CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205382Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	March 25, 2014
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	205-382, SN00
Applicant	GlaxoSmithKline (GSK)
Date of Submission	April 30, 2013
PDUFA Goal Date	April 30, 2014
Proprietary Name / Established (USAN) names	Incruse Ellipta/umeclidinium inhalation powder
Dosage forms / Strength	Umeclidinium 62.5 mcg once daily
Proposed Indication(s)	1. Long-term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	*Approval*

1. Introduction

On April 30, 2013, GlaxoSmithKline (GSK) submitted a 505(b)(1) New Drug Application (NDA 205-382) for umeclidinium inhalation powder, proposed at a dose of 62.5 mcg for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema The proposed tradename is Incruse Ellipta.

Umeclidinium (UMEC) is a novel long-acting antimuscarinic agent (LAMA) and a new molecular entity. UMEC is supplied as a dry powder inhalation formulation administered by the Ellipta inhaler device. It is also available for use in combination with vilanterol (VI), a long-acting beta-agonist (LABA) in the same Ellipta device and was recently approved in December 2013 under a separate NDA (Anoro Ellipta, NDA 203-975). To support the 62.5 mcg once daily dose for the proposed indication, GSK conducted a clinical program that included dose-ranging trials of varying duration for the individual components, two 6-month, placebo-controlled efficacy and safety trials, two 6-month, active-controlled efficacy and safety trials, and a 12-month safety trial.

The UMEC application is distinctive in that the related marketing application for UMEC/VI for the same COPD indication was submitted first and has already been reviewed and discussed at an Advisory Committee Meeting on September 10, 2013. In order to develop UMEC/VI, GSK was required to development the individual components as well, so the review of UMEC/VI encompassed the review of UMEC as a monotherapy. Therefore, the data in support of UMEC for the proposed indication has largely been reviewed in previous reviews completed for UMEC/VI under NDA 203-975. This CDTL review briefly

summarizes the development program for UMEC and the major conclusions of each of the review disciplines, focusing primarily on the secondary labeling claims which are unique to the UMEC product.

2. Background

Several drug classes are available for the treatment of COPD. These include beta-adrenergic agonists, combination products containing long-acting beta-adrenergic agonists and corticosteroids, anticholinergic agents, combination products containing anticholinergic and beta-adrenergic agonists, methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. With the exception of methylxanthines and PDE4 inhibitors, these are all inhalation products.

Inhaled anticholinergics are widely used in the US and worldwide. In the US, a short-acting anticholinergic, ipratropium bromide, has been approved as a bronchodilator for patients with COPD since 1986. Two long-acting anticholinergics are currently marketed in the US, tiotropium bromide (Spiriva Handihaler) and aclidinium bromide (Tudorza Pressair). Common anticholinergic adverse effects include dry mouth, constipation, and urinary retention. Anticholinergic agents can also cause tachycardia, but this effect is not prominent with approved inhaled products, and current class labeling for LAMAs does not mention cardiovascular safety specifically.

However, the issue of cardiovascular safety and stroke risk and LAMAs in COPD has become a topic of interest in recent years. In the US, a short-acting anticholinergic, ipratropium bromide, has been approved as a bronchodilator for patients with COPD since 1986. Two long-acting anticholinergics are currently marketed in the US, tiotropium bromide (Spiriva Handihaler) and aclidinium bromide (Tudorza Pressair). Safety concerns regarding a possible increased risk of stroke, cardiovascular death, and myocardial infarction (MI) associated with inhaled anticholinergic use were raised following a meta-analysis of 17 clinical trials in COPD,[1] [2] [3] but other data have been reassuring in terms of safety. A large, 4-year, randomized, controlled trial (Understanding Potential Long-Term Impacts on Function with Tiotropium; UPLIFT) with pre-specified safety endpoints did not show any increased mortality risk with Spiriva Handihaler compared to placebo.[4] The UPLIFT results were discussed at a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting held on November 19, 2009. Given the strength of the UPLIFT study design and findings, the committee and the Agency subsequently concluded that the available data did not support an increased risk of stroke, myocardial infarction, or death associated with Spiriva Handihaler.[5]

Cardiovascular safety concerns were also raised with an alternate tiotropium formulation delivered by the Respimat device, which is not approved in the US. In the development

[1] Singh S, Loke YK, Furberg CD. JAMA 2008; 300: 1439-50.
[2] Lee TA, Pickard S, et al. Annals of Internal Medicine 2008; 149: 380-390.
[3] FDA Early Communication dated October 7, 2008.
http://www fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/drugsafetyinformationforheathcareprofessionals/ucm070651.htm
[4] Tashkin DP, Celli B, Senn S, et al. N Engl J Med 2008; 359: 1543-54.
[5] Michele TM, Pinheiro S, Iyasu S. N Engl J Med 2010; 363:1097-99.

program, three, 1-year, placebo-controlled trials of tiotropium Respimat showed a numerical imbalance in all-cause mortality over placebo, without any consistent cause of death. Based upon this information, FDA did not approve tiotropium Respimat. Meta-analysis of the tiotropium Respimat data showed a significant increase in mortality compared to placebo, which led some to request withdrawal of tiotropium Respimat from the market in the UK and other countries.[6] [7] To characterize the safety of tiotropium Respimat further, the manufacturer conducted a large, prospective safety trial with feedback from DPARP in 17,135 patients with COPD (Tiotropium Safety and Performance in Respimat trial; TIOSPIR) to compare tiotropium Respimat with Spiriva HandiHaler, which the Agency had concluded did not have an increased risk of stroke, MI, or death. According to the September 2013 article published in the New England Journal of Medicine, Respimat was noninferior to HandiHaler with respect to death (hazard ratio 0.96, 95% CI [0.87, 1.14]), and reported causes of death and the incidence of major cardiovascular adverse events (MACE) were similar in patients who received tiotropium Respimat 2.5 mcg or 5 mcg versus tiotropium HandiHaler 18 mcg.[8] These results appear reassuring, although they have yet to be reviewed by the Agency.

Prior to the publication of the TIOSPIR results, another LAMA, aclidinium bromide (Tudorza Pressair) was approved for COPD.[9] The approval letter dated July 23, 2012, identified major cardiovascular adverse events as a potential safety signal and outlined a PMR to conduct a randomized, controlled trial 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. However, it is worth noting that the recommendation for a PMR was not universal, including dissenting opinions expressed by one of the statisticians on the PADAC and the internal cardiology consult obtained from the Division of Cardiovascular and Renal Products.

The available evidence regarding cardiovascular safety for the drug class and for the UMEC/VI product was discussed at the September 2013 PADAC meeting and at a subsequent Regulatory Briefing. While small imbalances in the UMEC/VI safety database were observed, most notably for nonfatal myocardial infarctions, the review concluded that the clinical program was adequate to support safety without further postmarketing safety trials. Unlike the aclidinium development program, the UMEC/VI program did not intentionally 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,

[6] Singh S et al. BMJ 2011; 342:d3215.
[7] Beasley R et al. BMJ 2012; 345: e7390.
[8] Wise RA et al. N Engl J Med Aug 2013 (Epub ahead of print).
[9] July 23, 2012, Approval Letter, accessed from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000Approv.pdf

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 postmarketing safety studies were not requested for the UMEC/VI product.

The issues surrounding the concurrent development of UMEC, VI, and UMEC/VI have been the subject of extensive discussion with GSK, as described in the next section. GSK was asked to provide data to support the nominal dose and dosing frequency for each of the components, as well as efficacy and safety data to support the use of UMEC and VI alone in COPD. These data were viewed as necessary for evaluating the UMEC/VI combination, in addition to data to support the added benefit of UMEC/VI over either component alone (the relative contribution of each individual component).

Relevant Regulatory History for UMEC/VI

GSK studied several different doses and formulations UMEC in its COPD development program. As mentioned in the Introduction, the program for UMEC overlapped with the development of UMEC/VI and FF/VI, so many of the regulatory interactions encompassed one or more components and combinations as well as both asthma and COPD indications. The following timeline highlights the major discussions that occurred during clinical development:

- **June 4, 2009, Pre-IND meeting for UMEC (IND 104,479):** Discussed the need for adequate demonstration of efficacy and safety for individual components in addition to the proposed UMEC/VI combination and the preliminary plans for evaluation of the nominal dose and dosing frequency.
- **October 29, 2010, End-of-Phase 2 meeting for UMEC/VI (IND 106,616):** Based on the information available at the meeting, the Division was unable to confirm the proposed UMEC 125 mcg dose and noted that lower doses may be efficacious. The Division stated that additional data were required to support nominal dose selection and the proposed once-daily dosing frequency for UMEC. Demonstration of a dose response would be useful, particularly in light of ongoing concerns regarding anticholinergic safety in COPD. The Division also noted that while the proposed trough FEV1 endpoint was acceptable, other spirometric parameters would be considered.
- **December 17, 2010, Written communication (IND 106,616)** regarding Phase 3 trial design for UMEC/VI. The Division stated that replicate evidence of safety and efficacy for UMEC as a stand-alone product would be required.
- **January 18, 2012, Pre-NDA meeting for UMEC/VI (IND 106,616):** The Division reiterated that replicate evidence of efficacy and safety for UMEC and VI and for the UMEC/VI combination compared to each monocomponent would be required.
- **December 18, 2012, NDA submission for UMEC/VI 125/25 mcg and 62.5/25 mcg (NDA 203975):** While two dose levels of UMEC/VI were initially submitted, GSK later revised its application and proposed UMEC/VI 62.5/25 only, noting that there were insufficient efficacy data to distinguish the two dose levels.
- **April 30, 2013, NDA submission for UMEC 62.5 mcg (NDA 205382)**
- **December 17, 2013, Approval action, NDA 203975, Anoro Ellipta (UMEC/VI)**

3. CMC/Device

The recommended action from a CMC perspective is Approval. An acceptable recommendation from the Office of Compliance was issued on March 25, 2014. No other CMC issues are outstanding at this time.

