Anoro Ellipta for the claimed benefits of bronchodilation over the single ingredients umeclidinium and vilanterol.

Umeclidinium dose ranging and dose regimen in COPD:

As discussed in section 2 above, selection of an appropriate dose and dosing regimen is important for the development of an anticholinergic for COPD. GSK conducted adequate exploration of dose ranges and dose regimen in patients with COPD (Table 1).

Dose ranging data are available from studies 3073, 3589, 5321, and 5408. Studies 3073 and 3589 showed no bronchodilation benefit for doses over the 125 mcg once-daily dose, and the difference between the 125 mcg and the 62.5 mcg once daily doses (lowest two doses explored) was not consistent (data not shown in this review). To explore lower doses, study 5321 evaluated doses ranging from 15.6 mcg to 125 mcg once daily. Time profile FEV1 over 6 hours on day 1 (Figure 1) and over 24 hours on day 7 (Figure 2) from study 5321 showed a dose response, with the lowest umeclidinium 15.6 mcg once daily dose falling off in bronchodilation efficacy compared to the higher doses, and the 125 mcg once daily umeclidinium dose showing higher bronchodilation efficacy compared to other lower doses and to the benchmark tiotropium. Dose separation between umeclidinium 62.5 mcg once daily and 125 mcg once daily was supported by data from study 5408 (Table 3). These data suggest 62.5 mcg as a reasonable optimum dose for umeclidinium, and also supports GSK's decision to carry forward the 62.5 mcg and the 125 mcg umeclidinium doses to phase 3 studies.

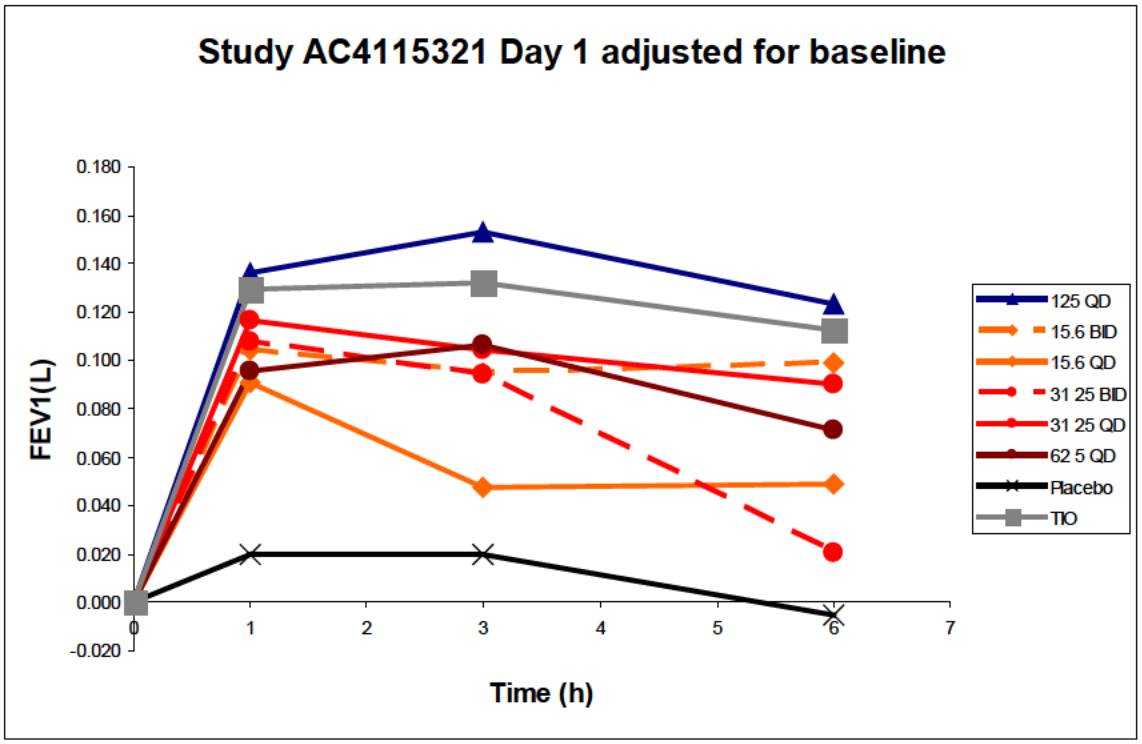

Figure 1. Adjusted mean change from baseline in FEV1 over time on day 1, study 115321

