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RESEARCH**

APPLICATION NUMBER:

203975Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 9, 2013
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	203-975, SN00
Supplement#	
Applicant	GlaxoSmithKline (GSK)
Date of Submission	December 18, 2012
PDUFA Goal Date	December 18, 2013
Proprietary Name / Established (USAN) names	Anoro Ellipta/umeclidinium and vilanterol inhalation powder
Dosage forms / Strength	Umeclidinium/vilanterol 62.5 mcg/25 mcg once daily
Proposed Indication(s)	1. Long-term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	<i>Approval</i>

1. Introduction

On December 18, 2012, GlaxoSmithKline (GSK) submitted a 505(b)(1) New Drug Application (NDA 203-975) for umeclidinium and vilanterol inhalation powder, proposed at a dose of 62.5 mcg/25 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 Anoro Ellipta.

Umeclidinium/vilanterol (UMEC/VI) is a new combination inhalation product comprised of a long-acting antimuscarinic agent (LAMA) and a long-acting beta-agonist (LABA). Neither component is currently marketed as a single-ingredient inhalation product. UMEC, the anticholinergic component, is a new molecular entity. VI, the LABA component, was recently approved in combination with fluticasone furoate (FF), an inhaled corticosteroid, as a combination product for COPD, Breo Ellipta. UMEC/VI is supplied as a dry powder inhalation formulation administered by the Ellipta inhaler device. To support the 62.5/25 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, two 12-week crossover efficacy trials, and a 12-month safety trial.

The UMEC/VI program is distinctive in terms of the nature of the combination and the relative experience available with the monocomponents. While short-acting antimuscarinic agents and short-acting beta-agonists have been previously combined, UMEC/VI represents a new type of combination product comprised of a novel LAMA and LABA. Similar to the Breo Ellipta development program, which was notable for the concurrent development of the ICS and LABA components with the ICS/LABA combination, the UMEC/VI program was conducted

concurrently with the development of the individual LAMA and LABA components. Neither UMEC nor VI is currently marketed as a single-ingredient inhalation product, although the Applicant has proposed UMEC 62.5 mcg as a monotherapy for marketing (NDA 205-382, application currently under review).

This CDTL review summarizes the development program for UMEC/VI and the recommendations of each of the review disciplines. In particular, the review focuses on the data that support UMEC dose selection, the benefit of the UMEC/VI combination over the individual components, and the cardiovascular safety data.

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.

LABAs currently marketed in the United States for the treatment of COPD include salmeterol, formoterol, arformoterol, indacaterol, and vilanterol. Arformoterol and indacaterol are marketed as single-ingredient products, while salmeterol and formoterol are marketed individually and in combination with inhaled corticosteroids (fluticasone propionate and mometasone furoate, respectively). Salmeterol, formoterol, and arformoterol are dosed twice-daily and indacaterol is dosed once-daily. Vilanterol is also dosed once-daily, but is only available in combination with fluticasone furoate, an inhaled corticosteroid (ICS). As a drug class, LABAs have known pharmacologic effects on the cardiovascular system, including increases in heart rate and blood pressure. Labeling for both short-acting and long-acting beta-agonists includes a Warnings and Precautions statement regarding these effects, and caution is recommended when used in patients with cardiovascular disorders.

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 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

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/postmarketdrugssafetyinformationforpatientsandproviders/drugsafetyinformationforhealthcareprofessionals/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.

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

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.

Currently, there are no LAMA/LABA combination products approved for COPD in the US. GOLD 2013 practice guidelines recommend the use of a LAMA or a LABA for symptom relief in patients with stable, relatively milder disease (GOLD stage 1 or 2).¹⁰ Patients with more symptomatic disease (GOLD stage 3 or 4) may consider the addition of an ICS to the LABA, either used independently or in conjunction with a LAMA. The GOLD guidelines state that the combination of different pharmacologic classes of bronchodilator may provide added benefit with a lower risk of adverse effects compared to increasing the dose of a single bronchodilator. However, the choice among bronchodilators ultimately depends on a patient's individual response, and there is no consensus recommendation for when a LAMA should be combined with LABA.

As mentioned in the Introduction, the development of a new combination product relies on the development of the single-ingredient components. The selection of an appropriate dose and dosing frequency for each component is impacted by safety concerns specific to each drug class. For LABAs, dose exploration is conducted in the context of safety concerns regarding severe asthma exacerbations and asthma-related deaths which have been associated with both short-acting and long-acting beta-2 adrenergic agonists.^{11, 12, 13, 14, 15} The issue has been discussed at previous FDA Advisory Committee meetings¹⁶ and in the literature,^{17, 18, 19} and is the subject of a safe use strategy outlined by the Agency.²⁰ Controlled postmarketing trials for all LABAs approved for asthma in the US are ongoing to further assess the safety of LABAs when used in conjunction with ICS.²¹ While the underlying pathophysiology for these asthma-related severe adverse events remains uncertain, studies suggest that these events may be dose-related²². As a result, a higher dose of inhaled formoterol was not approved in the US due to

¹⁰ *Global Strategy for the Diagnosis, Management and Prevention of COPD*, Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2013. Available from: <http://www.goldcopd.org/>.

¹¹ Benson RL, Perlman F. *J Allergy* 1948; 19:129-140.

¹² Lowell FC, Curry JJ, Schiller IW. *N Eng J Med* 1949; 240:45-51.

¹³ Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. *Thorax* 1991; 46:105-111.

¹⁴ Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al. *N Eng J Med* 1992; 326:501-506.

¹⁵ US Product Labels of salmeterol and formoterol containing products

¹⁶ Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.

¹⁷ Martinez FD. *New Eng J Med* 2005; 353:2637-2639.

¹⁸ Kramer JM. *New Eng J Med* 2009; 360:1952-1955.

¹⁹ Drazen JM, O'Byrne PM. *New Eng J Med* 2009; 360:1671-1672.

²⁰ Chowdhury BA, DalPan G. *New Eng J Med* 2010; 362:1169-1171.

²¹ Chowdhury BA, Seymour SM, Levenson MS. *New Eng J Med* 2011;364:2473-5

²² Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. *Chest* 2003; 124:70-74.

the occurrence of severe asthma-related adverse events²³. Although the same risk in COPD has not been identified, the selection of an appropriate dose is a priority for all LABAs, including VI. For this reason, FDA requested that GSK fully characterize the dose-response curve and optimal dosing frequency for VI in bronchodilator-sensitive patients, i.e., asthmatic patients, prior to conducting confirmatory trials in COPD. These issues for VI were discussed at the April 17, 2013, PADAC meeting convened to discuss Breo Ellipta (fluticasone furoate 100 mcg/vilanterol 25 mcg) program, which was later approved on May 10, 2013.²⁴

For LAMAs, dose selection can be challenging given relatively flat dose-response curves and the relative lack of effect in asthmatic patients. For this reason, FDA has recommended that sponsors consider carrying forward more than one dose of LAMA into confirmatory trials for COPD.

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

- **January 31, 2007, Pre-IND meeting for VI (IND 74,696):** The Division recommended that GSK characterize the VI monocomponent fully prior to developing the FF/VI combination.
- **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 LAMA/LABA combination and the preliminary plans for evaluation of the nominal dose and dosing frequency.
- **June 17, 2009, End-of-Phase-2 meeting for FF/VI (IND 77,855, COPD program):** The Division noted that it was difficult to confirm the selection of the 25 mcg nominal dose or QD dosing interval for VI based on the available information. The Division agreed that dosing interval studies in asthma could be extrapolated to COPD. The Division also stated that replicate clinical trials were expected to support a bronchodilator claim and an exacerbation claim.

²³ Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. N Eng J Med 2011; 365:2247-2249.