- General product quality considerations

UMEC inhalation powder is an anticholinergic administered by oral inhalation. The same dry powder inhaler device with dose counter is approved for Breo Ellipta and Anoro Ellipta. The Ellipta inhaler is a plastic inhaler with dose counter. While the device contains the capacity for two separate, double-foil, (b) (4) blister strips that are activated in parallel, the to-be-marketed UMEC product contains a single strip and provides a total of 30 doses. The strip contains micronized umeclidinium, magnesium stearate, and lactose. Each inhalation contains UMEC 62.5 mcg.

The inhaler is sealed inside a hermetically sealed aluminum foil tray with a dessicant packet and packaged in a cardboard carton. Stability data support a shelf-life of 24 months with a 6-weeks' in-use expiry once the protective foil packaging is opened. The recommended storage conditions are at room temperature from 20º to 25º C (68 to 77ºF); excursions permitted from 15º to 30ºC (59º - 86ºF)." The review has found the drug substances specifications, excipients, and container-closure systems to be acceptable. The Product Quality Microbiology review recommends approval of the product, which is a non-sterile dry powder.

In addition to routine bench testing for device ruggedness, the Applicant sampled partially used devices from the clinical trials and all complaint/malfunctioning devices. The rate of malfunctioning devices was low (<0.5%) and did not indicate any systematic problems with device design. Patient use did not appear to influence the functionality of the device.

- Facilities review/inspection

The drug substances are manufactured by Glaxo Wellcome Manufacturing (b) (4) ((b) (4) and micronized by Glaxo Operations (b) (4) ((b) (4) The drug product is manufactured by Glaxo Operations (b) (4) ((b) (4) The drug substances and device DMFs were deemed adequate. The Office of Compliance issued an overall recommendation of Acceptable for the application on XX.

- Other notable issues (resolved or outstanding)

The Applicant provided data to demonstrate comparability in aerosolization performance for the to-be-marketed single-strip UMEC product and the dual-strip UMEC monocomparator used in the clinical trials. The dual-strip product was used in early dose-ranging trials and the factorial design trials to ensure pharmaceutical comparability between the combination and the monocomponents for the purposes of addressing the requirements of the Combination Rule as outlined in 21CFR 300.50. FDA previously concurred with the Applicant that the presence of a second strip without active drug in the to-be-marketed formulation was not warranted and

would result in the exposure of patients to unnecessary excipient (End-of-Phase 2 meeting, October 29, 2010). The CMC review in conjunction with the clinical team's input concluded that the differences observed between the UMEC single-strip and double-strip formulations was acceptable and would not interfere with interpretation of the clinical trial data from the factorial trials..

4. Nonclinical Pharmacology/Toxicology

The recommended action from the nonclinical perspective is Approval. There are no outstanding pharmacology/toxicology issues at this time.

The preclinical program included studies in which animals were dosed with the individual monocomponents and in combination via inhalation to assess the general toxicity, genetic toxicity, carcinogenicity, and reproductive toxicity of UMEC and VI individually. In general, these studies showed that UMEC and VI 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 relevant nonclinical studies for VI are summarized in the current Breo Ellipta package insert.

The general toxicity of UMEC 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. Relevant target organs were the lung and tracheal bifurcation in the rate and the heart, lung, larynx, and nasal turbinates in the dog. A 13-week study with the combination of UMEC and VI in dogs found toxicity as consistent with the monoproducts, without evidence of additive or synergistic toxicity with the combination.

In terms of genetic testing, UMEC tested negative in the Ames assay, rat bone marrow micronucleus assay in vivo, and the mouse lymphoma assay. Two-year carcinogenicity studies with UMEC in rodents showed no evidence of tumorigenicity.

A battery of reproductive and developmental studies evaluated the effects of UMEC on male and female fertility in rats, teratogenicity of UMEC in rats and rabbits, and peri- and post-natal development of UMEC in rats. UMEC had no effects on fertility in the rat or on embryofetal survival and development in either the rat or rabbit.

5. Clinical Pharmacology/Biopharmaceutics

The recommended action from a clinical pharmacology perspective is Approval. There are no outstanding issues at this time.

GSK submitted results from a comprehensive clinical pharmacology program that included studies to assess the pharmacokinetics and metabolism after single and multiple inhaled doses of UMEC. 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.

Inhaled UMEC has an approximate systemic bioavailability of 13%. Given low oral bioavailability, systemic exposure is primarily due to absorption of the inhaled portion. T_{max} was reached by approximately 0.08 to 1 hour for UMEC. The estimated half-life after oral inhalation administration is 11 hours. UMEC C_{max} and $AUC_{(0-24)}$ were <50% lower in COPD patients compared to healthy subjects. No significant effects due to age, renal, or hepatic impairment, on pharmacokinetic parameters were observed, so no dose adjustment for age, hepatic function, or renal function is recommended.

UMEC is metabolized primarily by CYP2D6. No clinically meaningful differences were observed in normal and 2YP2D6 poor metabolizer subjects following administration of UMEC 500 mcg.

A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval. A more detailed discussion of the pharmacokinetic information can be found in the Clinical Pharmacology Summary included in these background materials.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Overview of the clinical program

As noted in the background, GSK conducted a development program for UMEC that was largely concurrent with development of the UMEC/VI combination product which was recently approved. **Table 1** and **Table 2** summarize the main studies conducted to support dose selection, efficacy, and safety for the UMEC monocomponent. Efficacy for UMEC 62.5 is derived primarily from the two placebo-controlled trials, Trials 5408 and 3373, that specifically evaluated the 62.5 mcg dose. Other efficacy trials conducted with UMEC 125 (Trials 3373 and 3374) and two exercise trials (Trials 4417 and 4418) provide secondary support for efficacy. The safety of UMEC 62.5 is based on these trials and the long-term safety trial, Trial 3359.

This memorandum summarizes the main results from these trials; additional information regarding these trials can be found in the other supporting documents included in the backgrounder. For brevity, the trials are identified here by the last four digits of the study number for the remainder of this memorandum (e.g., Trial AC4115321 is Trial 5321).

Table 1 UMEC dose selection

Trial *Trial period*	Design[a]	N[b]	Treatment[c]	Endpoint	Sites *% US subjects*
AC4115321 *Jul 2011-Oct 2011*	R, DB, PC, 7-day XO	60 56 57 58 59 60 56 60	UMEC 15.6 QD UMEC 15.6 BID UMEC 31.25 QD UMEC 31.25 BID UMEC 62.5 QD UMEC 125 QD Tio 18 QD Placebo	Trough FEV1	15 US sites *100%*
AC4113073 *Oct 2009-Mar 2010*	R, DB, PC, 14-day XO	35 34 34 37 36 38 38 32 35 158	UMEC 62.5 QD UMEC 62.5 BID UMEC 125 QD UMEC 125 BID UMEC 250 QD UMEC 250 BID UMEC 500 QD UMEC 1000 QD Tio 18 QD Placebo	Trough FEV1	20 sites (US, Germany) *65%*
AC4113589 *Dec 2009 – Jul 2010*	28-day, R, DB, PC, PG	71 72 71 71	UMEC 125 QD UMEC 250 QD UMEC 500 QD Placebo	Trough FEV1	21 sites (US, E. Europe, W. Europe) *33%*

[a] R=randomized, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, SD=single dose, XO=crossover
[b] modified ITT
[c] UMEC=umeclidinium, VI=vilanterol, Tio=tiotropium, QD=once daily, BID=twice daily

Table 2 UMEC clinical development program

Trial *Trial period*	Design[a]	N[b]	Treatment[c]	Endpoint	Sites *% US patients*
Primary efficacy and safety trials					
AC4115408 *Jul 2011 – Feb 2012*	12-wk, R, DB, PC PG	69 69 68	UMEC 62.5 QD UMEC 125 QD Placebo	Trough FEV1	27 sites (US, Germany, Japan)
DB2113373 *Mar 2011 – Apr 2012*	24-wk, R, DB, PC, PG	413 418 421 280	UMEC 62.5/25 UMEC 62.5 VI 25 Placebo	Trough FEV1	163 sites (US, E and W Europe, Chile, S Africa, Japan, Mexico, Thailand *28%*
Other efficacy and safety trials					
DB2113361 *Mar 2011 – Sep 2012*	24-wk, R, DB, PC, PG	403 407 404 275	UMEC/VI 125/25 UMEC 125 VI 25 Placebo	Trough FEV1	153 site (US, E and W Europe, Japan, Philippines *21%*
DB2113374 *Mar 2011 – Apr 2012*	24-wk, R, DB, DD, AC, PG	215 217 222 215	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 Tio 18	Trough FEV1	95 sites (US, E and W Europe, S. America, Australia, Canada, Mexico, S Korea, S Africa) *26%*
DB2114417 *Mar 2011 – Jun 2012*	R, DB, PC, XO	144 152 76 50 49 170	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 UMEC 125 UMEC 62.5 Placebo	Exercise endurance time Trough FEV1	31 sites (US, W Eur, E Eur) *56%*
DB2114418 *Mar 2011 – Jul 2012*	R, DB, PC, XO	128 130 64 41 40 151	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 UMEC 125 UMEC 62.5 Placebo	Exercise endurance time Trough FEV1	42 sites (US, E Eur, W Eur, S Africa, Canada) *45%*
52-week safety trial					
DB2113359 Jan 2011 – Jul 2012	R, DB, PG, PC	226 227 109	UMEC/VI 125/25 UMEC 125 Placebo	Safety parameters	53 sites (US, Chile, E Eur, S Africa) *28%*