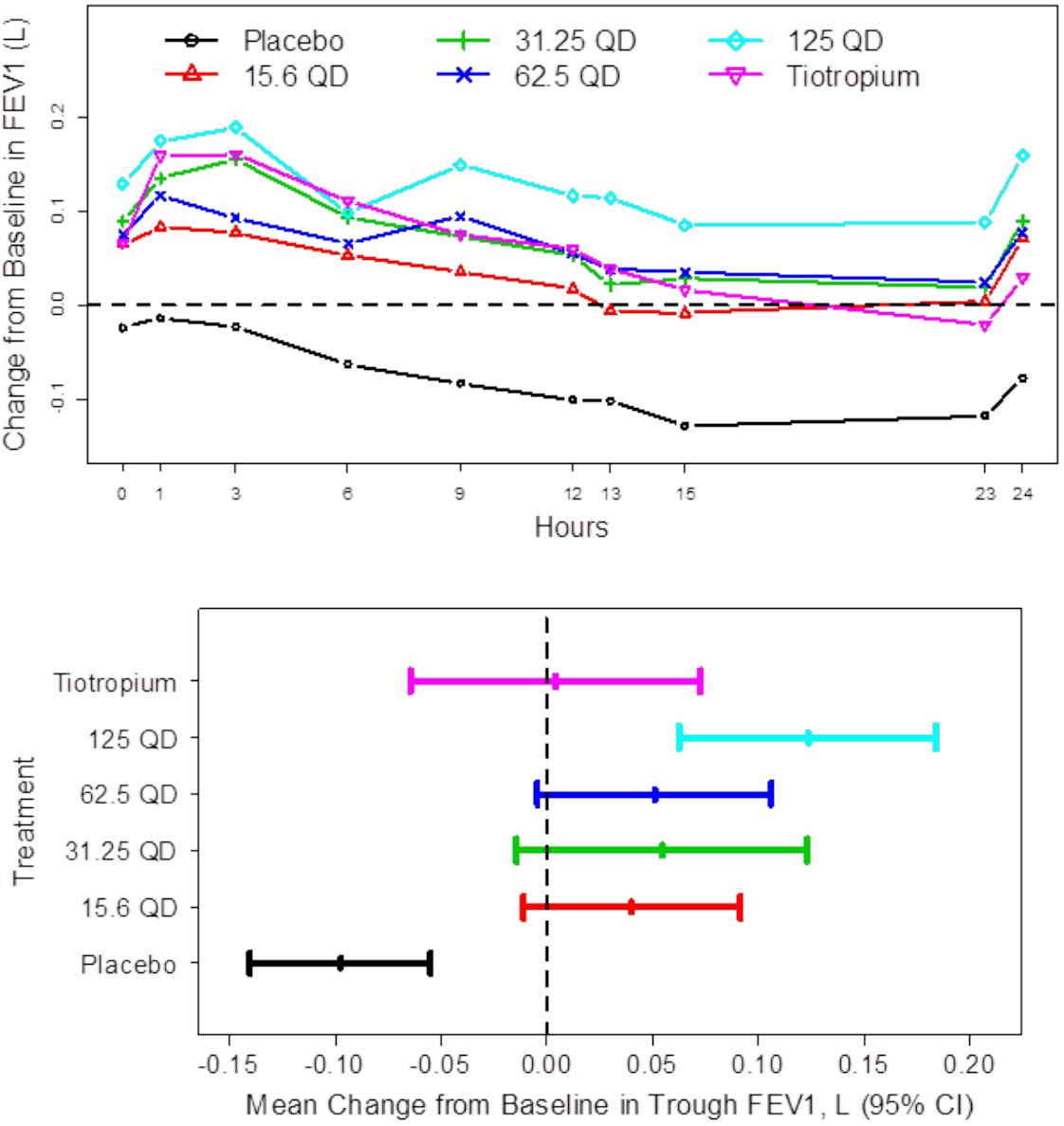

Figure 2. Post-dose 24-hour serial mean change from baseline in FEV1 on day 7 (top panel) and mean change from baseline in trough FEV1 on day 8 (bottom panel) for once-daily umeclidinium (125 mcg, 62.5 mcg, 31.25 mcg, 15.6 mcg), tiotropium (18 mcg), and placebo, Study 115321.

Table 3. Mean change from baseline in trough FEV1 at day 85

Treatment	n	LS mean change from baseline	Difference from placebo (95% CI)	P value
Umec 62.5 mcg	69	0.12	0.13 (0.05, 0.20)	<0.001
Umec 125 mcg	69	0.15	0.15 (0.08, 0.23)	<0.001
Placebo	68	-0.01		

Dose regimen (dose frequency) of umeclidinium was evaluated in studies 3073 and 5321. Study 5321 is relevant because it explored doses identified as optimum in dose ranging studies (discussed above). The time profile FEV1 over 24 hours on day 7 did not show differences between the 62.5 mcg once-daily dose and 31.25 mcg or 15.6 mcg twice-daily dose (Figure 4), which did not suggest that twice-daily was preferable to once-daily dosing. These data support 62.5 mcg twice-daily as a reasonable optimum dose and dose regimen for umeclidinium, and also supports GSK's decision to carry forward the 62.5 mcg and the 125 mcg umeclidinium once-daily doses to phase 3 studies.

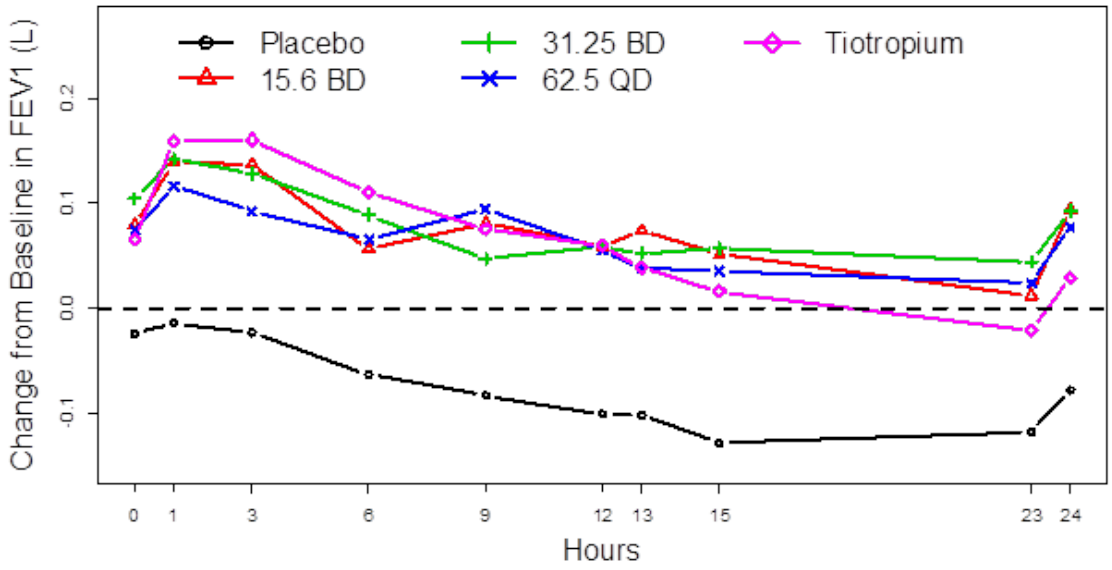

Figure 3. Post-dose 24-hour serial mean change from baseline in FEV1 on day 7 for once-daily and twice daily umeclidinium (62.5 mcg once-daily, 31.25 mcg twice-daily, and 15.6 mcg twice-daily), and tiotropium (18 mcg once-daily), Study 115321.