²⁴ Pulmonary-Allergy Drugs Advisory Committee Meeting, April 17, 2013. Meeting materials and minutes available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/ucm329187.htm>

- **March 24, 2010, Type C teleconference meeting (IND 77, 855, asthma and COPD program):** The Division confirmed that the proposed VI 25 mg QD dose appeared reasonable for further evaluation in Phase 3 trials.
- **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. 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. In terms of secondary claims, the Division commented that the evaluation of dyspnea is challenging and the successful development of a measurement instrument was without regulatory precedent.
- **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.
- **July 13, 2011, Pre-NDA meeting for FF/VI (IND 77, 855, COPD program):** GSK stated that they do not plan to market VI as a monotherapy.
- **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. GSK described their plan to market UMEC monotherapy, primarily as add-on therapy for patients on existing non-anticholinergic therapies.
- **December 18, 2012, NDA submission for UMEC/VI 125/25 mcg and 62.5/25 mcg (NDA 203975)**
- **April 30, 2013, NDA submission for UMEC 62.5 mcg (NDA 205382)**
- **May 10, 2013, Approval action, NDA 204275 for FF/VI 100/25 mcg (Breo Ellipta)**

3. CMC/Device

The recommended action from a CMC perspective is Approval, pending methods validation. No other CMC issues are outstanding at this time.

- General product quality considerations

UMEC/VI inhalation powder is a novel, fixed-dose, combination product administered by oral inhalation. The same dry powder inhaler device with dose counter is approved for Breo Ellipta. The Ellipta inhaler is a plastic inhaler with dose counter. The device contains two separate, double-foil, laminate blister strips that are activated in parallel and provide a total of 30 doses. One strip contains micronized umeclidinium, magnesium stearate, and lactose. The second strip contains micronized VI, magnesium stearate, and lactose. The device is designed to deliver the contents from a single blister from each of the two blister strips simultaneously. Each inhalation contains UMEC 62.5 mcg and VI 25 mcg.

The inhaler is sealed inside a hermetically sealed aluminum foil tray with a desiccant 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 20° to 25° C (68 to 77°F); excursions permitted from 15° to 30°C (59° - 86°F).” 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 PTE Ltd. (Jurong, Singapore) and micronized by Glaxo Operations UK Ltd. (Ware, UK). The drug product is manufactured by Glaxo Operations UK Ltd. (Ware, UK). The drug substances and device DMFs were deemed adequate. The Office of Compliance issued an overall recommendation of Acceptable for the application on August 21, 2013.

- Other notable issues (resolved or outstanding)

In order to meet the requirements of a combination product as outlined in 21 CFR 300.50, the Applicant provided data to demonstrate comparability in aerosolization performance for UMEC and VI as monoproducts and in combination. The CMC review concluded that the degree of variability observed was typical for inhalation products and did not indicate a performance difference between the combination product and the related monoproducts that would interfere with interpretation of the clinical trial data. The submitted data supported the use of the monoproducts in the confirmatory clinical 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 rat 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, VI, and UMEC/VI. 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 and VI have an approximate systemic bioavailability of 13% and 26%, respectively. Given low oral bioavailability, systemic exposure for both components is primarily due to absorption of the inhaled portion. T_{max} was reached by approximately 0.08 to 1 hour for both UMEC and VI. The estimated half-life for both UMEC and VI after oral inhalation administration of UMEC/VI is 11 hours. UMEC C_{max} and $AUC_{(0-24)}$ were <50% lower in COPD patients compared to healthy subjects. For VI, C_{max} and $AUC_{(0-24)}$ were 62% lower and 43% higher 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. A study to assess QTc effects did not indicate any clinically relevant prolongation of the QTc interval.

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. VI is metabolized principally via CYP3A4. Co-administration with ketoconazole, a strong CYP3A4 and potent P-gp inhibitor, resulted in 65% and 22% increase in mean $AUC_{(0-24)}$ and C_{max} , respectively. No dose adjustment is recommended for UMEC/VI when co-administered with ketoconazole.

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 the UMEC/VI combination product that was largely concurrent with development of the individual monocomponents. Table 1 and Table 2 summarize the main studies conducted in both COPD to support dose selection and dosing frequency for the UMEC monocomponent and the UMEC/VI combination with the to-be-marketed device, and the confirmatory trials conducted specifically for the combination.

The selection of the nominal dose and dosing frequency for VI 25 mcg QD was supported by dose-ranging trials conducted in a bronchodilator-sensitive patient population (asthmatic patients) as well as in COPD patients. These data were previously reviewed as part of the Breo Ellipta program and are summarized in the relevant reviews and current package insert for Breo Ellipta. The data to support VI dose selection will not be revisited here.

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 background. 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 <i>Trial period</i>	Design^a	N^b	Treatment^c	Endpoint	Sites <i>% US subjects</i>
AC4115321 <i>Jul 2011-Oct 2011</i>	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 <i>Oct 2009-Mar 2010</i>	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%
AC4115408 <i>Jul 2011 – Feb 2012</i>	12-wk, R, DB, PC PG	69 69 68	UMEC 62.5 QD UMEC 125 QD Placebo	Trough FEV1	27 sites (US, Germany, Japan)
AC4113589 <i>Dec 2009 – Jul 2010</i>	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/VI clinical development program					
Trial Trial period	Design^a	N^b	Treatment^c	Endpoint	Sites % US patients
24-week primary efficacy and safety trials					
DB2113361 <i>Mar 2011 – Sep 2012</i>	R, DB, PC, PG	403 407 404 275	UMEC/VI 125/25 UMEC 125 VI 25 Placebo	Trough FEV1	153 sites (US, E and W Europe, Japan, Philippines) 21%
DB2113373 <i>Mar 2011 – Apr 2012</i>	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%
DB2113360 <i>Mar 2011 – Apr 2012</i>	R, DB, DD, AC, PG	214 212 209 208	UMEC/VI 125/25 UMECVI 62.5/25 VI 25 Tio 18	Trough FEV1	91 sites (US, E and W Europe, Peru, Mexico) 27%
DB2113374 <i>Mar 2011 – Apr 2012</i>	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%
12-week exercise trials					
DB2114417 <i>Mar 2011 – Jun 2012</i>	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 <i>Mar 2011 – Jul 2012</i>	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 <i>Jan 2011 – Jul 2012</i>	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 modified intent-to-treat

^c UMEC=umeclidinium, VI=vilanterol, Tio=tiotropium, QD=once daily, BID=twice daily

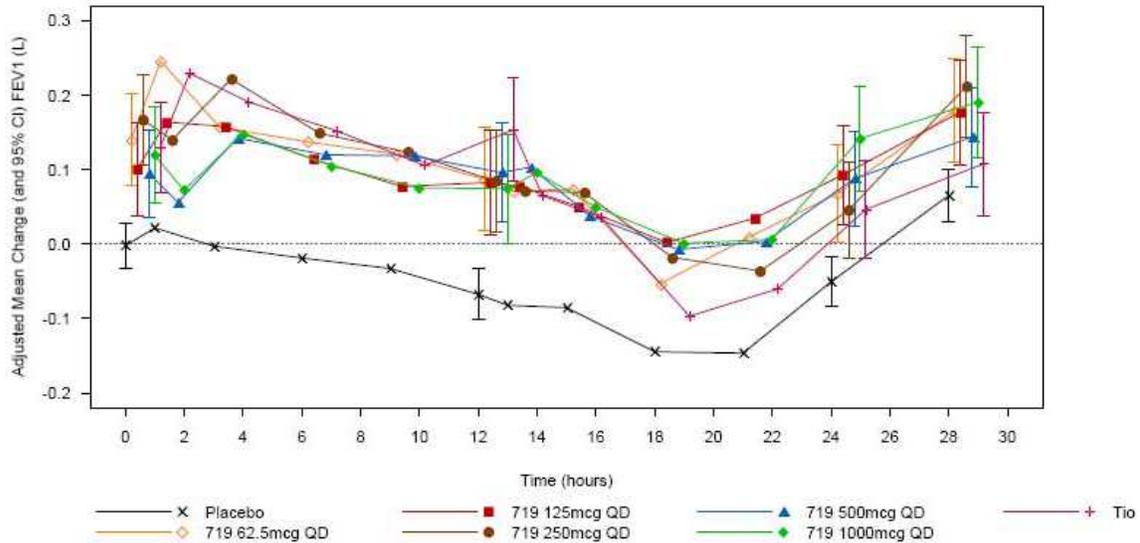
Dose selection

UMEC component

- **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.