[a] AC= active-controlled, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, R=randomized, SD=single dose, XO=crossover
[b] Intent-to-treat
[c] UMEC=umeclidinium, VI=vilanterol, Tio=tiotropium, QD=once daily, BID=twice daily

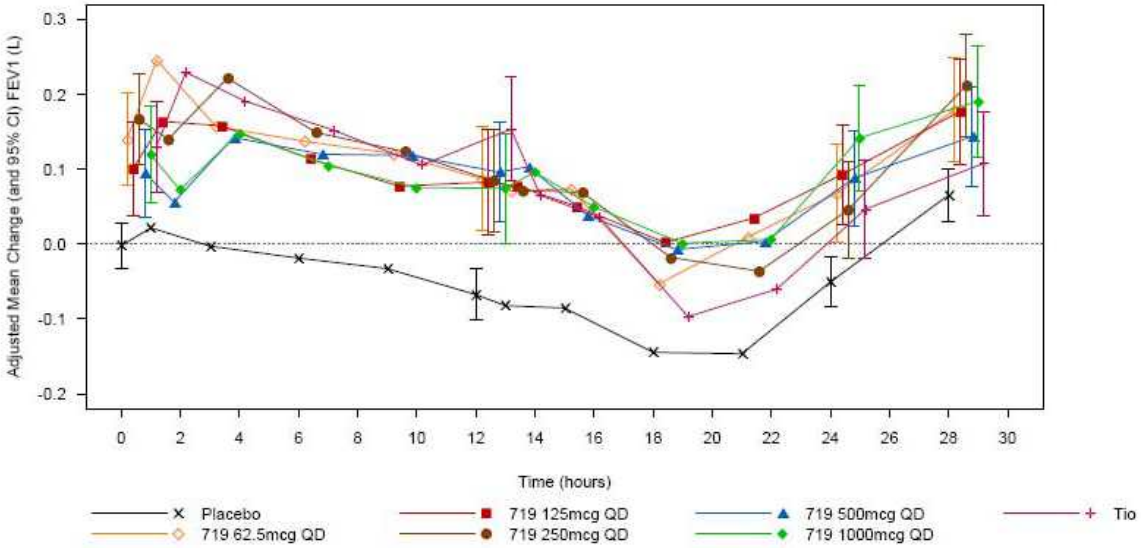
UMEC dose selection

- **Nominal dose selection**

Data to support nominal dose selection for the UMEC component are available from four trials: 3073, 5321, 5408, and 3589. Initial results from Trials 3073 (**Figure 1**) and 3589 (data

not shown) suggested no additional benefit for doses over 125 mcg, and the distinction between 62.5 and 125 mcg was not consistent over the 24-hour dosing period.

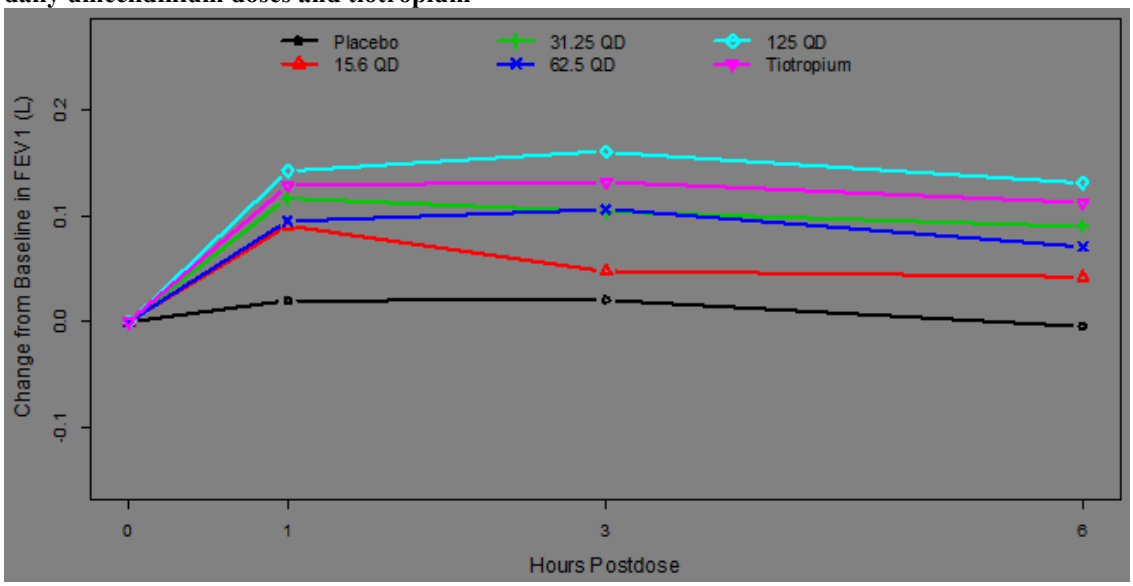
Figure 1 Trial 3073: Adjusted mean change from baseline in FEV1 (L) over 24 hours at Day14



Source: CSR AC4113073, Figure 6

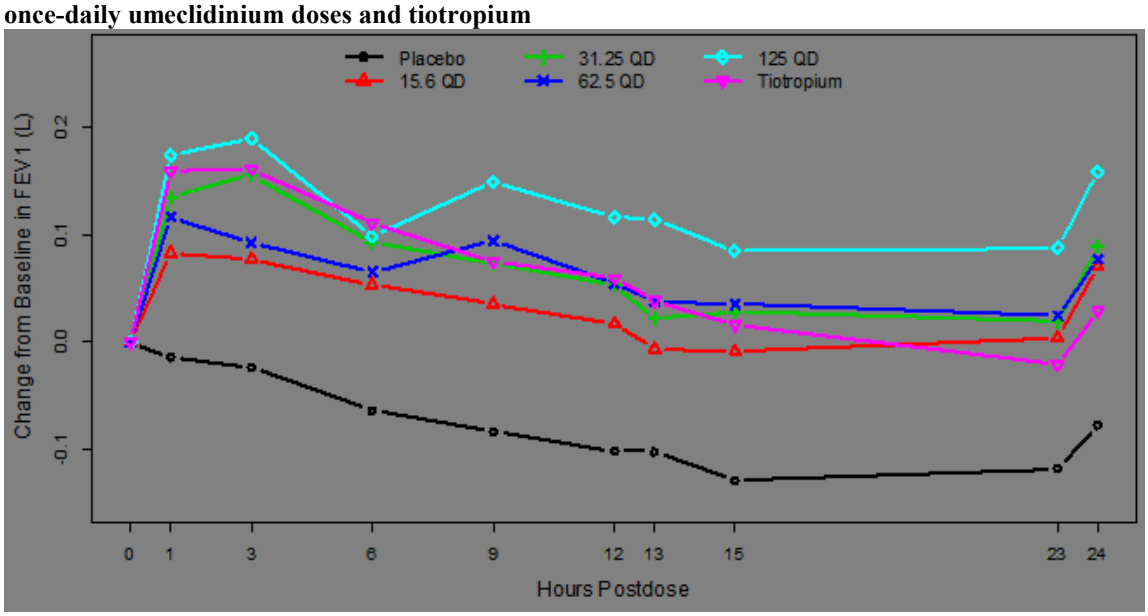
To explore the lower end of the dose range further, Trial 5321 evaluated doses ranging from 15.6 mcg to 125 mcg once daily. The serial FEV1 over 6 hours at Day 1 demonstrated a dose response, with the lowest UMEC 15.6 mcg dose overlapping with placebo at the peak 3-hour timepoint (**Figure 2**). While there was inconsistent dose response for doses of 62.5 mcg and lower, for the serial FEV1 over 24 hours, a dose separation between UMEC 125 and 62.5 was observed at Day 7 in terms of serial FEV1 (Figure 3) and trough FEV1 (**Figure 4**). Benchmark comparison to an approved LAMA, tiotropium, at Days 1 and 7, did not suggest that UMEC was dosed excessively high.

