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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	April 30, 2014
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	20-5382
Applicant Name:	GlaxoSmithKline
Date of Submission:	April 30, 2013
PDUFA Goal Date:	April 30, 2014
Proprietary Name:	Incruse Ellipta
Established Name:	Umeclidinium
Dosage form:	Inhalation Powder (inhaler contains a foil blister strip with 30 blisters containing powder for oral inhalation)
Strength:	Umeclidinium 62.5 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 Incruse Ellipta (umeclidinium 62.5 mcg) 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) once daily. Umeclidinium is an anticholinergic agent, and is available for use in combination with vilanterol, a long-acting beta-agonist, in the same Ellipta device and marketed as Anoro Ellipta (NDA 20-3975, approved in December 2013). The program supporting the Incruse Ellipta program was largely encompassed in the application for Anoro Ellipta because in order to develop the Anoro Ellipta combination product for COPD, GSK needed to develop the individual components as well. So the data in support of this Incruse Ellipta application has largely been reviewed in the previous review for the Anoro Ellipta under NDA 20-3975. 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.

Incruse Ellipta is a new inhalation product comprised of the long-acting anticholinergic umeclidinium. As mentioned above, umeclidinium is approved for marketing in the US in combination with vilanterol, a long-acting beta-agonist, in the same Ellipta device as Anoro Ellipta. The data necessary to support the Incruse Ellipta product was largely encompassed in the submission that supported approval of Anoro Ellipta. In the subsequent sections of this review, safety issues related to other anticholinergic drug class for COPD are discussed, followed by a discussion of regulatory interaction between the Agency and GSK related to this application.

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 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 a 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.

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[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

[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.

Prior to the publication of the TIOSPIR results, another long-acting anticholinergic, aclidinium bromide (Tudorza Pressair) was approved for COPD.[6] The approval letter dated July 23, 2012, identified major cardiovascular adverse events as a potential safety signal and outlined a required post-marketing study (PMR study) to evaluate the risk of these events in patients with COPD. The FDA reviews noted that while the actual number of MACE events was low in the Tudorza program, the overall size of the safety database was relatively small compared to other COPD development programs, patients with cardiovascular history were excluded, and pending the results of the ongoing TIOSPIR trial, uncertainty remained regarding cardiovascular adverse events and stroke for this drug class. Therefore, a PMR to expand the safety database and further evaluate cardiovascular safety in an enriched population with cardiovascular risk factors was deemed to be reasonable and was generally consistent with the recommendations of the PADAC meeting convened earlier in February 2013 to discuss the aclidinium program.

The available evidence regarding cardiovascular safety for the drug class and for the Anoro Ellipta (umeclidinium and vilanterol) product was discussed at the September 2013 Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting and at a subsequent CDER Regulatory Briefing. While small imbalances in the Anoro Ellipta safety database were observed, most notably for nonfatal myocardial infarctions, the review concluded that the clinical program was adequate to support safety without further post-marketing safety trials. Unlike the aclidinium development program, the Anoro Ellipta program did not exclude patients with a history of cardiovascular disease. Cardiovascular safety analyses based on the pooled COPD trials of 12-weeks' duration or longer (integrated COPD database) were mostly unremarkable, including evaluations for death and other MACE events (ischemia/infarction, stroke, and cardiovascular death), and the total number of cardiovascular-related events in the program was fairly low. Based on the totality of the evidence, further post-marketing safety studies were not requested for the Anoro Ellipta product.

Regulatory interaction between the Agency and GSK:

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

- 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.
- 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.

[6] July 23, 2012, Approval Letter, accessed from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000Approv.pdf

- 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.
- Anoro Ellipta for COPD approved on December 17, 2013.