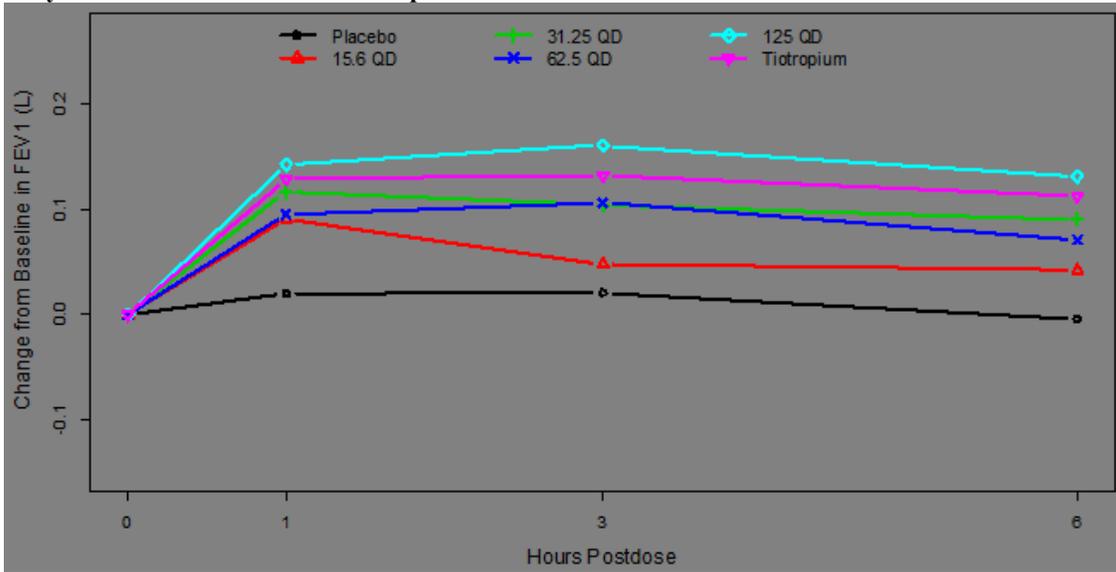
Figure 1 Trial 3073: Adjusted mean change from baseline in FEV1 (L) over 24 hours at Day14



Source: CSR AC4113073, Figure 6

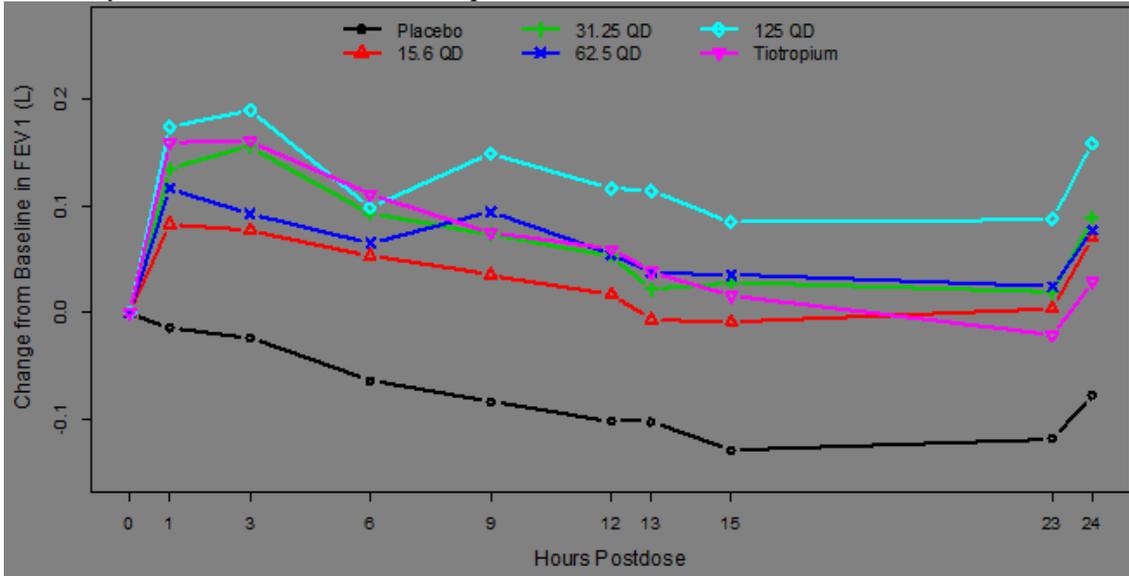
To explore the lower end of the dose range further, Trial 5321 evaluated doses ranging from 15.6 mcg to 125 mcg once daily. The serial FEV1 over 6 hours at Day 1 demonstrated a dose response, with the lowest UMEC 15.6 mcg dose overlapping with placebo at the peak 3-hour timepoint (Figure 2). While there 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 FEV₁ at Day 1 for different once-daily umeclidinium doses and tiotropium



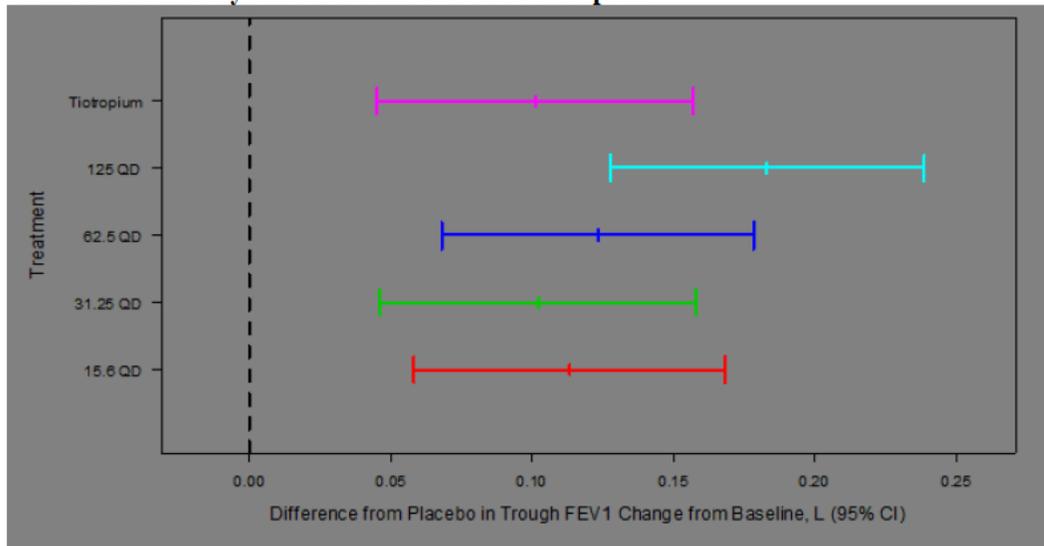
Source: FDA Statistical Review

Figure 3 Trial 5321: Postdose 24-hour serial mean change from baseline in FEV₁ at Day 7 for different once-daily umeclidinium doses and tiotropium