Figure 2 Trial 5321: Postdose 6-hour serial mean change from baseline in FEV_1 at Day 1 for different once-daily umeclidinium doses and tiotropium



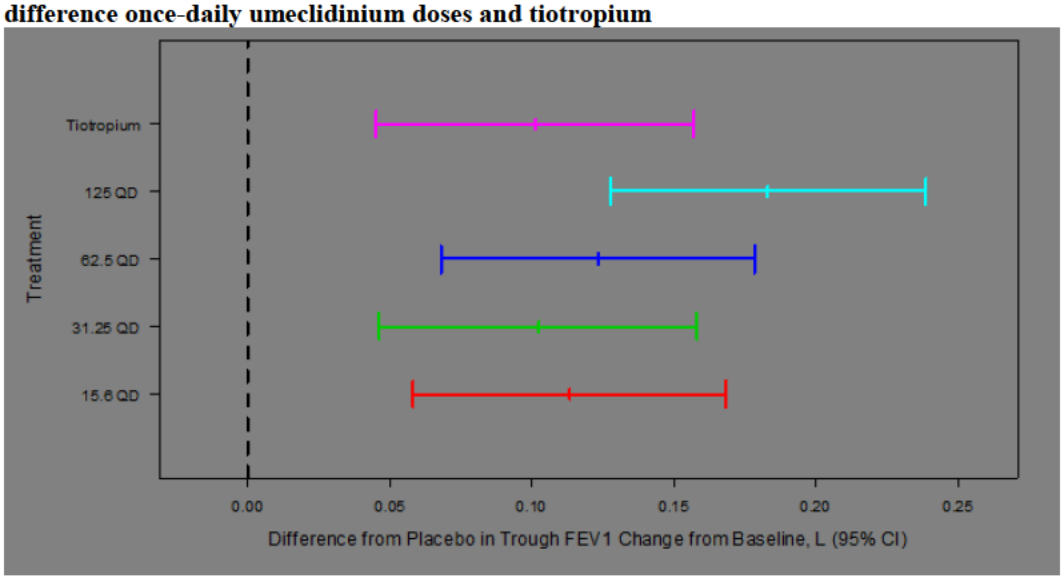
Source: FDA Statistical Review

Figure 3 Trial 5321: Postdose 24-hour serial mean change from baseline in FEV_1 at Day 7 for different once-daily umeclidinium doses and tiotropium



Source: FDA Statistical review

Figure 4Trial 5321: Difference from placebo in mean change from baseline in trough FEV1 at Day 8 for difference once-daily umeclidinium doses and tiotropium



Source: FDA statistical review

The results from Trial 5321 suggest that UMEC 15.6 is at the low end of the dose response curve and subtherapeutic with overlap with placebo on some analyses. Doses of UMEC from 31.25 through 125 separate from placebo and while the dose response was not consistent, UMEC 125 appears to have a greater numerical response compared to the 31.25 and 62.5 UMEC doses, suggesting dose ordering.

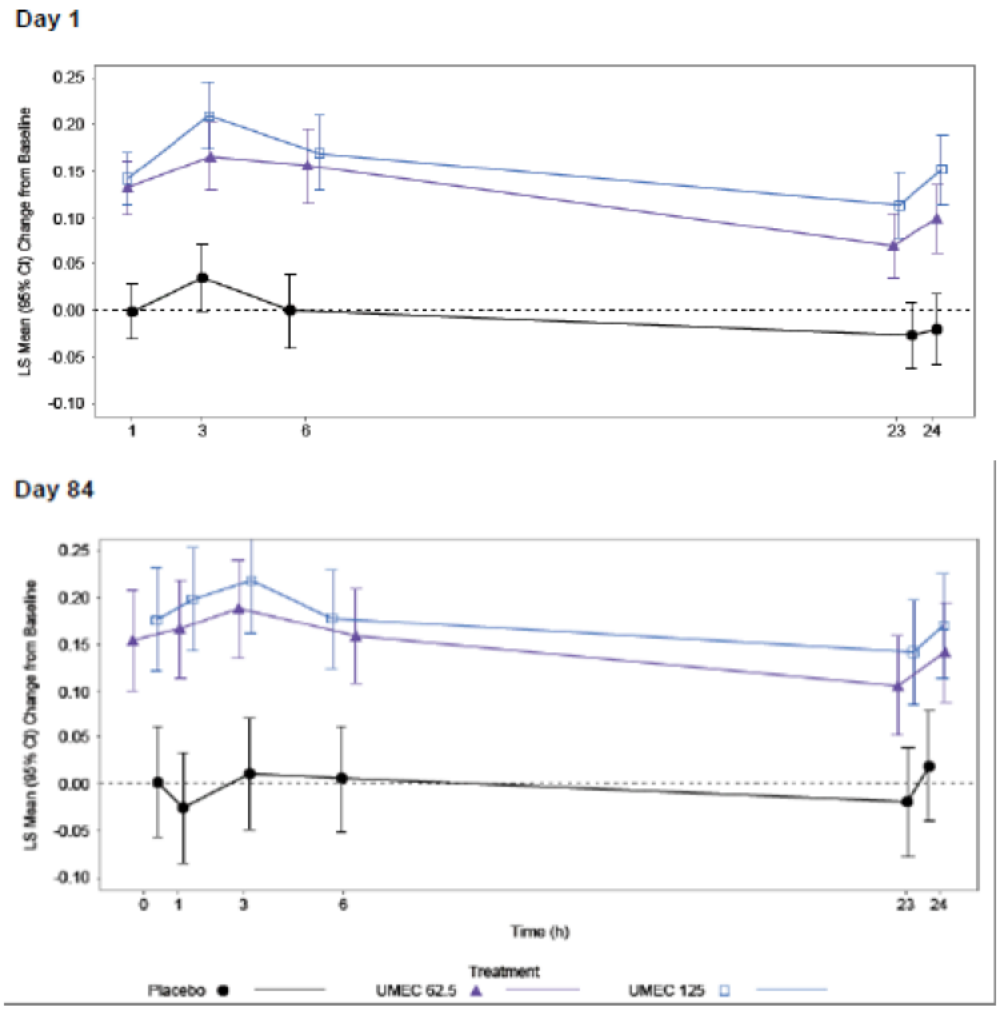
The dose separation between UMEC 62.5 and 125 was further supported by trough FEV1 values observed at Day 85 in Trial 5408 (Table 3) and mean change from baseline FEV1 at Day 1 and Day 84 (Figure 5). Based on these results, the selection of nominal UMEC doses of 62.5 mcg and 125 mcg for further evaluation appeared reasonable, although the Applicant ultimately chose to pursue only the UMEC 62.5 dose level for marketing.

Table 3 Trial 5408: Mean change from baseline in trough FEV1 at Day 85

Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
UMEC 62.5	69	1.363	0.120	0.127 (0.052, 0.202)	<0.001
UMEC 125	69	1.388	0.145	0.152 (0.076, 0.229)	<0.001
Placebo	68	1.235	-0.007	-	-

Source: CSR AC4115408, Table 22

Figure 5 Trial 5408: Mean change from baseline in FEV1 over 24 hours at Day 1 and Day 84

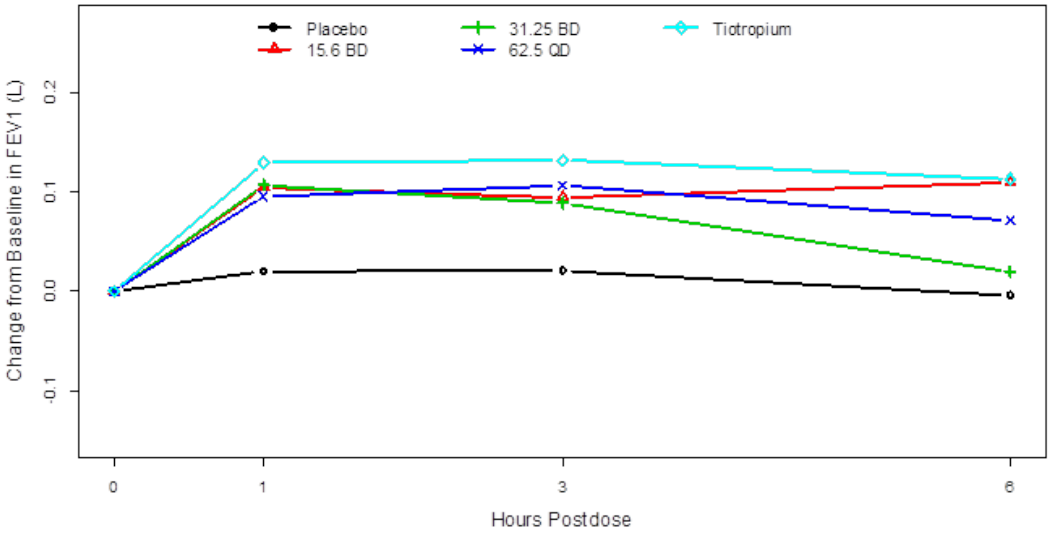


Source: Module 5.3.5.1, CSR AC4115408, Figures 6.13 and 6.17

- **Dosing frequency**

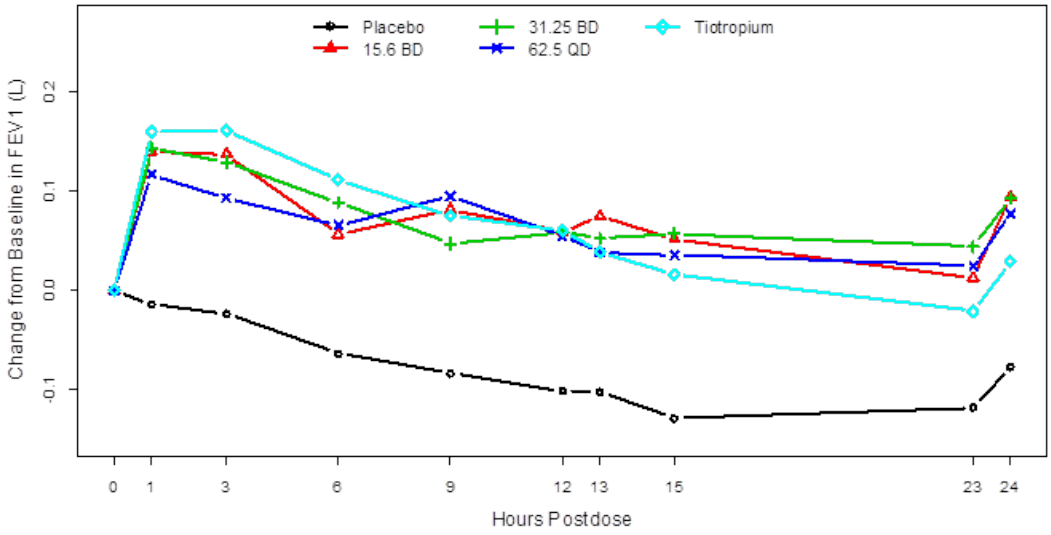
The dosing frequency of UMEC was evaluated in Trials 5321 and 3073. In Trial 5321, there was inconsistent dose separation among nominal daily doses below 125 mcg. However, the results did not suggest that twice-daily dosing was preferable to once-daily dosing for a given nominal dose at Days 1 and 7 (**Figure 6** and **Figure 7**). A similar overlap between the same nominal daily doses was also observed in Trial 3073 (data not shown). Based on these results, the selection of a UMEC once-daily dosing regimen for further evaluation in confirmatory trials appeared reasonable.