Vilanterol dose ranging and dose regimen in asthma and COPD:

As discussed in section 2 above, the selection of an appropriate dose and dosing regimen is important for development of LABAs, and these studies need to be conducted in patients with asthma in addition to COPD because the bronchodilator response is greater in bronchoresponsive patients, such as patients with asthma who can show larger separation between doses. GSK conducted adequate exploration of the dose ranges and dose regimens in patients with asthma and COPD (Table 1). These and other studies were reviewed for the Breo Ellipta (fluticasone furoate and vilanterol) NDA and it was determined that vilanterol 25 mcg once daily is the optimum dose for COPD. Data supporting that conclusion are briefly summarized below.

In the asthma dose ranging study (9575), vilanterol 3 mcg and 6.25 mcg once daily were not statistically significantly different from placebo for the primary endpoint of trough FEV1; vilanterol 12.5 mcg, 25 mcg, and 50 mcg once daily resulted in similar level of

improvement in the primary endpoint of trough FEV1 that were all statistically significantly greater than that observed with placebo (Figure 5). In the COPD dose ranging study (1045), all doses of vilanterol were statistically significantly different from placebo for the primary endpoint of trough FEV1 with a numerical increasing trend with increasing dose (Figure 5). Based on the results of these two studies, GSK selected the vilanterol 25 mcg nominal dose in combination with umeclidinium for confirmatory COPD studies for the Anoro Ellipta program. This was reasonable and acceptable to the Agency.

Lack of an active comparator was a limitation in these dose-ranging studies. GSK has conducted a study (2060) that compared vilanterol 25 mcg once daily to salmeterol 50 mg twice daily (approved dose of salmeterol) in patients with asthma. The study showed a larger increase in trough FEV1 with vilanterol compared to salmeterol (359 mL vs 283 mL), but neither of the treatment groups were statistically significantly different from placebo, because placebo unexpectedly also increased trough FEV1 (289 mL). This study was therefore not helpful. Comparative efficacy studies conducted later with combination product (studies 3107, 3109, 2352, and 3091) showed comparable FEV1 time response curves after the first dose and also at later time points (Figure 6 shows two representative curves after the first done). The first dose bronchodilator response allowed comparison between vilanterol 25 mcg and salmeterol 50 mcg that was relatively unaffected by the ICS component. These results further supported the vilanterol 25 mcg dose.

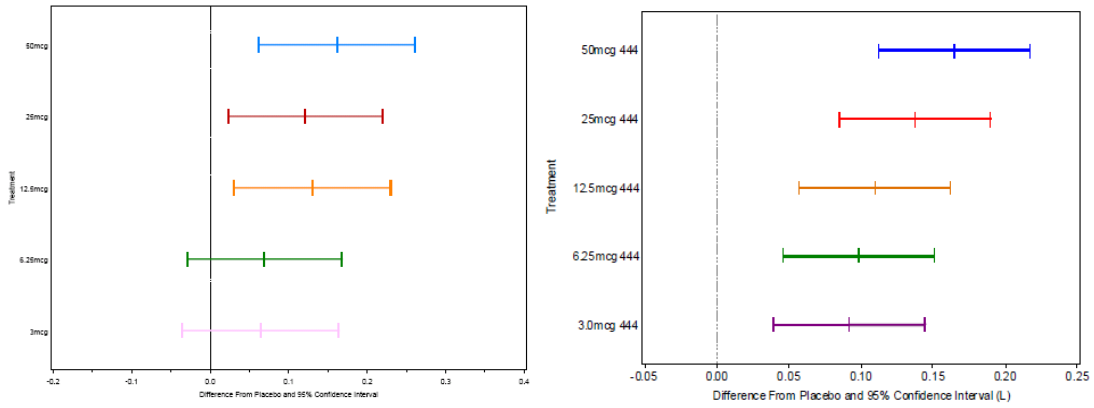

Figure 4. Adjusted treatment difference from placebo change from baseline in trough FEV1 and 95% confidence interval in liters at day 29 in patients with asthma (study 9575, left panel) and COPD (study 1045, right panel).

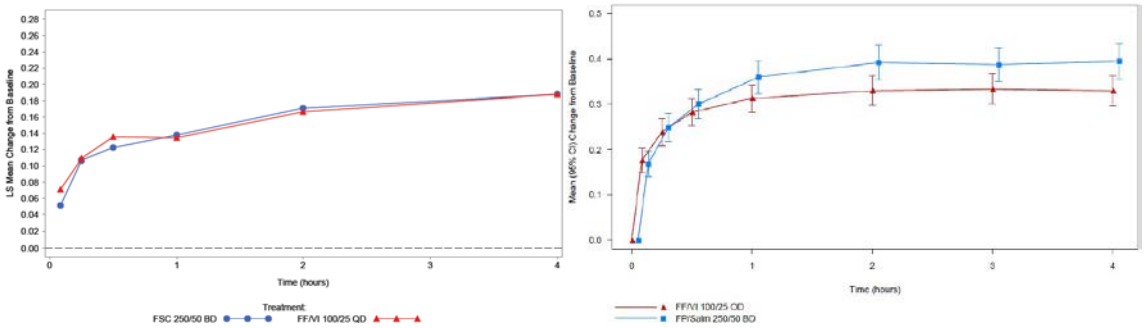

Figure 5. Mean change in FEV1 over time after the first done from COPD study 2352 (left panel) and asthma study 3091 (right panel).