3. Chemistry, Manufacturing, and Controls

The product Incruse Ellipta (umeclidinium 62.5 mcg inhalation powder) includes a dry powder inhaler device, the Ellipta inhaler, which contains a foil blister strip with 30 blisters. Each blister contains micronized umeclidinium bromide (74.2 mcg equivalent to 62.5 mcg umeclidinium), magnesium stearate, and lactose monohydrate. The lactose monohydrate may contain trace amounts of milk proteins. The proposed commercial presentation of Incruse Ellipta has 30 blisters of umeclidinium, 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 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 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.

Incruse 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. Incruse Ellipta should be discarded after all doses are used or 6 weeks after removal from the protective package, whichever comes first.

The drug substance is manufactured at a GSK facility in (b) (4) and drug product including the Incruse Ellipta device is assembled at a GSK facility in (b) (4). 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.

4. Nonclinical Pharmacology and Toxicology

GSK submitted results from a full preclinical program to the Agency. The program included studies that assessed the general toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity of umeclidinium. In general, these studies showed that umeclidinium possessed a toxicity profile typical of its pharmacological class.

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, rats, and dogs,

respectively. These studies identified the lungs, tracheal bifurcation, larynx, nasal turbinates, and heart as target organs of toxicity. There were adequate margins of safety between doses that induced 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 did not have any effects on pre- or post-natal development 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. The majority of studies were conducted in healthy volunteers, but several studies were done specifically to assess pharmacokinetics in COPD patients and the effects of renal and hepatic impairment. Umeclidinium has low oral bioavailability and systemic exposure is primarily due to absorption of the inhaled portion. Following inhaled administration, Cmax of umeclidinium occurred at 5 to 15 minutes. The primary metabolic pathway for umeclidinium is CYP2D6. No clinically meaningful difference in systemic exposure to umeclidinium was observed following repeat daily inhaled dosing in CYP2D6 normal and poor metabolizing subjects. The drug-drug interaction potential for umeclidinium is low when administered by the inhaled route and no specific dose adjustments are recommended when umeclidinium 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. Table 1 summarizes the main studies conducted to support dose selection and dosing frequency for umeclidinium. Table 2 summarizes the main studies conducted to support umeclidinium in COPD. 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

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%)

* 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;
§ 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 Incurse Ellipta (umeclidinium 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
115408 Trial 2	- ≥ 40 yr - COPD	Umec 125 mcg QD Umec 62.5 mcg QD	69 69	ΔFEV_1 trough at day 85	US (23%), Germany, Japan

ID Year*	**Study Characteristics † - Patient age - Patient characteristics - Study design,objective - Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variable ¶**	**Regions and Countries //**
[July 2011 - Feb 2012]	- PG, placebo controlled - 12 weeks	Placebo	68		
113361 [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
113374 [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 Incruse 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
§ 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) 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 evaluated 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.

Pivotal bronchodilator (or lung function) studies (studies 3373 and 5408); and other bronchodilator (or lung function) studies (studies 3361 and 3374) 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, [7] with post-bronchodilator FEV1 of ≤70% predicted, a post-bronchodilator FEV1/FVC ratio of ≤0.70, and a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC). Eligible patients entered a 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 Incruse Ellipta 62.5 mcg once-daily (umeclidinium 62.5 mcg) for bronchodilation in patients with COPD.

[7] 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.

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).

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. 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 pivotal efficacy and safety studies.