Figure 6 Trial 5321: Postdose 24-hour serial mean change from baseline in FEV_1 at Day 1 for once- versus twice-daily umeclidinium doses and tiotropium



Source: FDA statistical briefing document

Figure 7 Trial 5321: Postdose 24-hour serial mean change from baseline in FEV_1 at Day 1 for once- versus twice-daily umeclidinium doses and tiotropium



Source: FDA statistical briefing document

Confirmatory trial design

12-week placebo-controlled Trial 5408

Trial 5408 was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel group. After a 5- to 9-day run-in period, patients were randomized 1:1:1 to UMEC 62.5, 125, or placebo. Trough FEV1 at Day 85 was assessed as the primary endpoint. Other spirometry

parameters, rescue medication use, and SGRQ were assessed as other efficacy endpoints. The trials enrolled patients 40 years or older who were required to have a clinical history of COPD as defined by ATS/ERS criteria,[10] a post-bronchodilator FEV1/FVC ratio ≤0.70, a post-bronchodilator FEV1 ≤70% predicted, and a score of ≥2 on the Modified Medical Research Council Dyspnea Scale (mMRC). Bronchodilator responsiveness to salbutamol and ipratropium was assessed at baseline but was not a requirement for inclusion in the trial. Inhaled corticosteroids at a dose of ≤1000 mcg/day at a constant dose, mucolytics, oxygen therapy ≤12 hours/day, and albuterol/salbutamol for rescue were permitted as concomitant treatments. Patients who were on an ICS/LABA product for at least 30 days prior to Visit 1 could be switched to an ICS product alone at doses as outlined above. Prohibited medications included systemic corticosteroids, LABAs, ICS/LABA products, SAMA, SAMA/SABA products, tiotropium, PDE4 inhibitors, leukotriene inhibitors, and theophylline preparations.

24-week placebo-controlled trials: Trial 3373 and 3361

In addition to Trial 5408, the Applicant conducted a 24-week, placebo-controlled trials, Trial 3373, in support of the UMEC 62.5 bronchodilation claim. The trials were 24-week, multinational, randomized, double-blind, placebo-controlled, parallel group trials in patients with moderate to severe COPD. Trial 3373 assessed UMEC/VI 62.5/25, UMEC 62.5, VI 25, and placebo. The full factorial design was intended to help evaluate the relative contributions of the individual components to the combination product. Patient selection criteria and concomitant medications were similar to that outlined for Trial 5408. The use of a placebo control for up to 6 months was considered ethically acceptable given the availability of rescue SABA and stable ICS doses in conjunction with close clinical monitoring for exacerbation symptoms, and withdrawal criteria. Patients who experienced an exacerbation during the Treatment Period were withdrawn.

After an initial screening and a run-in period of 1 to 2 weeks on placebo, patients were randomized in a 3:3:3:2 ratio to UMEC/VI, UMEC, VI, and placebo, respectively. The primary efficacy endpoint was trough FEV1 on Treatment Day 169, with sequential comparisons of each active treatment against placebo followed by comparison of UMEC/VI versus VI (to assess the contribution of UMEC) and UMEC/VI versus UMEC (to assess the contribution of VI). The trough FEV1 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on the prior treatment day. Secondary endpoints included the weighted mean FEV1 over 0 to 6 hours and Transitional Dyspnea Index (TDI) focal scores. Other endpoints assessed included time to onset, serial FEV1, peak FEV1, rescue salbutamol use, St. George's Respiratory Questionnaire (SGRQ), Shortness of Breath with Daily Activities Questionnaire (SOBDA) score, and time to first COPD exacerbation. A COPD exacerbation was defined as an acute worsening of COPD symptoms requiring the use of any other medication besides study medication or rescue bronchodilator.

Safety assessments included adverse events (AEs), physical exams, clinical laboratory parameters, vital signs, serial ECGs, and in a subset of patients, 24-hour Holter monitoring. AEs of special interest included cardiovascular events, anticholinergic effects, and

[10] 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: 932-46.

pneumonias. Treatment compliance was assessed via dose counter checks at interval clinical visits.

The Applicant also conducted a similarly designed 24-week, placebo-controlled trial,Trial 3361, that evaluated the UMEC 125 dose level. Trial 3361 assessed UMEC/VI 125/25, UMEC 125, VI 25, and placebo and provides secondary support for efficacy as well as safety information.

Long-term safety trial: Trial 3359

GSK conducted Trial 3359 to assess long-term safety of UMEC. Following screening and a 7- to 10-day run-in period, patients were randomized 2:2:1 to UMEC/VI 125/25, UMEC 125, or placebo for a 52-week treatment period. Concurrent use of ICS was permitted, in addition to salbutamol and/or ipratropium bromide as needed. Patients were reassessed at Month 1, Month 3, and at 3-month intervals subsequently. Trial 3359 was designed to enroll a more stable COPD patient population than the 24-week efficacy trials. There was no inclusion criterion for a threshold level of active COPD symptoms and there was a criterion for a minimum post-salbutamol FEV1 value at screening (FEV1 $\geq$35 and $\leq$80%). Patients with history of hospitalization within the previous 12 weeks or who experienced an exacerbation during the run-in period (while off any baseline medications, including LABA, ICS/LABA, and/or LAMA) were excluded. Exacerbation was defined as a worsening of COPD symptoms requiring systemic corticosteroids, antibiotic, and/or hospitalization. Patients who experienced COPD exacerbations were treated with systemic steroids and/or antibiotics per investigator discretion and were permitted to continue in the trial. The inclusion of a placebo arm was deemed acceptable in the context of appropriate informed consent given the close monitoring during the study, the relative stability of the COPD population targeted, and the permitted concomitant use of ICS, SABA, and SAMA. The majority of patients were not on a LABA (80%) or LAMA (93%) at baseline prior to screening.

Trial 3359 was designed primarily as a safety trial. Similar AEs of interest as those specified in the four main efficacy trials were assessed. No formal efficacy endpoints were evaluated, but data on COPD exacerbations, rescue medication use, trough FEV1 and trough FVC were collected.

Exercise trials: 4417 and 4418

The Applicant also conducted two, incomplete block, crossover exercise trials in support of UMEC/VI. Trials 4417 and 4418 were randomized, double-blind, placebo-controlled, 2-period trials with 12-week treatment periods that assessed UMEC/VI 62.5/25, UMEC/VI 125/25, UMEC 62.5, UMEC 125, VI 25, and placebo. The co-primary efficacy endpoints were the exercise endurance time (EET) as measured by the endurance shuttle walk test and the trough FEV1 at Day 85 (pre-bronchodilator and predose FEV1 obtained 24 hours after dosing on Treatment Day 84). While the Applicant does not seek an exercise claim, these trials provide additional support for the bronchodilation claim.

Efficacy findings

The main efficacy trials (5408 and 3373) included 206 and 1601 patients, respectively treated with at least one dose of study drug, of which a total of 487 patients received the proposed UMEC/VI 62.5 dose. The mean age was 63 years, and approximately half were current smokers. Roughly one-third demonstrated reversibility to salbutamol alone, while half demonstrated reversibility after administration of salbutamol and ipratropium.
Study completion rates ranged from 70 to 79% for the treatment arms. Lack of efficacy was cited as a reason for discontinuation most frequently in patients randomized to placebo. Details regarding dropout rates and the reasons cited for dropout can be found in the Clinical and Statistical Reviews. Early discontinuation secondary to adverse events is discussed separately in the following safety section.

- **Trough FEV1**

In trials 5408 and 3373, the change from baseline in mean trough FEV1 at Day 85 and Day 169, respectively, was assessed as the primary endpoint. . A statistically significant difference was observed for the comparison of each of UMEC against placebo (Table 4 and Table 5), demonstrating the efficacy of UMEC 62.5 in replicate fashion. A statistically significant difference was also observed for UMEC 125 in Trial 5408 (Table 4) and in Trial 3361 (0.160 L, 95% CI [0.141, 0.216]). The numerical separation between UMEC 62.5 and 125 suggests a slightly greater bronchodilator response in terms of trough FEV1 with the higher dose.