The vilanterol dose regimen was investigated in study 3310 that compared once- and twice-daily dosing in patients with asthma (Table 1). The dose selected for comparison was 12.5 mcg (12.5 mcg once daily compared to 6.25 mcg twice daily), which is expected to be at the steep part of the dose-response curve, where differences between dose regimens would be easier to detect. Mean change in trough FEV1 on day 7 is shown on Figure 7. The trough FEV1 measure at day 7 suggests that vilanterol twice-daily provides a numerically better response than once-daily. The trough FEV1 with vilanterol 6.25 mcg twice daily was numerically comparable to vilanterol 25 mg once daily (Figure 7 left panel). GSK contended that the weighted mean FEV1 time response curve (measures efficacy over 24 hours rather than at trough) is a better way to compare the doses. Using the weighted mean FEV1 time response, vilanterol 6.25 mcg twice daily and vilanterol 12.5 mcg once daily was similar with LS mean differences from placebo of 166 mL and 168 mL, respectively (time response curve shown in Figure 7 right panel). As an additional analysis, the Agency's Clinical Pharmacology team generated the FEV1 time response curve for day 7 using raw FEV1 (Figure 8). The FEV1 time response curves (using either repeated measures or raw FEV1) show higher FEV1 response with higher nominal doses in the first 12 hours of dosing interval, and the curve for the 6.25 mcg twice-daily shifts upwards with the evening dose and is comparable to the 25 mcg and 12.5 mcg once-daily doses for the second 12 hours of the 24-hour interval. These results support a once-daily dosing frequency for vilanterol.

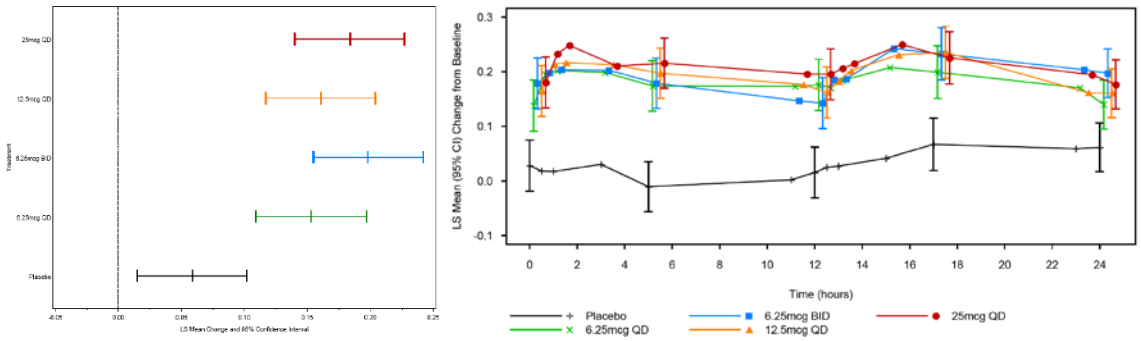

Figure 6. LS mean change in trough FEV1 on day 7 (left panel) and repeated measure adjusted mean change without placebo correction (right panel) on day 7 in patients with asthma, (vilatererol dose regimen study 3310 in asthma).

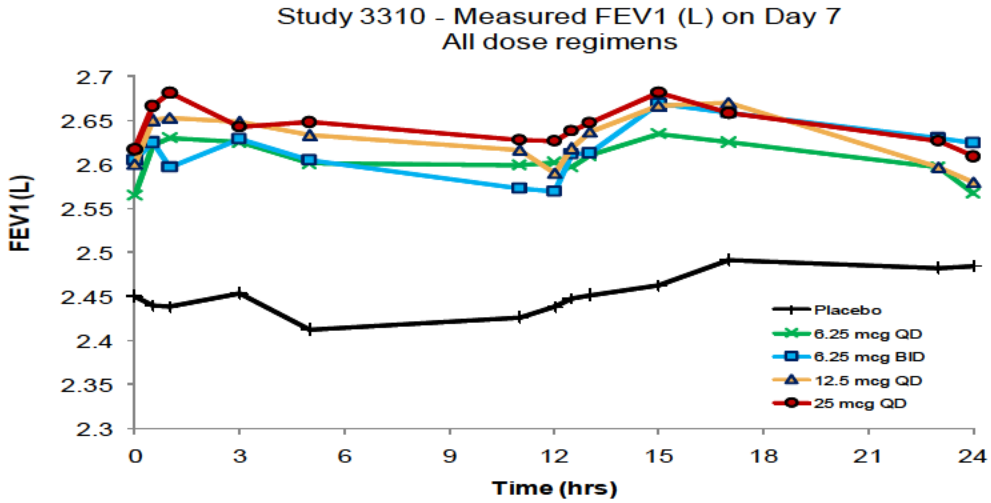

Figure 7. FEV1 time profile for 24 hours on day 7 using raw FEV1 values (vilanterol dose regimen study 3310 in asthma).

Anoro Ellipta, bronchodilator effects:

Studies 3373, 3361, 3360, and 3374 were the primary studies designed to support the bronchodilator claim for Anoro Ellipta. In all these studies there were missing data due to patient dropouts ranging from 15% to 33%. Despite the dropouts, the pre-specified primary analysis remains valid because various sensitivity analyses (that applied different missing data assumptions) were consistent in the magnitude and direction of the results with the primary analysis (applying mixed-model repeated measures method that GSK proposed, and other methods applied by GSK and FDA).