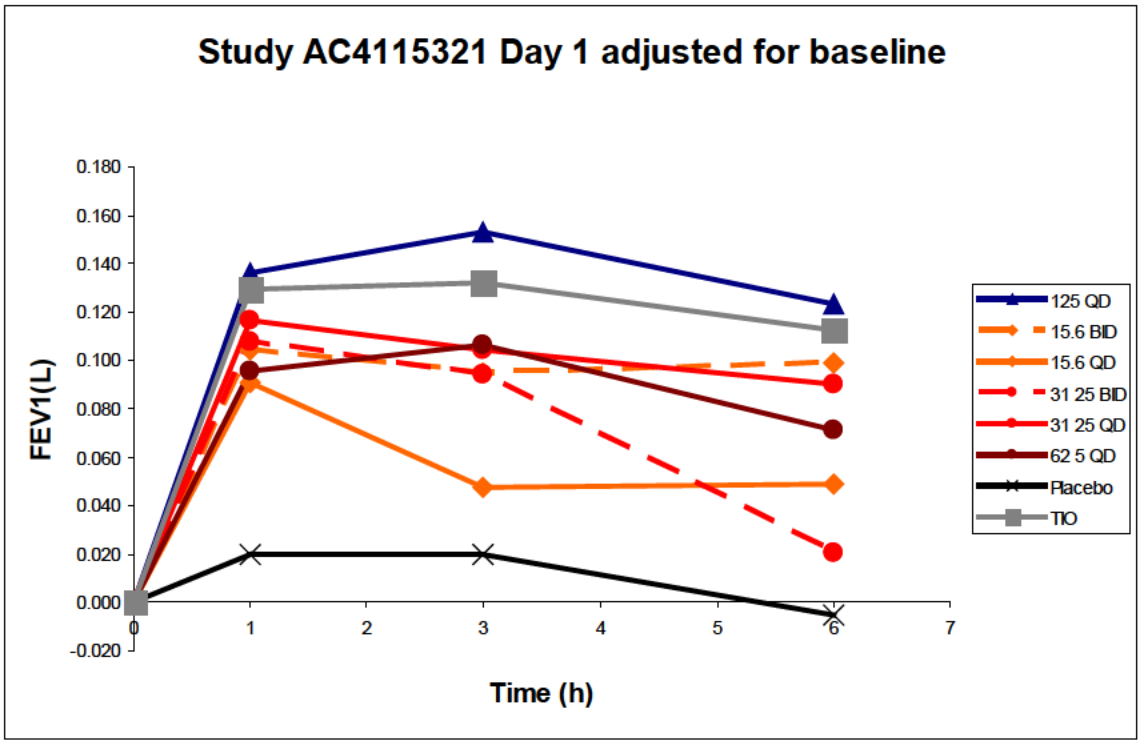

Figure 1. Adjusted mean change from baseline in FEV1 over time on day 1, study 5321