Source: FDA Statistical review

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



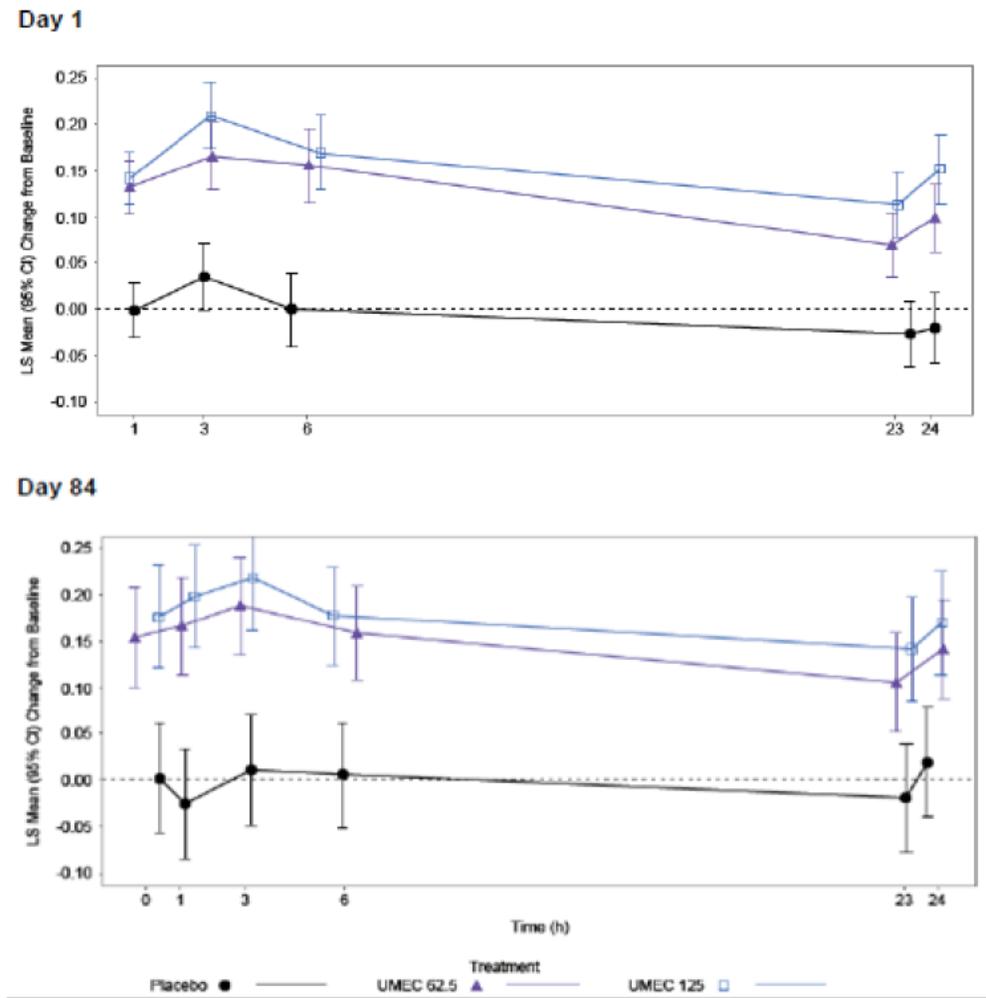
Source: FDA statistical review

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 in confirmatory trials appeared reasonable.

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

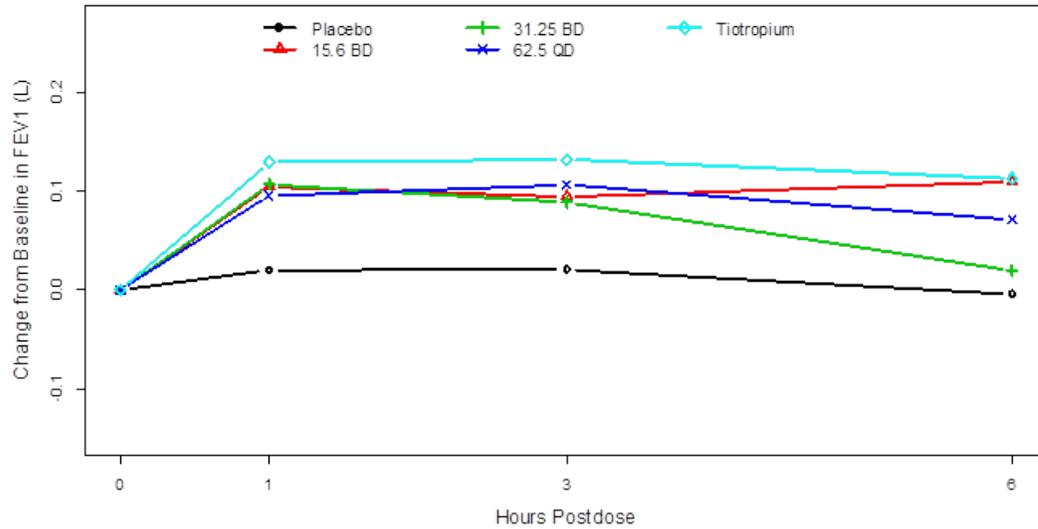


Source: Module 5.3.5.1, CSR AC4115408, Figures 6.13 and 6.17

- **Dosing frequency**

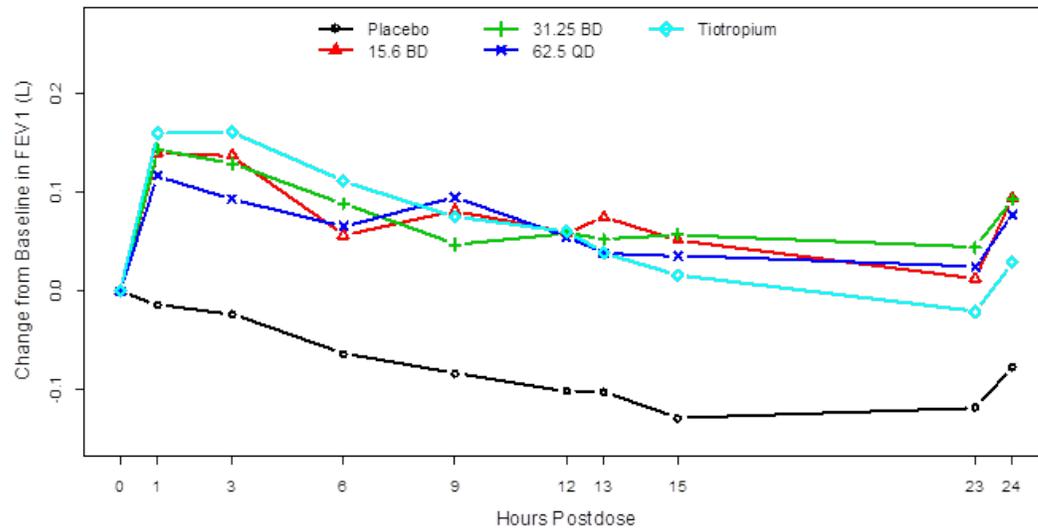
The dosing frequency of UMEC was evaluated in Trials 5321 and 3073. In Trial 5321, there was inconsistent dose separation among nominal daily doses below 125 mcg. However, the results did not suggest that twice-daily dosing was preferable to once-daily dosing for a given nominal dose at Days 1 and 7 (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 FEV₁ 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 FEV₁ at Day 1 for once- versus twice-daily umeclidinium doses and tiotropium



Source: FDA statistical briefing document

VI component

Dose selection summary for UMEC/VI

In summary, dose selection for the UMEC component was complicated by the lack of a consistent dose-response in the individual dose-ranging trials, particularly for doses below 62.5 mcg and above 125 mcg. However, the totality of the data, including benchmark

comparison to an approved LAMA, suggested that UMEC 62.5 and 125 mcg QD represented doses on the steeper part of the dose-response curve. Comparison of once-daily and twice-daily dosing regimens for UMEC was similar. Therefore, the selection of these UMEC doses for further evaluation in the confirmatory trials appeared reasonable. As previously mentioned, confirmation of the VI 25 mcg QD dose was previously established as part of the Breo Ellipta program.