Studies conducted to support combination products compare the combination to each active component to show the contribution of each component, and also to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination to justify the use of the combination product by patients. Studies 3373, 3361, 3360, and 3374 compared Anoro to umeclidinium and to vilanterol and also compared multiple doses of Anoro (Table 2). For a combination product such as Anoro, the bronchodilation benefit will be from both umeclidinium and vilanterol.

The primary efficacy variable of trough FEV1 at day 169 is intended to show the benefit of Anoro over both single ingredients. Anoro was compared to vilanterol alone to show the contribution of umeclidinium, and Anoro was compared to umeclidinium to show the contribution of vilanterol. Results from the analysis of this primary efficacy variable showed a statistically significant difference between Anoro at both the 125/25 mcg and 62.5/25 mcg doses over each of the respective single ingredients (Table 4). The single ingredients were also statistically significantly different from placebo (Table 4). The differences between Anoro and the single ingredients and placebo were maintained over

various time points (data from one representative study for the Anoro 62.5/25 mcg dose is shown in Figure 9). Direct comparison between Anoro 125/25 mcg and 62.5/25 mcg doses are available from the two active comparator studies 3360 and 3374. These studies do not show higher bronchodilator efficacy with the higher dose of Anoro (Table 4). Trough FEV1 results from the exercise endurance studies also allowed for direct comparison between Anoro 125/25 mcg and 62.5/25 mcg doses, which also did not show higher bronchodilator efficacy with the higher dose of Anoro (Table 5). The higher Anoro 125/25 mcg dose was not consistently statistically superior to the corresponding umeclidinium 125 mcg dose (study 1337 in Table 4, and studies 4417 and 4418 in Table 5) suggesting that the addition of vilanterol 25 mcg did not provide substantial benefit over the higher 125 mcg umeclidinium dose. Replicate evidence of the contribution of each component for the Anoro 62.5/25 mcg doses are available from various sources, such as studies 3373, 3360, 3374, 4417, and 4418, which show statistically significant differences for Anoro 62.5/25 mcg over umeclidinium 62.5 mcg and vilanterol 25 mcg (Table 4, Table 5). The submitted data are adequate to support the bronchodilation claim of Anoro Ellipta.

Table 4. Bronchodilator studies; Mean change from baseline in trough FEV1 at day 169 (ITT population)

Treatment *	N	Change (L)	Diff vs comp † (95% CI)	P value	Diff vs treatment ‡ (95% CI)	P value
Study 13373 (Trial 1)						
Umec/VI 62.5/25	413	0.20	0.17 (0.13, 0.21)	<0.001	-	-
Umec 62.5	418	0.17	0.12 (0.08, 0.16)	<0.001	0.05 (0.02, 0.09)	<0.001
VI 25	421	0.08	0.07 (0.03, 0.11)	<0.001	0.10 (0.06, 0.13)	<0.001
Placebo	280	0.00	-	-	0.17 (0.13, 0.21)	<0.001
Study 13361 (Trial 2)						
Umec/VI 125/25	403	0.20	0.24 (0.20, 0.28)	<0.001	-	-
Umec 125	407	0.13	0.16 (0.12, 0.20)	<0.001	0.08 (0.05, 0.11)	<0.001
VI 25	404	0.09	0.12 (0.09, 0.16)	<0.001	0.11 (0.08, 0.15)	<0.001
Placebo	275	-0.03	-	-	0.24 (0.20, 0.28)	<0.001
Study 13360 (Trial 3)						
Umec/VI 125/25	208	0.21	0.09 (0.04, 0.14)	0.004	0.09 (0.04, 0.14)	<0.001
Umec/VI 62.5/25	207	0.21	0.09 (0.04, 0.14)	0.006	0.09 (0.04, 0.14)	<0.001
VI 25	209	0.12	0.00 (-0.05, 0.05)	0.995	-	-
Tiotropium 18	203	0.12	-	-	-	-
Study 13374 (Trial 4)						
Umec/VI 125/25	215	0.22	0.07 (0.03, 0.12)	0.003	0.04 (-0.01, 0.09)	0.142
Umec/VI 62.5/25	217	0.21	0.06 (0.01, 0.11)	0.018 §	-	-
Umec 125	222	0.19	0.04 (-0.01, 0.09)	0.138	-	-
Tiotropium 18	215	0.15	-	-	-	-

* Umec/VI = Umeclidinium and vilanterol in Ellipta; Umec = Umeclidinium in Ellipta; VI=vilanterol in Ellipta

† Diff vs comp (difference versus comparator) for studies 13373 and 13361 is from placebo, and for studies 13360 and 13374 is from tiotropium

‡ Diff (difference) for study13360 is from VI, and for study 13374 is from Umec

§ Nominal p-value. The p-values reported here do not take into account the testing hierarchy pre-specified in the statistical analysis plan. Statistical significance for this difference cannot be claimed as a result of failure of predefined testing hierarchy in the clinical trial design.