Table 4 Trial 5408: Mean change from baseline in trough FEV1 at Day 85

Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
UMEC 62.5	69	1.363	0.120	0.127 (0.052, 0.202)	<0.001
UMEC 125	69	1.388	0.145	0.152 (0.076, 0.229)	<0.001
Placebo	68	1.235	-0.007	-	-

Source: FDA statistical review

Table 5 Trial 3373: Mean change from baseline in trough FEV1 at Day 169

Treatment	N	LS mean (L)	LS mean change from period baseline	Difference from placebo (95% CI)	P
UMEC 62.5	418	1.354	0.119	0.115 (0.076, 0.155)	<0.001
VI 25	421	1.311	0.076	0.072 (0.032, 0.112)	0.004
UMEC/VI 62.5/25	413	1.406	0.171	0.167 (0.128, 0.207)	<0.001
Placebo	280	1.239	0.004	-	-

Source: FDA statistical review

The active-controlled Trial 3374 compared UMEC 125 to tiotropium 18 mcg. While UMEC 125 is not proposed in this application, the comparison is of interest for benchmarking and comparing the UMEC monocomponent to the related combination product.

Table 6 Trial 3374: Mean change from baseline in trough FEV1 at Day 169					
Treatment	**N**	**LS mean (L)**	**LS mean change from period baseline**	**Difference from tiotropium (95% CI)**	**P**
UMEC 125	222	1.332	0.186	0.037 (-0.012, 0.086)	0.138
UMEC/VI 62.5/25	217	1.355	0.208	0.060 (0.010, 0.109)	0.018
UMEC/VI 125/25	215	1.369	0.223	0.074 (0.025, 0.123)	0.003
Tiotropium 18	215	1.295	0.149	-	-

Source: FDA statistical review

To assess the potential impact of missing data, the Applicant submitted several sensitivity analyses using different imputation strategies, including a more conservative approach requested by FDA. The results were statistically robust according to these various analyses. Further discussion on the issue of missing data is located in the FDA Statistical Review.

Further support for the efficacy of UMEC 62.5 on the basis of trough FEV1 was provided by the crossover exercise trials, 4417 and 4418, and there was a clear dosing order for the UMEC 62.5 and UMEC 125 in each trial (**Error! Reference source not found.**).

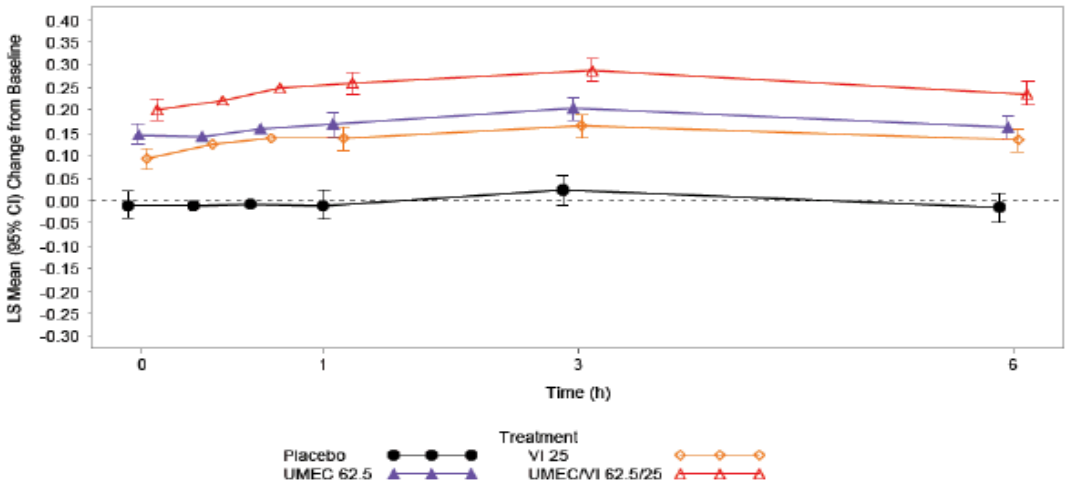
Table 7 Trial 4417 and 4418: Mean change from baseline in trough FEV1 at Day					
Treatment	**N**	**LS mean (L)**	**LS mean change from period baseline**	**Difference from placebo (95% CI)**	**P**
Trial 4417					
UMEC 62.5/25	152	1.615	0.178	0.211 (0.172, 0.249)	<0.001
UMEC/VI 125/25	144	1.573	0.136	0.169 (0.129, 0.209)	<0.001
UMEC 62.5	49	1.491	0.054	0.087 (0.030, 0.143)	0.003
UMEC 125	50	1.544	0.108	0.140 (0.084, 0.197)	0.03
VI 25	76	1.503	0.067	0.099 (0.050, 0.148)	<0.001
Placebo	170	1.404	-0.032	-	-
Trial 4418					
UMEC 62.5/25	130	1.520	0.200	0.243 (0.202, 0.284)	<0.001
UMEC/VI 125/25	128	1.538	0.218	0.261 (0.220, 0.303)	<0.001
UMEC 62.5	40	1.421	0.101	0.144 (0.086, 0.203)	<0.001
UMEC 125	41	1.532	0.212	0.256 (0.193, 0.318)	<0.001
VI 25	64	1.388	0.069	0.112 (0.061, 0.163)	<0.001
Placebo	151	1.277	-0.043	-	-

Source: Module 5.3.5.1, CSR DB2114417 and DB114418, Table 40 and Table 40, and FDA Statistical Review

- **Serial FEV1**

Serial FEV1 0-6h was assessed as an alternative spirometric endpoint in the efficacy trials. Representative results for the proposed UMEC 62.5 from Trial 3373 are shown in **Figure 8**.

Figure 8 Trial 3373: Serial FEV1 0-6h at Day 84

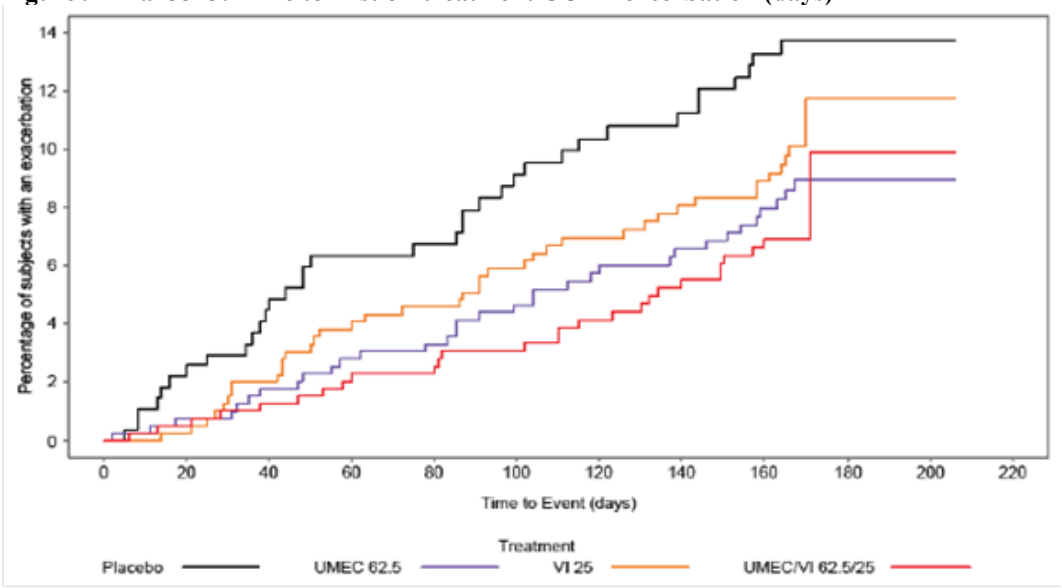


Source: Module 5.3.5.1, CSR DB213373, Figure 10

- **COPD exacerbation**

While the efficacy trials were not designed to assess COPD exacerbations, data on exacerbations were collected as an additional assessment of both safety and efficacy. Representative results for UMEC 62.5 from the placebo-controlled Trial 3373 are shown (**Figure 9**). Similar results were observed for UMEC 125 in Trial 3361.

Figure 9 Trial 3373: Time to first on-treatment COPD excerbation (days)



Source: Module 5.3.5.1, CSR DB2113373 Figure 17and FDA Statistical Briefing Document

- **SGRQ**

The St. George's Respiratory Questionnaire (SGRQ) was used to assess health-related quality of life. Replicate evidence of a clinically meaningful change from baseline (defined as a change ≥ 4 units) was demonstrated for UMEC 62.5 in Trial 5408 and 3373. However, the benefit was not consistent in Trial 3361, which evaluated the UMEC 125 dose. Also, the result for Trial 5408 is notable for marked worsening in the placebo group, which drives the treatment difference.

Table 8 Trials 5408, 3373, and 3361: SGRQ

Treatment	N	Mean change from baseline	Difference from placebo (95% CI)	P
Trial 5408 at 12 weeks				
UMEC 62.5	69	-3.1	-7.9 (-12.2, -3.6)	<0.001
UMEC 125	69	-6.1	-10.9 (-15.2, -6.5)	<0.001
Placebo	68	4.8	-	-
Trial 3373 at 24 weeks				
UMEC 62.5	418	-7.3	-4.7 (-7.1, -2.3)	<0.001
Placebo	280	-2.6	-	-
Trial 3361 at 24 weeks				
UMEC 125	407	-4.1	-0.3 (-2.5, 1.8)	0.78
Placebo	275	-3.8	-	-

Source: FDA statistical review

A responder analysis provides an alternative perspective of these results. In Trial 3373, the proportion of patients with a clinically meaningful decrease at Week 24 for patients who received UMEC 62.5 versus placebo was 42% versus 31%.