Confirmatory trial design

Confirmatory placebo-controlled trials: 3361 and 3373

Two 24-week, placebo-controlled trials, Trials 3361 and 3371, were conducted in support of the bronchodilation claim. The trials were similar in design with the exception of the nominal dose levels that were evaluated. Trial 3361 assessed UMEC/VI 125/25, UMEC 125, VI 25, and placebo administered once daily in the AM. Trial 3373 assessed UMEC/VI 62.5/25, UMEC 62.5, VI 25, and placebo. The trials were 24-week, multinational, randomized, double-blind, placebo-controlled, parallel group trials in patients with moderate to severe COPD. The full factorial design was intended to help evaluate the relative contributions of the individual components to the combination product. Patients 40 years or older were required to have a clinical history of COPD as defined by ATS/ERS criteria,²⁵ 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. 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

²⁵ 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.

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

Active-controlled trials: 3360 and 3374

In addition to the confirmatory placebo-controlled trials, the UMEC/VI development program included two active-controlled efficacy and safety trials, Trials 3360 and 3374. These trials were 24-week, multicenter, randomized, active-controlled, double-blind, double dummy, parallel group trials. Trial 3360 assessed UMEC/VI 125/25, UMEC/VI 62.5/25, VI 25, and tiotropium (TIO) 18 mcg. Trial 3374 had similar treatment arms but assessed UMEC 125 instead of VI 25. These trials provide a direct comparison of the UMEC/VI 125/25 and UMEC/VI 62.5/25 mcg dose levels.

Inclusion and exclusion criteria and permitted concomitant therapies for Trials 3360 and 3374 were the same as those outlined for the placebo-controlled trials. Following initial screening and a 7- to 10-day run-in period, patients were randomized 1:1:1:1 to one of the four treatment arms for 24 weeks.

The primary efficacy endpoint was the trough FEV1 on Day 169. The secondary efficacy endpoint was the weighted mean postdose FEV1 (0-6h) at Week 24. Other efficacy endpoints included the TDI score, time to onset, rescue salbutamol use, serial FEV1 (0-6h), peak FEV1, SGRQ, SOBDA, and time to first COPD exacerbation. Exacerbations were defined as above. Safety assessments were similar to those outlined for the placebo-controlled trials.

Long-term safety trial: Trial 3359

GSK conducted Trial 3359 to assess long-term safety of UMEC/VI. 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 and are useful as another comparison of the two UMEC/VI dose levels of 62.5/25 and 125/25 mcg.

Efficacy findings

The four main efficacy trials (3361, 3373, 3360, and 3374) included a total of 4,733 patients treated with at least one dose of study drug, of which 842 patients received the proposed UMEC/VI 62.5/25 dose. The mean age was 63 years and 68% were male. Forty-nine percent were current smokers. At screening, 28% percent reported at least one exacerbation in the past year that required corticosteroids and/or antibiotics and approximately 10% reported a hospitalization in the past year due to an exacerbation. The majority of patients were categorized as GOLD Stage II (46%) or Stage III (43%). A total of 31% demonstrated reversibility to salbutamol alone, while 53% demonstrated reversibility after administration of salbutamol and ipratropium.

Among these trials, study completion rates ranged from 70 to 83%. 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 primary reviews. Early discontinuation secondary to adverse events is discussed separately in the following safety section.

- **Trough FEV1**

The change from baseline in mean trough FEV1 at Day 169 was assessed as the primary endpoint in both the placebo- and active-controlled trials. UMEC/VI was compared to VI alone to assess the contribution of the UMEC component and to UMEC alone to assess the contribution of the VI component. In the placebo-controlled trials (3361 and 3373), a statistically significant difference was observed for the comparison of each of the active treatments against placebo (all p-values <0.001), demonstrating the efficacy of the monocomponents (UMEC 62.5, UMEC 125, and VI 25) and replicating the efficacy demonstrated for each individual component in the previous dose-ranging trials. A statistically significant difference was also observed for the comparison of both dose levels of UMEC/VI versus each of the individual components (Table 4). In other words, Trial 3373 provided support for the efficacy contribution of UMEC 62.5 and VI 25 to the proposed combination UMEC/VI 62.5/25 product. Similar results were observed for the higher dose of UMEC/VI 125/25 studied in the development program. The placebo-controlled trials did not compare UMEC/VI 62.5/25 to UMEC/VI 125/25 directly.

Table 4 Trials 3361 and 3373: Mean change from baseline in trough FEV1 at Day 169 (ITT)							
Treatment	N	LS mean (L)	LS mean change	Difference from UMEC (95% CI)	P	Difference from VI (95% CI)	P
3361							
UMEC/VI 125/25	403	1.484	0.207	0.079 (0.046, 0.112)	<0.001	0.114 (0.081, 0.148)	<0.001
UMEC 125	407	1.405	0.129	-	-	-	-
VI 25	404	1.379	0.093	-	-	-	-
Placebo	275	1.245	-0.031	0.160 (0.122, 0.198)	<0.001	0.124 (0.086, 0.162)	<0.001
3373							
UMEC/VI 62.5/25	413	1.406	0.171	0.052 (0.017, 0.087)	0.004	0.095 (0.060, 0.130)	<0.001
UMEC 62.5	418	1.354	0.119	-	-	-	-
VI 25	421	1.311	0.076	-	-	-	-
Placebo	280	1.239	0.004	0.115 (0.076, 0.155)	<0.001	0.072 (0.032, 0.112)	<0.001

Source: Module 5.3.5.3, Integrated Summary of Efficacy, Table 47 and FDA Statistical Briefing Document

The active-controlled trials, 3360 and 3374, did include a direct comparison of the two dose levels of UMEC/VI. As shown in Table 5, there was no clear dose response between the two dose levels on the basis of trough FEV1.

Table 5 Trials 3360 and 3374: Mean change from baseline in trough FEV1 at Day 169 (ITT)							
Treatment	N	LS mean (L)	LS mean change	Difference from UMEC (95% CI)	P	Difference from VI (95% CI)	P
3360							
UMEC/VI 62.5/25	207	1.521	0.211	-	-	0.088 (0.037, 0.139)	<0.001
UMEC/VI 125/25	208	1.519	0.209	-	-	0.093 (0.041, 0.144)	<0.001
VI 25	205	1.431	0.121	-	-	-	-
Tiotropium 18	203	1.431	0.121	-	-	-	-
3374							
UMEC/VI 62.5/25	217	1.355	0.208	0.022 (-0.027, 0.072)	0.377	-	-
UMEC/VI 125/25	215	1.369	0.223	0.037 (-0.012, 0.087)	0.142	-	-
UMEC 125	222	1.332	0.186	-	-	-	-
Tiotropium 18	215	1.295	0.149	-	-	-	-

Source: Module 5.3.5.3, Integrated Summary of Efficacy, Table 47 and FDA Statistical Briefing Document

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 support for the factorial contribution of UMEC 62.5 and VI 25 in the combination on the basis of trough FEV1 was provided by the crossover exercise trials, 4417 and 4418 (Table 6). Comparison of UMEC/VI 62.5/25 versus UMEC 62.5 showed a treatment difference of 124 ml and 99 ml, respectively, in each trial, supporting the contribution of VI 25 to the combination. Comparison of UMEC/VI 62.5 versus VI 25 showed a treatment difference of 111 ml and 132 ml, demonstrating the contribution of UMEC 62.5 to the combination. While there was no dose separation between the two dose levels of UMEC/VI in either trial, there was dose ordering for the UMEC 62.5 and UMEC 125 in each trial.