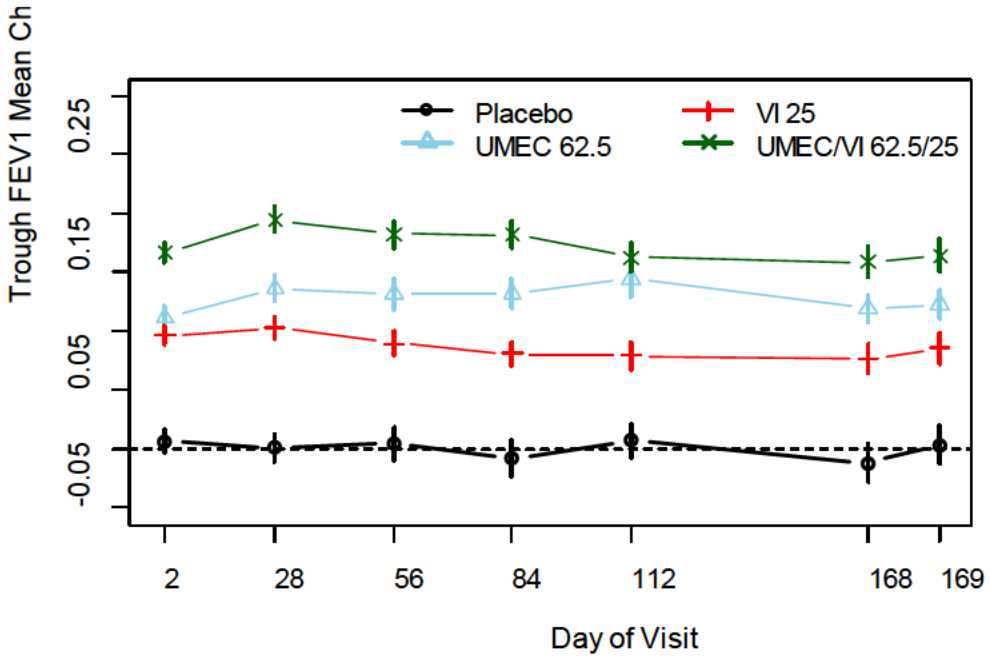

Figure 8. LS Mean change from baseline in trough FEV1 over time in study 13373 (ITT)

Table 5. Exercise endurance studies; Mean change from baseline in trough FEV1 at week 12 (ITT population)

Treatment *	N	Change (L)	Diff vs Umec † (95% CI)	P value	Diff vs VI ‡ (95% CI)	P value
Study 4417						
Umec/VI 125/25	144	0.14	0.03 (-0.03, 0.09)	0.320	0.07 (0.02, 0.12)	0.007
Umec/VI 62.5/25	152	0.18	0.12 (0.07, 0.18)	<0.001	0.11 (0.06, 0.17)	<0.001
Umec 125	50	0.11	-	-	-	-
Umec 62.5	49	0.05	-	-	-	-
VI 25	76	0.07	-	-	-	-
Placebo	170	-0.03	-	-	-	-
Study 4418						
Umec/VI 125/25	128	0.22	0.01 (-0.06, 0.07)	0.849	0.15 (0.10, 0.20)	<0.001
Umec 62.5/25	130	0.20	0.10 (0.04, 0.18)	<0.001	0.13 (0.08, 0.18)	<0.001
Umec 125	41	0.21	-	-	-	-
Umec 62.5	40	0.10	-	-	-	-
VI 25	64	0.07	-	-	-	-
Placebo	151	-0.04	-	-	-	-

* Umec/VI = Umeclidinium and vilanterol in Ellipta; Umec = Umeclidinium in Ellipta; VI=vilanterol in Ellipta
† Umec/VI 125/25 vs Umec 125, Umec/VI 62.5/25 vs Umec 62.5
‡ Umec/VI 125/25 vs VI 25, Umec/VI 62.5/25 vs VI 25

Anoro Ellipta, COPD exacerbation:

GSK is not seeking an exacerbation claim for Anoro Ellipta. While the four pivotal bronchodilator studies (Table 2) were not designed to assess COPD exacerbation, data on exacerbation were collected as an additional support of efficacy. Anoro Ellipta 62.5/25 mcg showed some numerical benefit over umeclidinium and vilanterol in some studies, but none of these findings were statistically significant.

Anoro Ellipta, shortness of breath:

(b) (4)

The SOBDA is based on daily patient recording of shortness of breath on 13 activities related to daily living. The SOBDA assessment has problems and is not fully validated. Nevertheless, the results based on SOBDA were not persuasive. Although Anoro Ellipta showed statistically significant difference from placebo in the pivotal placebo-controlled bronchodilator studies, the differences between Anoro Ellipta and umeclidinium and vilanterol were not consistent (data not shown).

Anoro Ellipta, St. George's Respiratory Questionnaire (SGRQ)

SGRQ is an important health status assessment instrument commonly used in COPD studies. All pivotal bronchodilator studies assessed SGRQ scores. There was a statistically significant difference in change in SGRQ score from baseline to assessment day 168 for both doses of Anoro Ellipta over placebo, but the threshold of 4 units (clinically meaningful improvement) was met only for Anoro 62.5/25 mcg dose with no replication from other studies. The data are not adequate to support a labeling claim for SGRQ because of lack of replication of the SGRQ results.

Anoro Ellipta, exercise endurance

GSK is not seeking an exercise endurance claims for Anoro Ellipta. Results of the two studies conducted to assess exercise endurance showed a statistically significant difference for the two primary endpoints (Table 2) between the two doses of Anoro Ellipta and placebo in study 4418, but not in study 4417 (data not shown in this review). Even in the study that showed separation between Anoro Ellipta and placebo, the effect size is questionable and did not reach the threshold originally defined by GSK. Furthermore, exercise endurance is an entity that is multi-factorial and influenced by many factors, and it is difficult to confirm that any changes noted in these studies is solely attributable to the beneficial effect of Anoro Ellipta.

8. Safety

a. Safety database

The safety assessment of Anoro Ellipta is based on studies shown in Table 1 and Table 2, and some other studies. The primary COPD safety database for Anoro is comprised of four pivotal 6-month primary efficacy COPD studies 3373, 3361, 3360, 3374, and the one-year safety study 3359 (Table 2). The safety database for Anoro was large and adequate.

b. Safety findings and conclusion

The submitted data support the safety of Anoro Ellipta for use as maintenance treatment of airflow obstruction in patients with COPD.

GSK conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[20]), common adverse events (AEs), and assessment for areas of interest such as cardiovascular safety, anticholinergic and adrenergic effects, and pneumonia.