- **Rescue medication use**

Rescue medication use was also assessed in Trials 5408, 3373, and 3361. While a numerical decrease in the number of puffs was reported in the three trials, a statistically significant difference for UMEC 62.5 was observed only in the shorter trial, Trial 5408 (-0.7 puffs/day, 95% CI [-1.3, -0.1]). There was no dose separation observed in this trial for UMEC 125 for this endpoint (-0.6 puffs/day, 95% CI [-1.2, 0.0]).

Efficacy conclusions

The UMEC development program includes replicate evidence of efficacy for the proposed bronchodilation indication for UMEC 62.5 mcg versus placebo in terms of trough FEV1 and serial FEV1. There is also replicate spirometric evidence to support the UMEC 125 dose. However, in terms of non-spirometric endpoints, such as SGRQ and rescue medication, the data to support dose separation are less consistent and do not clearly indicate a benefit for the higher dose over UMEC 62.5. Therefore, the Applicant's proposal to market only the UMEC 62.5 dose is not unreasonable.

8. Safety

Overview of the safety database
The safety database for UMEC 62.5 centers on the 12-week Trial 5408, the 6-month efficacy trials (3361, 3373, and 3374), and the one-year placebo-controlled safety trial (3359) that evaluated UMEC 125. These trials are supplemented by 28-day dose-ranging trial (3589), the two 12-week exercise trials (4417 and 4418), pharmacokinetic and dose-ranging trials of shorter duration, and safety data available for the UMEC/VI combination, Anoro Ellipta. From these trials, a total of 1,663 patients were treated with at least one dose of UMEC 62.5 or 125.

The application pooled the COPD safety database into several different groups for analysis. This memorandum focuses on the pooled results from the placebo-controlled trials, Trials 5408, 3373, and 3361 and results from the 1-year trial, 3589. The baseline demographic characteristics were as follows: mean age 63 years, 65% male, and 89% White. As the safety of UMEC was discussed extensively in the reviews for Anoro Ellipta, the information provided here is largely a summary of the information reviewed previously.

Deaths
Given a relatively older population with comorbidities, deaths are expected in a COPD development program. A total of 46 deaths in all COPD studies was reported and were evenly reported across the treatment arms, all occurring at a frequency of <1%: placebo (n=5/1637), UMEC 62.5 (n=3/576), UMEC 125 (n=7/1087), UMEC/VI 62.5/25 (n=6/1124), UMEC/VI 125/25 (n=1/1330), , VI (n=22/2051), and tiotropium (n=2/421). A variety of fatal AEs were reported, with each event occurring in 1 or 2 patients per treatment group reported. The cases of death were also adjudicated by an independent, external, blinded committee and divided into primary categories and subcategories. Based on the narratives, reported preferred AE terms, and adjudicated reports, there was no apparent mortality imbalance associated with UMEC.

Discontinuations due to adverse events
Overall rates for early withdrawal due to an AE were similar among treatment arms in the efficacy trials (5% to 7%); in the long-term trial, early withdrawal secondary to AE was slightly higher in placebo (12%) compared to the UMEC 125 and UMEC/VI 125/25 arms (9% and 8%). The types of AEs cited were fairly similar across studies and treatment arms, with COPD and pneumonia being the most commonly reported AE terms leading to early discontinuation. In the long-term safety trial, the most commonly reported AE leading to early dropout was ventricular extrasystoles, which occurred in 2% of patients assigned to UMEC 125 compared to <1% in the UMEC/VI 125/25 and placebo treatment arms.

Non-fatal serious adverse events (SAE)[11]

[11] 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.

The rates for all non-fatal serious adverse events were evenly distributed across treatment arms, ranging between 5-6% in efficacy trials and 6-7% in the long-term safety trial. A wide range of events were reported in the clinical program. In most cases, one or two events in an individual AE category were reported for a given treatment arm, making it difficult to identify a specific safety signal or to assess causality. As with cases of death, non-fatal SAEs were adjudicated by an external, blinded committee. Overall, the most commonly reported SAE in was COPD exacerbation, which was distributed across all treatment arms (<1 to 3%). The next most commonly reported SAE was myocardial infarction/ischemic disease. While overall numbers of reports were low, a numerical imbalance was noted with no cases reported in the placebo arm, compared to <1% reported in the active treatment arms containing UMEC, VI, or UMEC/VI. No dose response was observed among these limited reports. In the long-term safety trials, COPD exacerbation and myocardial infarction were also reported most commonly but no differences were observed between placebo and the active treatment arms. Cardiovascular safety is discussed in further detail below.

Adverse events of interest

Adverse events of interest included cardiovascular safety, anticholinergic effects, effects related to adrenergic stimulation, and lower respiratory tract infection/pneumonia. In general, the pattern of AEs did not indicate a specific safety signal.

- **Cardiovascular safety**

The application included several prespecified evaluations to assess cardiovascular safety. In addition to the adjudication of deaths and SAEs described above and a thorough QT study, the application includes analyses of Major Adverse Cardiac Events (MACE) and a broader analyses of cardiovascular AEs of special interest (AESI), which encompass a wider set of AE terms. The same set of safety data were used for both the MACE and cardiovascular AESI analyses. ECG and Holter monitoring data were also obtained.

  - *MACE analyses*

The Applicant conducted two MACE analyses for ischemia/infarction, stroke, and cardiovascular death based on two sets of criteria. The broader criteria included all MedDRA preferred terms falling under the category of the Myocardial Infarction SMQ and Other Ischemic Disease SMQ, whereas the narrow criteria specified the preferred term, Acute Myocardial Infarction. The analyses were performed on a pooled ITT population drawn from all COPD studies with a treatment duration of at least 12 weeks. Since drug exposure varied across trials, exposure-adjusted rates were also assessed.

As seen in Table 9, the number of patients with MACE events was relatively low across treatment arms, and the exposure-adjusted rates did not suggest an increased risk of a MACE event for the active treatment arms compared to placebo, including the proposed UMEC 62.5. There was no apparent dose response and the combination of UMEC and VI did not appear to have an additive or synergistic effect.

Table 9 MACE analyses in integrated COPD database							
	Placebo **N=1053** **SY=369**	**UMEC/VI 62.5/25** **N=1124** **SY=408**	**UMEC/VI 125/25** **N=1330** **SY=573**	**UMEC 62.5** **N=576** **SY=202**	**UMEC 125** **N=1016** **SY=449**	**VI 25** **N=1174** **SY=441**	**TIO** **N=173** **SY=173**
Number (%) of Subjects							
Broad-definition	20 (2)	15 (1)	22 (2)	9 (2)	14 (1)	17 (1)	6 (1)
Narrow-definition	7 (<1)	5 (<1)	6 (<1)	2 (<1)	7 (<1)	8 (<1)	1 (<1)
Adjudicated CV death	2 (<1)	2 (<1)	0	0	1 (<1)	2 (<1)	0
Non-fatal cardiac ischemia	14 (1)	13 (1)	19 (1)	8 (1)	11 (1)	12 (1)	5 (1)
Non-fatal MI	1 (<1)	3 (<1)	3 (<1)	1 (<1)	4 (<1)	2 (<1)	0
Non-fatal stroke	4 (<1)	0	3 (<1)	1 (<1)	2 (<1)	4 (<1)	1 (<1)
Number of Subjects with Events per 1000 Subject-Years							
Broad-definition	54.3	36.8	38.4	44.5	31.2	38.5	34.7
Narrow-definition	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

Source: Module 5.3.5.3, ISS, Table 138
CV=cardiovascular; MACE=Major Adverse Cardiac Events; MI=myocardial infarction; SY=subject-years
Incidence rate calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

- *Cardiovascular AESI*

Cardiovascular AESI included terms for cardiac ischemia, stroke, and sudden death like the MACE analyses. In addition, the cardiovascular AESI search terms included terms for acquired long QT, cardiac arrhythmia, cardiac failure, and hypertension. Consistent with the MACE analyses, rates for cardiac ischemia, sudden death, or stroke appear fairly similar between UMEC 62.5 and placebo, and no consistent pattern is observed for the other related active treatment arms to suggest an increased risk with the UMEC component. Similarly, while a numerical imbalance between UMEC/VI 62.5/25 and placebo is observed for hypertension, a comparison of rates across active treatment arms is equivocal in terms of associating an increased risk with UMEC. Rates for cardiac arrhythmia and stroke actually favor UMEC/VI 62.5/25 over placebo.