Table 6 Trials 4417 and 4418: Mean change from baseline in trough FEV1 at Week 12 (ITT)							
Treatment	N	LS mean (L)	LS mean change	Difference from UMEC (95% CI)	P^c	Difference from VI (95% CI)	P
4417							
UMEC/VI 62.5/25	152	1.615	0.178	0.124 ^a (0.067, 0.181)	<0.001	0.111 (0.062, 0.161)	<0.001 ^c
UMEC/VI 125/25	144	1.573	0.136	0.029 ^b (-0.028, 0.086)	0.320	0.070 (0.019, 0.120)	0.007 ^c
UMEC 62.5	49	1.491	0.054	-	-	-	-
UMEC 125	50	1.544	0.108	-	-	-	-
VI 25	76	1.503	0.067	-	-	-	-
Placebo	170	1.404	-0.032	-	-	-	-
4418							
UMEC/VI 62.5/25	130	1.520	0.200	0.099 ^a (0.041, 0.157)	<0.001	0.132 (0.081, 0.183)	<0.001
UMEC/VI 125/25	128	1.538	0.218	0.006 ^b (-0.055, 0.067)	0.849	0.150 (0.098, 0.201)	<0.001
UMEC 62.5	40	1.421	0.101	-	-	-	-
UMEC 125	41	1.532	0.212	-	-	-	-
VI 25	64	1.388	0.069	-	-	-	-
Placebo	151	1.277	-0.043	-	-	-	-

^aUMEC/VI 62.5/25 versus UMEC 62.5

^bUMEC/VI 125/25 versus UMEC 125

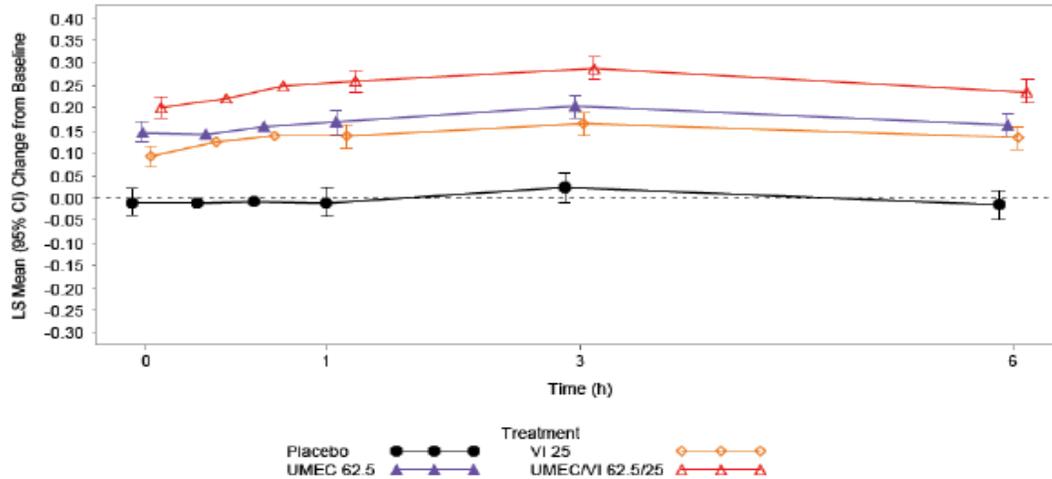
^cnominal p-values; not adjusted for multiplicity

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

- **Serial FEV1**

Serial FEV1 0-6h was assessed as an alternative spirometric endpoint in the four main efficacy trials. Representative results for the proposed UMEC/VI 62.5/25 dose from Trial 3374 are shown in Figure 8. These results were supportive of a benefit for UMEC/VI 62.5/25 over each monocomponent and placebo.

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

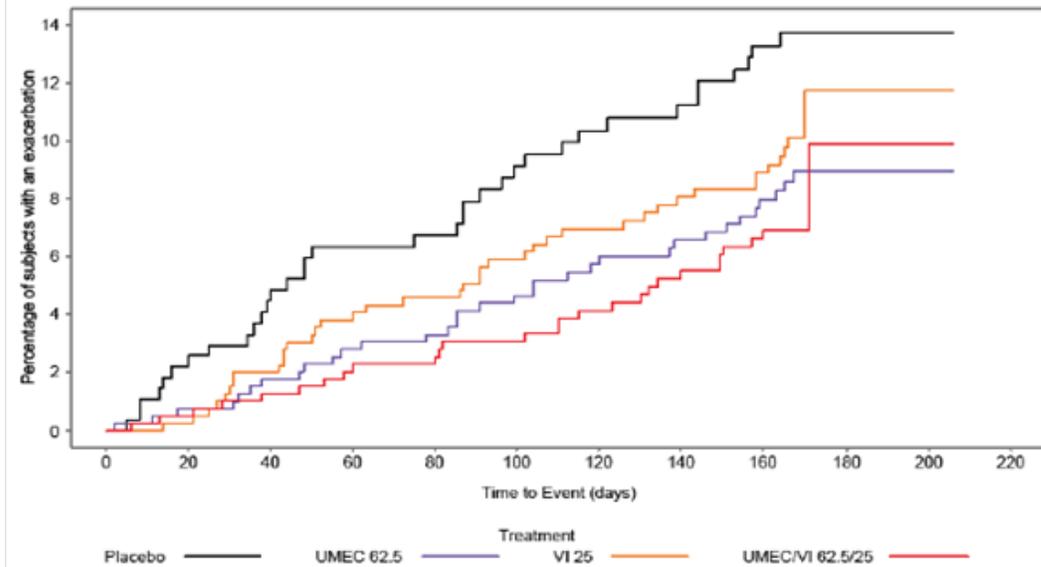


Source: Module 5.3.5.1, CSR DB213373, Figure 10

- **COPD exacerbation**

While the four main efficacy trials were not designed to assess COPD exacerbations, data on exacerbations were collected as an additional assessment of both safety and efficacy. In the placebo-controlled Trial 3373, factorial comparisons favored the combination UMEC/VI 62.5/25 over UMEC 62.5, VI 25, and placebo (Figure 9). Similar results were observed for UMEC 125 and UMEC/VI 125/25 in Trial 3361.

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



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

- **Other efficacy variables**

Data for other efficacy variables such as rescue medication use and symptom scores were generally supportive of benefit for UMEC/VI 62.5/25 over placebo and the individual components. These results are discussed in further detail in FDA's clinical and statistical briefing documents.

Efficacy conclusions

The UMEC/VI development program includes replicate evidence of efficacy for the UMEC 62.5 mcg monocomponent versus placebo in terms of trough FEV1 and serial FEV1 (Trials 3373, 5321, 3073, and 5408). Efficacy for the VI 25 monocomponent has been previously established as part of the Breo Ellipta development program and was reconfirmed in the UMEC/VI development program (Trials 3361, 3373, 4417, and 4418). Statistically significant differences in trough FEV1 between UMEC/VI 62.5/25 and VI 25 alone and UMEC 62.5 alone were observed in Trial 3373 and further supported by similar results in the exercise trials, Trials 4417 and 4418. The results of the factorial comparisons support the contribution of each component to the combination.