A total of 48 deaths were reported in the COPD program. These were balanced among the treatment groups. Common causes of deaths included COPD exacerbation, respiratory failure, myocardial infarction, and cancers, which are expected causes of death in older COPD patients. Reporting of SAEs was fairly common across treatment arms, as was discontinuation from the studies. These were also balanced among the treatment causes, and the events were typical and expected in COPD patients. Common adverse events included pharyngitis, gastrointestinal disorder, anticholinergic effects, effects related to adrenergic stimulation, and lower respiratory tract infections. The patterns of SAEs and adverse events did not indicate a specific safety concern.

One safety finding of interest identified in the program because of experience with other inhaled drugs of the class (as discussed in section 2 above) was cardiovascular safety.

GSK included several prespecified evaluations to assess cardiovascular safety that included adjudication of deaths and SAEs, analysis of Major Adverse Cardiac Events (MACE), and a separate analysis of cardiovascular adverse events of special interest (AESI) that encompassed a broader set of adverse events terms.

GSK conducted two MACE analyses based on two sets of criteria. The broader criteria included all MedDRA preferred terms falling under the category of Myocardial Infarction SMQ and Other Ischemic Disease SMQ, whereas the narrow criteria specified the preferred terms of "Acute Myocardial Infarction" and "Myocardial Ischemia." The analyses were performed on a pooled ITT population from all COPD studies with treatment duration of at least 12 weeks, with rates adjusted based on duration of

[20] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

exposure. As shown in Table 9, the numbers of patients with MACE events were relatively low across treatment arms, and the exposure-adjusted rates did not suggest an increased risk of MACE events in the active treatment arms compared to placebo. One difference of note was for non-fatal MI between placebo and Anoro 62.5/25 mcg, which was due to 1 versus 3 events in the two treatment groups. Analysis of AESI (included terms used in MACE, and other terms such as long QT, cardiac arrhythmia, cardiac failure, and hypertension) also did not suggest an increased risk of events in the active treatment arms compared to placebo (data not shown in this review). Analysis of cardiovascular SAEs showed an imbalance that favored placebo over active treatments in the primary efficacy studies, but not in all studies (Table 10).

Table 6. MACE analysis, Studies included are: 12-week dose ranging study (115408), 24-week bronchodilator efficacy and safety studies (113373, 113361, 113360, 113374), 12 week exercise endurance efficacy and safety studies (114417, 114418), and 52 week safety study (113359)

	Placebo	Umec/VI 62.5/25	Umec/VI 125/25	Umec 62.5	Umec 125	VI 25	Tio * 18
	N=1053 SY=369	N=1124 SY=408	N=1330 SY=573	N=576 SY=202	N=1016 SY=449	N=1174 SY=441	N=173 SY=173
Total MACE events	Number of events						
Broad-definition MACE †	22	16	22	11	15	18	6
Narrow-definition MACE †	8	5	6	2	7	8	1
Incidence Rate	Number of Subjects with Events per 1000 Subject-Years (SY)						
Broad-definition MACE	54.3	36.8	38.4	44.5	31.2	38.5	34.7
Narrow-definition MACE	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Adjudicated CV death	5.4	4.9	0	0	2.2	4.5	0
Non-fatal cardiac ischemia	38.0	31.9	33.2	39.5	24.5	27.2	28.9
Non-fatal MI	2.7	7.4	5.2	4.9	8.9	4.5	0
Non-fatal stroke	10.9	0	5.2	4.9	4.5	9.1	5.8

* Umec/VI = Umeclidinium and vilanterol in Ellipta; Umec = Umeclidinium in Ellipta; VI = vilanterol in Ellipta; Tio=Tiotropium in Spiriva HandiHaler
† Broad definition used the larger "cardiac ischemia special interest" adverse events, whereas the narrow definition used the preferred terms "myocardial infarction" and "myocardial ischemia"

Table 7. Adjudicated cardiovascular SAEs, number of events (incidence rate per 1000 patient-years)

	Placebo	Umec/VI *	Umec	VI	Tio
All efficacy and safety studies †	9 (27)	23 (25)	20 (32)	15 (35)	2 (12)
Primary efficacy and safety studies ‡	3 (14)	18 (26)	15 (36)	15 (37)	2 (12)

* Umec/VI = includes both 62.5/25 and 125/25 umeclidinium and vilanterol groups; Umec = includes both 62.5 and 125 umeclidinium groups; VI = vilanterol in Ellipta; Tio=Tiotropium in Spiriva HandiHaler
† Studies included are: 12-week dose ranging study (115408), 24-week bronchodilator efficacy and safety studies (113373, 113361, 113360, 113374), 12 week exercise endurance efficacy and safety studies (114417, 114418), and 52 week safety study (113359)
‡ Studies included are: 24-week bronchodilator efficacy and safety studies (113373, 113361, 113360, 113374)

While there were some imbalances seen in these analyses, as noted above, several features of the data decrease concern. In the MACE analyses, the imbalance in the narrow category of non-fatal myocardial infarction was not borne out in broader category

of non-fatal cardiac ischemia. In the cardiovascular SAE analyses, the imbalance noted in the primary efficacy studies was not borne out in the larger analysis set of all studies. The imbalances identified were not seen in the long-term safety study. It would be reasonable to expect that a signal of increased cardiac ischemia, if it represents a true risk, would be observed not just in the primary efficacy studies, but also in the pooled analyses of all studies, or in the long-term safety study. However, limitations of this reasoning are that the total number of events across all studies was small, and a large number of patients were withdrawn from the long-term safety study due to abnormalities on ECGs and on 24-hour Holter monitoring. The outcome of these patients after withdrawal in terms of safety is unknown. Nevertheless, the overall cardiovascular safety profile for Anoro, vilanterol, and umeclidinium as assessed from the safety analyses are reassuring and do not rise to a level that would preclude approval. In general, cardiovascular safety analyses based on the integrated COPD study database and the long-term safety trial were mostly unremarkable, including evaluations for death and MACE-related events, and the total number of cardiovascular-related events in the program was fairly low. Inhaled LABAs have known cardiovascular effects and all product labels of this class of drugs have language in the Warnings and Precautions sections of these labels. The Anoro label will also carry similar labeling language. The findings seen in the studies will be described in the label.