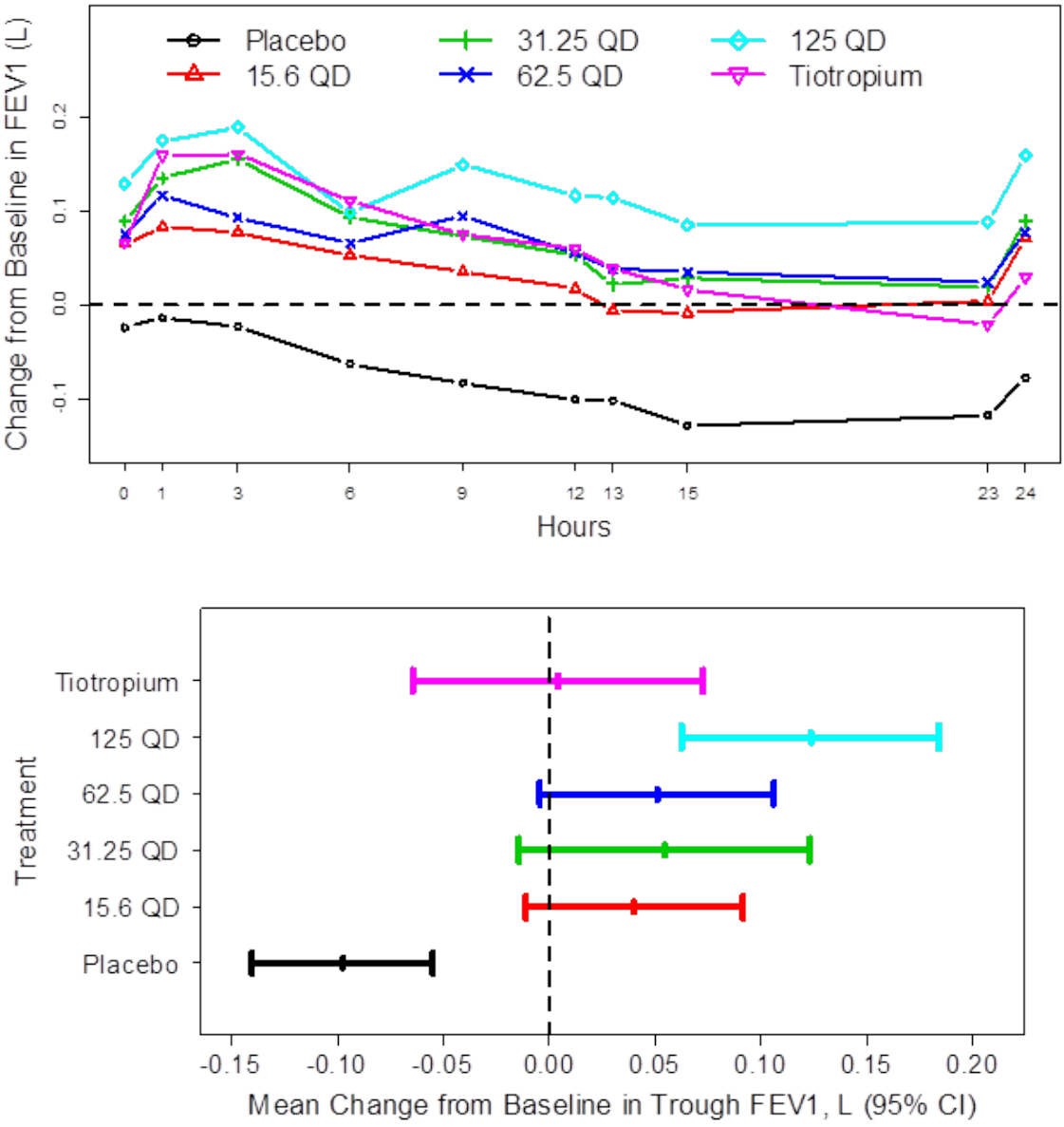

Figure 2. Post-dose 24-hour serial mean change from baseline in FEV1 on day 7 (top panel) and mean change from baseline in trough FEV1 on day 8 (bottom panel) for once-daily umeclidinium (125 mcg, 62.5 mcg, 31.25 mcg, 15.6 mcg), tiotropium (18 mcg), and placebo, Study 5321.

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 3), which did not suggest that twice-daily was preferable to once-daily dosing. These data support 62.5 mcg once-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 pivotal efficacy and safety studies.