8. Safety

Overview of the safety database

The safety database for UMEC/VI 62.5/125 centers on the four main 6-month efficacy trials (3361, 3373, 3360, and 3374) and the one-year placebo-controlled safety trial (3359) that evaluated a dose of UMEC/VI (125/25) higher than the proposed dose of UMEC/VI 62.5/25. These trials are supplemented by 12-week and 28-day dose-ranging trials (5408 and 3589), the two 12-week exercise trials (4417 and 4418), pharmacokinetic and dose-ranging trials of shorter duration, and safety data available for the VI component from the Breo Ellipta development program. From these trials, a total of 8138 patients were treated with at least one dose of UMEC/VI, UMEC, VI, placebo, or tiotropium, of which a total of 2454 patients received UMEC/VI 62.5/25 or 125/25 and 1663 patients received UMEC 62.5 or 125.

The application pooled the COPD safety database into several different groups for analysis. This memorandum focuses on the following three groupings:

1. "Primary efficacy studies" comprised of the the four main efficacy trials: 3361, 3373, 3360, and 3374
2. Trial 3359, the one-year, placebo-controlled safety trial
3. All COPD studies with a treatment duration of at least 12 weeks: 3361, 3373, 3360, 3374, 3359, 5408, 4417, and 4418 (basis of MACE analysis)

In the Primary Efficacy trials, the median duration of exposure ranged from 167 to 168 days across treatment arms. The median duration of exposure in Trial 3359 was 357 days. In the COPD program, a total of 1,312 subjects were exposed to UMEC 62.5, UMEC 125, UMEC/VI 62.5/25, or UMEC/VI 125/25 for 24 weeks or longer. A total of 279 patients were exposed to UMEC 125 or UMEC 125/25 for 48 weeks or longer.

The baseline demographic characteristics of the Primary Efficacy trial grouping were as follows: mean age 63 years, 68% male, and 84% White. The majority of patients reported a 1

to <10 year history of COPD and 66% and 61% reported diagnoses of chronic bronchitis and emphysema, respectively. Twenty-eight percent of patients reported a COPD exacerbation in the past year requiring systemic corticosteroids and/or antibiotics; another 10% reported an exacerbation required hospitalization in the past year. Comorbid medical conditions were generally similar across treatment groups in the four trials, with the exception of cardiac disorders, which were slightly lower in the placebo group (18%) compared to the active treatments (19-24%), and skin and subcutaneous disorders, which were slightly higher in the placebo arm (12%) compared to the active treatment arms (6-10%). Baseline demographic characteristics in Trial 3359 were overall similar to those described for the four efficacy trials. Comorbid conditions were similar across treatment arms, although the rate of current cardiovascular risk factors was slightly lower in placebo (64%) than in the UMEC 125 or UMEC/VI 125/25 arms (68% and 67%, respectively).

Study completion rates for the Primary Efficacy trials were lowest in the placebo group (70%) compared to the active treatment arms (76 to 83%). The most commonly cited reason for early withdrawal in the placebo group was lack of efficacy (15%) with COPD exacerbation reported among 11%. By comparison, lack of efficacy was cited in 5% to 10% of patients in the active treatment arms. In Trial 3359, rates of study completion ranged from 59% to 63%. As in the Primary Efficacy trials, lack of efficacy was reported more commonly in placebo (8%) as a reason for discontinuation compared to the active treatment arms (<1% to 1%). Early discontinuation secondary to adverse event or protocol-defined stopping criteria are discussed in the sections below.

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/VI 62.5/25 (n=6/1124), UMEC/VI 125/25 (n=1/1330), UMEC 62.5 (n=3/576), UMEC 125 (n=7/1087), VI (n=22/2501), and tiotropium (n=2/423). 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/VI or UMEC.

Discontinuations due to adverse events

Overall rates for early withdrawal due to an AE were similar among treatment arms in the Primary 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 treatment arms in Primary Efficacy trials, 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)²⁶

The rates for all non-fatal serious adverse events were evenly distributed across treatment arms, ranging between 5-6% in the Primary 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 the Primary Efficacy trials 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**

For this application, cardiovascular safety for UMEC, a new molecular entity, is a topic of interest given the general concerns associated with the LAMA drug class. 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 (grouping #3). Since drug exposure varied across trials, exposure-adjusted rates were also assessed.

²⁶ 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.

As seen in Table 7, 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/VI 62.5/25. However, when looking at non-fatal myocardial infarction, a subcategory of cardiac ischemia used for the narrow-definition MACE analysis, a small imbalance was observed in terms of exposure-adjusted rates. There was no apparent dose response and the combination of UMEC and VI did not appear to have an additive or synergistic effect.

Table 7 MACE analyses in integrated COPD database							
	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N=1053	N=1124	N=1330	N=576	N=1016	N=1174	N=423
	SY=369	SY=408	SY=573	SY=202	SY=449	SY=441	SY=173
<i>Number (%) of Subjects</i>							
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)
<i>Non-fatal MI</i>	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)
<i>Number of Subjects with Events per 1000 Subject-Years</i>							
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
<i>Non-fatal MI</i>	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.

The analysis for this broader set of search terms on the Primary Efficacy trials is shown in Table 8. Consistent with the MACE analyses shown above, rates for cardiac ischemia, sudden death, or stroke appear fairly similar between UMEC/VI 62.5/25 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 8 Cardiovascular serious and non-serious AE of special interest (Primary Efficacy trials)							
Adverse event	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N=555 SY=208	N=842 SY=346	N=832 SY=336	N=418 SY=168	N=629 SY=249	N=1034 SY=411	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, Table 113

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 9). While some imbalances were observed, the data do not show a clear treatment-related or dose-related pattern.

Table 9 Cardiovascular serious and non-serious AE of special interest (Trial 3359)			
Adverse event	Placebo	UMEC/VI 125/25	UMEC 125
	N=109 SY=80	N=226 SY=177	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, Table 123

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)

The Applicant conducted an analysis on the subgroup of on-treatment cardiovascular AESI which were reported as SAEs (Table 10). No imbalances were observed in the long-term safety trial, Trial 3359, which evaluated the higher dose of UMEC/VI 125.25. However, a small imbalance was observed in the Primary Efficacy trials, although a comparison across active treatment arms was somewhat inconsistent. A breakdown of the serious cardiovascular AESI reported in the Primary Efficacy trials indicates that the imbalance is largely attributable to the cases of non-fatal MI (a subcategory of cardiac ischemia events) that were identified in the MACE analysis. Overall numbers of patients were low, with <1% of patients experiencing a cardiac ischemic event in any treatment arm, including UMEC/VI 62.5/25 and placebo.

Table 10 Cardiovascular serious AE of special interest (Primary Efficacy trial and Trial 3359)							
Safety group	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO 18
Number (%) of Subjects							
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	2 (<1)	8 (<1)	7 (<1)	7 (2)	9 (1)	18 (2)	3 (<1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	2 (2)	--	4 (2)	--	5 (2)	--	--
Number of Subjects with Events per 1000 Subject-Years							
Primary Efficacy	SY=208	SY=346	SY=336	SY=168	SY=249	SY=411	SY=173
	9.6	23.1	20.8	41.7	36.2	43.8	17.3
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	24.9	--	22.7	--	29.9	--	--

Source: Module 5.3.5.3, ISS, Tables 119, 120, 126, and 127

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 ECGs 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 reported in both the Primary Efficacy trial and long-term safety population 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 Primary Efficacy trials. The ECG and Holter abnormalities that resulted in early withdrawal vary and are not specific for a particular AE, but the actual outcomes of these patients following their discontinuation from the trials remain an 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/VI 62.5/25.

- **Lower respiratory tract infection/pneumonia**

In general, the rates for lower respiratory tract infection (LTRI) and pneumonia were low. In the Primary Efficacy trials, the rate ranged from 1-4% and in the long-term safety trial, from 2-5%. While a small imbalance was observed between placebo (1%) and UMEC/VI 62.5/25 (3%) in the Primary Efficacy trial, the rates for the corresponding monocomponents, UMEC 62.5 and VI 25, were 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 as has been observed with ICS/LABA combination products in COPD.