A dedicated post-marketing controlled randomized safety trial (under the provision of the Federal Food, Drug, and Cosmetic Act, Section 505(o)(3)) is not necessary to further explore the cardiovascular safety of Anoro Ellipta. The safety database for Anoro Ellipta is sufficient and there is no consistent pattern for the few imbalances in cardiovascular events. Also UPLIFT (described in section 2 above) was reassuring for another inhaled anticholinergic, tiotropium. The product label will include information on the imbalances identified in the clinical development program.

Asthma exacerbation and asthma-related deaths with LABA are safety concerns for patients with asthma. While a similar safety concern has not been seen in COPD, the clinical experience with vilanterol in asthma is of interest as secondary safety information and as selection of the appropriate dose. GSK provided a summary of safety data from the asthma development program for Breo Ellipta (fluticasone furoate and vilanterol). The summary included an analysis of a composite safety endpoint for asthma-related hospitalizations, intubations, and deaths, which did not suggest an increased risk of severe asthma-related adverse events associated with vilanterol alone or in combination with fluticasone furoate. The asthma safety data related to vilanterol from the Breo Ellipta program also applies to Anoro Ellipta.

c. REMS/RiskMAP

GSK submitted a Risk Management Plan for Anoro Ellipta, which consists of routine pharmacovigilance practices. A REMS is not necessary for Anoro Ellipta. The product will have a Medication Guide to inform patients about the risk of asthma related deaths with LABAs.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on September 10, 2013, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indications of airflow obstruction, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for Anoro Ellipta 62.5/25 mcg once daily for the proposed indications. In general, the panel members concluded that there were sufficient data to support the efficacy of Anoro for the proposed indication of airflow obstruction. On voting questions, the Committee voted favorably regarding whether there was substantial evidence of efficacy for airflow obstruction in COPD (13 yes, 0 no, 0 abstain), and whether the safety of Anoro had been adequately demonstrated (10 yes, 3 no, and 0 abstain). Regarding the approvability question, which is essentially the sum of the demonstration of efficacy and safety, the results were in favor of approval for airflow obstruction in COPD (11 yes, 2 no, 0 abstain). The Committee expressed some concerns with safety assessment in the program, noting the small number of cardiovascular safety events in the program, the limited number of patients with cardiovascular risks factors from the studies, and withdrawal of patients from the studies due to abnormalities on ECGs and on 24-hour Holter monitoring. Some Committee members expressed interest in obtaining more safety data, particularly in sicker COPD patients with cardiovascular risks, but did not express a consensus view of what type of safety study would be desirable and what would be the comparative arms in such a study.

10. Pediatric

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

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two clinic representative sites in the pivotal COPD studies 3373 and 3361. The clinical and statistical review teams recommended the sites because these sites enrolled larger number of patients compared to other sites, had a large percentage of patient dropouts, and had a large efficacy trend. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. There were deviations from GCP for one investigator site, but FDA review determined that this did not impact the overall findings. With the exception, of this single site, all studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. One investigator had significant financial interest in GSK. The number of subjects enrolled in the investigator

site was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

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

12. Labeling

a. Proprietary Name

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

b. Physician Labeling

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

c. Carton and Immediate Container Labels

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

d. Patient Labeling and Medication Guide

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

13. Action and Risk Benefit Assessment

a. Regulatory Action

GSK has submitted adequate data to support approval of Anoro Ellipta (umeclidinium 62.5 mcg mcg and vilanterol 25 mg inhalation powder) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), at the dose of one inhalation (umeclidinium 62.5 mcg and vilanterol 25 mcg) once daily. The recommended regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Anoro Ellipta inhalation powder at a dose of one inhalation (umeclidinium 62.5 mcg and vilanterol 25 mcg) once daily for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

A major safety concern with vilanterol is linked to the selection of an appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators. GSK conducted a comprehensive program, including dose ranging through pivotal confirmatory studies, to select the 25 mcg once daily dose for the Breo combination product. The same dose is appropriate for the Breo Ellipta and Anoro Ellipta combination products. The safety concerns with umeclidinium, similar to other anticholinergics, are the risk of cardiovascular adverse events, and systemic anticholinergic adverse events at high doses. GSK conducted adequate dose ranging studies for umeclidinium and selected 125 mcg and 62.5 mcg doses for the pivotal studies. Based on the overall data, GSK proposed 62.5 mcg umeclidinium for the Anoro Ellipta combination product. The final proposed doses of 25 mcg for vilanterol and 62.5 mcg for umeclidinium are reasonable and supported by the submitted data. The safety profile of Anoro 62.5/25 mcg was acceptable. The major safety findings were related to cardiovascular safety, anticholinergic effects, and effects related to adrenergic stimulation. These are known safety risks of these classes of drugs, and seemed to occur at frequencies comparable to other products of the class approved for COPD. The efficacy data submitted were adequate to support the indications of maintenance of airflow obstruction in COPD patients. Anoro showed benefit over umeclidinium alone and over vilanterol alone in bronchodilation that was supported by other efficacy measures. The efficacy data showed contribution of each component present in Anoro, and also showed that Anoro provides a clinically meaningful benefit over each single ingredient present in the combination.

c. Post-marketing Risk Management Activities

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

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
11/26/2013