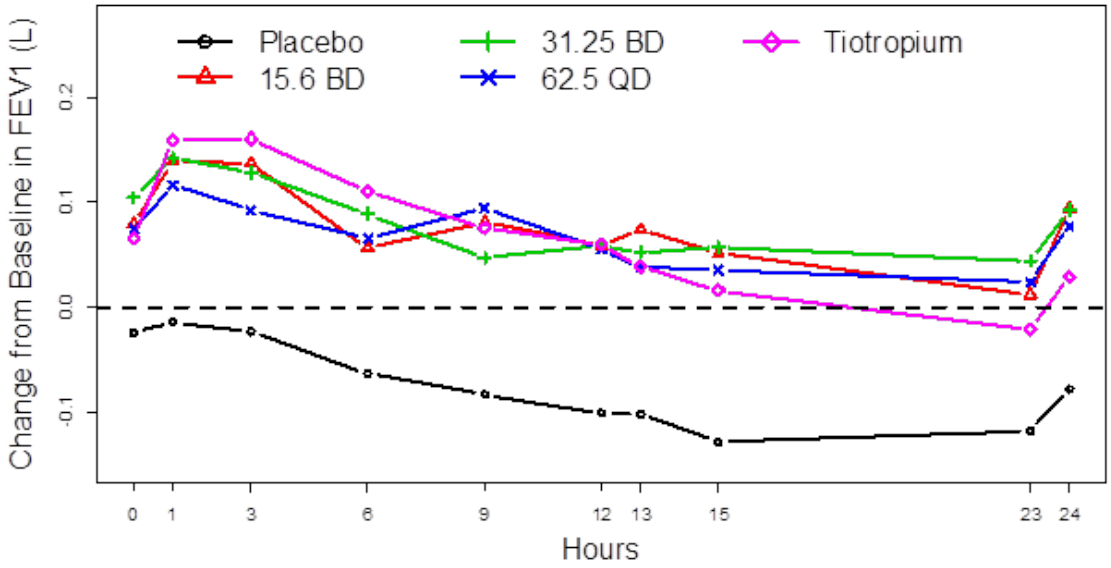

Figure 3. Post-dose 24-hour serial mean change from baseline in FEV1 on day 7 for once-daily and twice daily umeclidinium (62.5 mcg once-daily, 31.25 mcg twice-daily, and 15.6 mcg twice-daily), and tiotropium (18 mcg once-daily), Study 5321.

Incruse Ellipta, bronchodilator effects:

Studies 3373 and 5408 were the primary studies that support the bronchodilator claim for Incruse Ellipta, and studies 3361 and 3374 provide supporting evidence. In 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 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).

The primary efficacy variable of trough FEV1 at the primary analysis time point is intended to show the benefit of Incruse over placebo. Results from the analysis of this efficacy variable showed a statistically significant difference between Incruse and placebo (Table 3, and Table 4). The differences between the treatment arms were maintained over various time points (data from one representative study is shown in Figure 8). Results from study 5408 (Table 3) and 3373 (Table 4) provide replicate evidence of statistically significant difference between umeclidinium 62.5 mcg once-daily and placebo.

The umeclidinium 62.5 mcg appears to be the optimum dose for COPD. Direct comparison between the 62.5 mcg and 125 mcg dose did not show much separation between the doses (Table 3). Comparison between the 62.5 mcg and 125 mcg umeclidinium doses were also available from the Anoro combination product studies where the dose of umeclidinium varied and the dose of vilanterol was the same. In these studies, Anoro 125/25 did not show higher bronchodilator efficacy compared to Anoro 62.5/25 (data from study 3374 is shown in Table 4).

Table 3. Mean change from baseline in trough FEV1 at day 85, Study 5408 (Trial 2)

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		

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						
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 13374						
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.