Common adverse events

The rates for any AE varied among the treatment arms (48-55% in the Primary Efficacy trials; 52-58% in the long-term safety trial). Adverse events occurring in $\geq 3\%$ and more commonly than in placebo are summarized in Table 11 and Table 12.

Table 11 Common adverse events reported in $\geq 3\%$ and occurring more commonly than in placebo (Primary Efficacy trials)							
	Placebo N=555	UMEC/ VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=103 4	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE	264 (48)	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)
Headache	58 (10)	76 (9)	75 (9)	32 (8)	62 (10)	87 (8)	24 (6)
Nasopharyngitis	48 (9)	74 (9)	77 (9)	29 (7)	43 (7)	98 (9)	33 (8)
Cough	23 (4)	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)
URTI	21 (4)	27 (3)	24 (3)	21 (5)	23 (4)	32 (3)	22 (5)
Back pain	20 (4)	31 (4)	23 (3)	8 (2)	27 (4)	20 (2)	15 (4)
Hypertension	10 (2)	13 (2)	15 (2)	10 (2)	18 (3)	24 (2)	8 (2)
Oropharyngeal pain	9 (2)	17 (2)	17 (2)	6 (1)	12 (2)	29 (3)	5 (1)
COPD	14 (3)	19 (2)	15 (2)	12 (3)	8 (1)	14 (1)	6 (1)
Arthralgia	8 (1)	10 (1)	17 (2)	12 (3)	10 (2)	14 (1)	7 (2)

Source: Module.3.5.3, ISS, Table 74

This table includes on-treatment AEs

AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease; URTI=upper respiratory tract infection

Table 12 Common adverse events reported in $\geq 3\%$ and occurring more commonly than in placebo (Trial 3359)			
	Placebo	UMEC/VI	UMEC
	N=109	125/25 N=226	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/VI 62.5/25.

Ongoing and future studies

While the safety data available for review has already been described, GSK has also provided information on the following ongoing or future studies:

- Additional controlled data from other ongoing UMEC/VI studies, ranging in duration from 12 weeks to 24 weeks, in approximately 1880 more patients will be made available by the first quarter of 2014. (b) (4)

(b) (4)

Safety summary

The safety database for UMEC/VI includes safety information for the individual components, UMEC and VI, as well as for the combination. The nature of the adverse events identified for UMEC/VI appears generally consistent with the safety profile associated with the LAMA and LABA drug classes. For this application, cardiovascular safety for UMEC, a new molecular entity, is a topic of interest given the general concerns associated with the LAMA drug class. 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. On the other hand, imbalances can be found when examining subsets of the data. Namely, a small imbalance in the Primary Efficacy trials was observed for non-fatal myocardial infarction that was not seen in the 12-month safety trial or in the larger integrated, exposure-adjusted COPD safety database. Likewise, differential withdrawal for protocol-specified ECG and Holter abnormalities was seen in the long-term safety trial but not in the Primary Efficacy trials. ECG and Holter data obtained from the large sample of patients that remained in the trials was fairly unremarkable.

These data, in the context of the information available for other LAMA products, suggests that there may an increased risk of cardiovascular events associated with UMEC/VI, but the magnitude of the risk is likely to be limited. This reviewer believes that a controlled trial to quantify this risk would require a very large sample and would not be justified, as the additional data would not necessarily improve on the information already available from the completed clinical program nor would the data be likely to assist in risk mitigation. This view of the UMEC/VI safety data is informed in part by the UPLIFT trial and the recently published TIOSPIR trial, for which the overall results appear reassuring. As a result, the CDTL review does not recommend a dedicated, randomized, controlled trial to further evaluate cardiovascular risk under FDAAA Section 505(o)(3). For similar reasons, the CDTL review does not endorse GSK's

(b) (4)

(b) (4)

While the CDTL review concludes at this time that the safety data appear adequate to support approval of UMEC/VI 62.5/26 mcg and do not warrant a PMR trial, it is worth noting that the application of the regulations under FDAAA Section 505(o)(3) have been subject to interpretation and are influenced by precedent, emerging science, and other factors specific to the disease indication and patient population in question. For these reasons, the Division will be presenting the question of a possible PMR trial for this NDA at a Regulatory Briefing, scheduled for December 6, 2013. Pending the discussion at the briefing, the final recommendation regarding the need for a PMR trial or other postmarketing studies is subject to change.

9. Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on September 10, 2013, to discuss the application. The panel members largely agreed that the data support the efficacy of UMEC/VI 62.5/25 mcg once daily for the proposed bronchodilation indication (Yes-No vote, 13-0). The issue of missing data was noted, although one panel member noted that the data for an exacerbation benefit were also supportive and impacted less by the missing data. On the issue of safety, the majority of panel members stated that the data were also largely supportive (Yes-No vote, 10-3), but concerns were raised regarding the generalizability of the safety data to patients with a history of more significant cardiovascular disease, comorbid conditions, or more severe pulmonary disease. Several suggestions were made to obtain additional data in the postmarketing setting under “real-world” conditions. A few members of the committee felt that safety data, particularly in reference to cardiovascular risk, were insufficient and recommended additional premarketing information. Overall, the committee voted for approval (Yes-No, 11-2) for UMEC/VI 62.5/25 mcg for the proposed indication in COPD.

As noted above, a Regulatory Briefing to discuss the issue of a possible PMR trial is scheduled for December 6, 2013.

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 the package insert and Medication Guide, which remain pending at the time of this memorandum. The proposed tradename is Anoro Ellipta, which has been found acceptable by DMEPA. Consults from PLT 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 5, Warnings and Precautions: Inclusion of clinical trial data relevant to possible increased cardiovascular risk
- Section 6, Adverse Reactions: [REDACTED] (b) (4)
- Sections 8, 10, and 12: [REDACTED] (b) (4)
- Section 14, Clinical Studies: Addition of dose-ranging information for both the individual UMEC and VI components, include serial time curves at Day 1 and 7 from the UMEC dose-ranging trial (Trial 5321) and Day 1 and Day 28 from the VI dose-ranging trial in COPD (Trial 1045). Inclusion of description of other supportive trials for the trough FEV1 endpoint [REDACTED] (b) (4).
- Medication Guide: Revised to maintain consistency with related inhaled products.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended Regulatory Action is Approval. This recommendation is in concurrence with the recommendations of the different review disciplines.

- Risk Benefit Assessment

The UMEC/VI development program includes replicate evidence of efficacy for the UMEC 62.5 mcg monocomponent as a bronchodilator versus placebo. Efficacy for the VI 25 monocomponent has been previously established as part of the Breo Ellipta development program and was reconfirmed in the UMEC/VI development program. Statistically significant differences in trough FEV1 between UMEC/VI 62.5/25 and VI 25 alone and UMEC 62.5 alone were observed in Trial 3373 and further supported by similar results in the exercise trials, Trials 4417 and 4418. These factorial comparisons demonstrate the relative bronchodilatory benefit of UMEC/VI 62.5/25 over the individual components.

In terms of safety, the safety database for UMEC/VI 62.5/25 appears consistent with the general safety profile observed with LABAs and LAMAs. There are some imbalances in the safety data when examining subsets of the integrated safety database. That being said, this reviewer concludes that while there may be some increased risk, the risk is small and does not outweigh the overall benefit demonstrated for the product. The CDTL review does recommend inclusion of the available cardiovascular data to inform healthcare professionals in their decision-making process when formulating a risk-benefit assessment for individual patients.

- 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, pending discussion at the December 6, 2013, Regulatory Briefing.

- Recommended Comments to Applicant

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN L LIMB
11/09/2013