Table 10 Cardiovascular serious and non-serious AE of special interest (Primary Efficacy trials)							
Adverse event	**Placebo N=555 SY=208**	**UMEC/VI 62.5/25 N=842 SY=346**	**UMEC/VI 125/25 N=832 SY=336**	**UMEC 62.5 N=418 SY=168**	**UMEC 125 N=629 SY=249**	**VI 25 N=1034 SY=411**	**TIO N=423 SY=173**
Number (%) of Subjects							
Acquired long QT	0	0	2 (<1)	1 (<1)	0	0	0
Cardiac arrhythmias	18 (3)	24 (3)	19 (2)	20 (5)	20 (3)	46 (4)	9 (2)
Cardiac failure	6 (1)	11 (1)	11 (1)	7 (2)	7 (1)	12 (1)	5 (1)
Cardiac ischemia	5 (<1)	11 (1)	12 (1)	7 (2)	5 (<1)	12 (1)	4 (<1)
Hypertension	11 (2)	25 (3)	17 (2)	12 (3)	21 (3)	29 (3)	11 (3)
Sudden death	0	0	0	0	0	1 (<1)	0
Stroke	2 (<1)	1 (<1)	1 (<1)	1 (<1)	1 (<1)	3 (<1)	1 (<1)
Number of Subjects with Events per 1000 Subject-Years							
Acquired long QT	0	0	5.9	6.0	0	0	0
Cardiac arrhythmias	86.7	69.4	56.5	119.1	80.4	111.9	52.0
Cardiac failure	28.9	31.8	32.7	41.7	28.1	29.2	28.9
Cardiac ischemia	24.1	31.8	35.7	41.7	20.1	29.2	23.1
Hypertension	53.0	72.3	50.6	71.5	84.4	70.5	63.6
Sudden death	0	0	0	0	0	2.4	0
Stroke	9.6	2.9	3.0	6.0	4.0	7.3	5.8

Source: Module 5.3.5.3, ISS
SY=subject-years
Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

A similar analysis of cardiovascular AESI was performed for the long-term safety trial 3359 (Table 11). While some imbalances were observed, the data do not show a clear treatment-related or dose-related pattern.

Table 11 Cardiovascular serious and non-serious AE of special interest (Trial 3359)			
Adverse event	**Placebo N=109 SY=80**	**UMEC/VI 125/25 N=226 SY=177**	**UMEC 125 N=227 SY=167**
Number (%) of Subjects			
Acquired long QT	0	0	0
Cardiac arrhythmias	17 (16)	26 (12)	39 (17)
Cardiac failure	1 (<1)	2 (<1)	4 (2)
Cardiac ischemia	4 (4)	4 (2)	4 (2)
Hypertension	7 (6)	8 (4)	6 (3)
Sudden death	0	0	0
Stroke	0	0	1 (<1)
Number of Subjects with Events per 1000 Subject-Years			
Acquired long QT	0	0	0
Cardiac arrhythmias	211.5	147.3	233.3
Cardiac failure	12.4	11.3	23.9
Cardiac ischemia	49.8	22.7	23.9
Hypertension	87.1	45.3	35.9
Sudden death	0	0	0
Stroke	0	0	6.0

Source: Module 5.3.5.3, ISS

SY=subject-years
Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

- *ECG and Holter monitoring*

In addition to a dedicated thorough QT study, the clinical program obtained ECG in all patients and performed 24-hour Holter monitoring in a subset of patients (approximately 13%). The protocols contained prespecified early discontinuation criteria for abnormalities on these assessments. A review of mean changes and clinically significant abnormalities in various ECG parameters did not reveal any clear treatment-related effects. Similarly, a review of the proportions of patients with clinically significant abnormalities on Holter monitoring did not demonstrate any clear differences between the active treatment arms and placebo.

One area of uncertainty that remains are those patients who discontinued early from the clinical program secondary to reaching protocol-defining stopping criteria for ECG and Holter abnormalities. A relative imbalance was observed in the long-term safety trial, with 5% of UMEC 125 patients and 6% of UMEC/VI 125/25 patients discontinuing early secondary to an ECG abnormality, compared to none in the placebo group. Likewise, an imbalance was also observed for early discontinuation secondary to Holter abnormalities (11-12% in the UMEC and UMEC/VI arm vs. 7% in placebo). No imbalance was observed in the shorter efficacy trials. While the nature of the ECG and Holter abnormalities that resulted in early withdrawal was varied and did not suggest an obvious drug-induced arrhythmia, the actual outcomes for these patients following their discontinuation from the trials remain unknown.

- **Anticholinergic and adrenergic effects**

An assessment of AE terms related to anticholinergic effects (e.g., urinary retention, blurred vision, dry mouth, bowel obstruction, etc.) and adrenergic effects (e.g., electrolyte shifts, tachycardia, tremor, etc.) does not indicate any specific safety signals associated with UMEC 62.5.

- **Lower respiratory tract infection/pneumonia**

In general, the rates for lower respiratory tract infection (LTRI) and pneumonia were low. The rate for UMEC 62.5 was the same as placebo (1%) and less than the active comparator, tiotropium (4%). Overall, these data do not suggest an increased risk of LTRI or pneumonia.

Common adverse events

Adverse events occurring in ≥1% in the efficacy trials and more commonly than in placebo are summarized in Table 12. Adverse events occurring in ≥3% in the long-term safety trial are shown Table 13.

Table 12 Common adverse events reported in ≥3% and occurring more commonly than in placebo (Trials 5408, 3373, 3361, and 3374)

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
Upper respiratory tract infection	21 (3)	23 (5)	25 (4)
Hypertension	10 (2)	10 (2)	19 (3)
Chronic obstructive pulmonary disease	14 (2)	12 (2)	10 (1)

Arthralgia	9 (1)	12 (2)	11 (2)
Rhinitis	8 (1)	8 (2)	5 (<1)
Myalgia	4 (<1)	7 (1)	8 (1)
Sinusitis	5 (<1)	5 (1)	9 (1)
Oedema peripheral	5 (<1)	6 (1)	4 (<1)
Pharyngitis	2 (<1)	6 (1)	7 (1)
Contusion	1 (<1)	6 (1)	7 (1)
Tachycardia	2 (<1)	5 (1)	2 (<1)
Viral upper respiratory tract infection	1 (<1)	7 (1)	1 (<1)

Source: Module 1.11.3, Table 1230.43
Note: This table includes on-treatment AEs

Table 13 Common adverse events reported in ≥3% and occurring more commonly than in placebo (Trial 3359)

	Placebo N=109	**UMEC/VI 125/25 N=226**	**UMEC 125 N=227**
	n (%)	n (%)	n (%)
Any AE	**57 (52)**	**120 (53)**	**132 (58)**
Headache	9 (8)	20 (9)	25 (11)
Ventricular extrasystoles	5 (5)	11 (5)	12 (5)
Extrasystoles	4 (4)	10 (4)	10 (4)
Back pain	3 (3)	10 (4)	9 (4)
Sinusitis	3 (3)	8 (4)	6 (3)
Cough	1 (<1)	6 (3)	6 (3)
URTI	3 (3)	2 (<1)	8 (4)
Supraventricular tachycardia	1 (<1)	2 (<1)	6 (3)
Supraventricular extrasystoles	1 (<1)	1 (<1)	6 (3)
Sinus tachycardia	1 (<1)	0	6 (3)
Pneumonia	0	0	6 (3)

Source: Module 5.3.5.3, ISS, Table 76
Note: This table includes on-treatment AEs
AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease; URTI=upper respiratory tract infection

The application included subgroup analysis of AEs by age, gender, race, and COPD severity. The overall rate of adverse events trended higher with age, but the distribution of AEs was similar to the profile observed in younger patients. Likewise, while overall rates were higher in females than males, the overall distribution of events was similar. No consistent differences by salbutamol reversibility were observed as well. Subgroup analysis by race was limited by the low number of non-White patients.

Other safety parameters

Other safety assessments performed in the clinical program included laboratory parameters and vital signs. While some clinically relevant shifts were observed in a few individuals, the overall distribution did not indicate a specific safety signal for UMEC 62.5.

Safety summary

The nature of the adverse events identified for UMEC appears generally consistent with the general safety profile associated with the LAMA and LABA drug classes. There was no

apparent dose-related increase in adverse events comparing the UMEC 62.5 and 125 dose levels. No post-marketing safety trials are recommended at this time.

9. Advisory Committee Meeting

As the efficacy and safety for UMEC 62.5 was discussed in the context of the September 10, 2013, Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting for Anoro Ellipta, a separate meeting was not convened for this application.

10. Pediatrics

As COPD is largely a disease of adults, the requirement for pediatric trials under the Pediatric Research Equity Act (PREA) was waived. The Pediatric Research Committee (PeRC) concurred with the waiver.

11. Other Relevant Regulatory Issues

The Applicant conducted the clinical trials using Good Clinical Practices and provided the required financial disclosure information for investigators, which did not suggest a conflict of interest that would have impacted the overall conclusions of the review.

12. Labeling

This section provides a high level overview of labeling, which remains pending at the time of this memorandum. The proposed tradename is Incruse Ellipta, which has been found acceptable by DMEPA. Consults from OPDP and OSE were received and included in the labeling process. Carton and container labeling were also reviewed. Regarding the package insert, the following are high level revisions proposed for the product label:

- Highlights: Revise to conform with labeling for other LAMA- and LABA-containing products
- Section 6, Adverse Reactions: Removal of comparator safety information for (b) (4)
- Section 14, Clinical Studies: Addition of dose-ranging information for UMEC. Inclusion of responder analysis in addition to mean SGRQ data from Trial 3373. Removal of (b) (4).

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended Regulatory Action is Approval.

- Risk Benefit Assessment

The UMEC development program includes replicate evidence of efficacy for the UMEC 62.5 mcg as a bronchodilator versus placebo. The safety profile for UMEC 62.5 appears similar to other once-daily LAMA products. The risk-benefit assessment favors approval for the proposed indication.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No postmarketing risk evaluation and management strategies (REMS) are recommended for this application.

- Recommendation for other Postmarketing Requirements and Commitments

No postmarketing requirements are recommended for this application.

- Recommended Comments to Applicant

None

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/s/

SUSAN L LIMB
03/26/2014