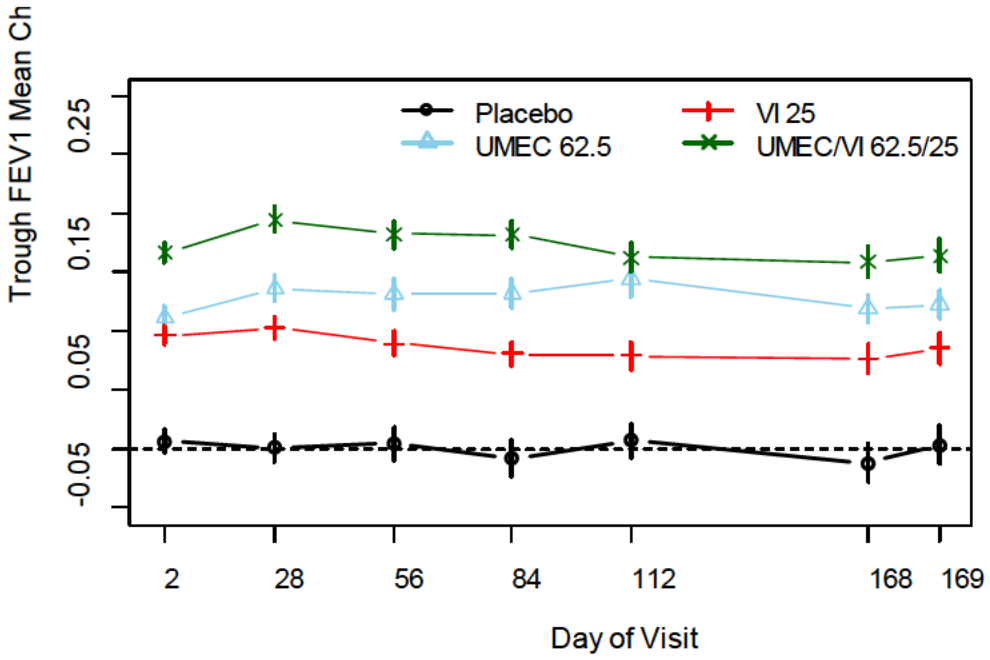

Figure 4. LS Mean change from baseline in trough FEV1 over time in study 13373 (ITT)

Incruse Ellipta, COPD exacerbation:

GSK is not seeking an exacerbation claim for Incruse Ellipta. While the bronchodilator studies (Table 2) were not designed to assess COPD exacerbation, data on exacerbation were collected as an additional support of efficacy. Incruse Ellipta 62.5 mcg showed some numerical benefit over placebo, but these findings were not consistently statistically significant.

Incruse Ellipta, (b) (4)

(b) (4)

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

SGRQ is a health status assessment instrument commonly used in COPD studies. There was a statistically significant difference in change in SGRQ score from baseline to predefined assessment day for umeclidinium 62.5 mcg over placebo in studies 3373 and 5408 and the threshold of 4 units (clinically meaningful improvement) was met. However, the benefit was not consistent in study 3361, which evaluated the umeclidinium 125 mcg dose. Also, the result in study 5408 is notable for marked worsening in the placebo group, which drives the treatment difference.

Incruse Ellipta, exercise endurance:

GSK is not seeking an exercise endurance claims for Incruse Ellipta. 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 are solely attributable to the beneficial effect of Incruse Ellipta.

8. Safety

a. Safety database

The safety assessment of Incruse Ellipta is based on studies shown in Table 1 and Table 2, and some other studies. The safety database for Incruse was large and adequate.

b. Safety findings and conclusion

The submitted data support the safety of Incruse 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[8]), 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.

[8] 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.

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 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 5. 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 6. 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 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 the labels. (b) (4) 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 Incruse Ellipta. The safety database for Incruse 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. As discussed in section 3 above, based on the totality of the evidence, further post-marketing safety studies were not requested for the Anoro Ellipta combination product.

c. REMS/RiskMAP

(b) (4) A REMS is not necessary for Incruse Ellipta.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application as the umeclidinium data were discussed in the context of the September 10, 2013, meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) for Anoro Ellipta.

10. Pediatric

GSK is requesting a claim for Incuse 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. OSI Audits

OSI audited two clinic representative sites in the pivotal COPD studies 3373 and 3361 during review of the Anoro Ellipta application. 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 originally proposed (b) (4) Ellipta as the proprietary name, which was not accepted by DMEPA. GSK later submitted Incruse 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. 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

Incruse Ellipta will carry a patient labeling to help safe use of the product. There will be no Medication Guide for Incruse Ellipta.

13. Action and Risk Benefit Assessment

a. Regulatory Action

GSK has submitted adequate data to support approval of Incruse Ellipta (umeclidinium 62.5 mcg 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) once daily. The recommended regulatory action on this application is Approval.

b. Risk-Benefit Assessment

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

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 Incruse Ellipta product. The proposed dose and once-daily dosing regimen and supported by the submitted data. The dose and dosing regimen for umeclidinium in Incruse Ellipta is same as that for umeclidinium the combination product Anoro Ellipta. The safety profile of Incruse Ellipta 62.5 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. Incruse Ellipta showed benefit over placebo in bronchodilation that was supported by other efficacy measures.

c. Post-marketing Risk Management Activities

No post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
04/30/2014