PULMONARY ALLERGY DRUGS ADVISORY COMMITTEE MEETING

FDA Briefing Document

September 10, 2013

NDA 203-975: umeclidinium and vilanterol inhalation powder for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application (NDA) 203-975, umeclidinium and vilanterol inhalation powder, for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

FDA Briefing Package

Division Memorandum

Date: September 10, 2013

From: Susan Limb, MD
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To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for New Drug Application (NDA) 203-975, umeclidinium and vilanterol inhalation powder, at a dose of 62.5 mcg/25 mcg once daily for the long-term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on September 10, 2013. As members of the PADAC, you provide important expert scientific advice and recommendations to the US Food and Drug Administration (the Agency) on the regulatory decision-making process related to the approval of a drug or biologic product for marketing in the United States. The upcoming meeting is to discuss (NDA) 203-975 from GlaxoSmithKline (GSK), umeclidinium and vilanterol inhalation powder, 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, 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 (application currently under review).

As both LAMA and LABA are used to treat airflow obstruction in COPD, GSK was tasked with demonstrating that the use of two bronchodilatory agents in combination provides an added benefit over either bronchodilator alone. GSK was asked to provide data to support the following: 1) the nominal dose and dosing frequency for each of the components, including evidence of efficacy and safety for UMEC and VI alone in COPD; 2) data demonstrating the efficacy contribution of VI to the UMEC/VI combination; 3) data demonstrating the efficacy contribution of UMEC to the UMEC/VI combination.

The data to support the dose selection and efficacy and safety of VI were previously reviewed and vetted as part of the Breo Ellipta program. Therefore, the discussion at this PADAC meeting will focus more closely on the data in support of the UMEC component and the UMEC/VI combination. As you deliberate on the data submitted in support of the proposed indication, you will be asked to consider the strength of the data to support the benefit of the UMEC/VI combination over either UMEC or VI alone. We will also request that you provide your interpretation of the various safety analyses, particularly cardiovascular safety.

The content of this document and the materials prepared by the Agency reflect the preliminary findings and opinions based on reviews of the information submitted by GSK. These materials do not represent the final position of the Agency. The opinions and insights provided by you at this PADAC meeting will be an important factor in our decision on this application.

The clinical and statistical issues related to the FF/VI clinical trial results are the primary focus of this PADAC meeting. In determining approvability of a product, the Agency takes into consideration other factors in the regulatory decision-making process, including the manufacturing and controls of a product and preclinical data. These will not be the focus of this PADAC meeting.

Attached are the background materials for this meeting. In addition to this memorandum, the FDA background materials include the following: Clinical Briefing Document, Statistical Briefing Document, and a summary of the clinical pharmacology program.

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. Arfomoterol 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).

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. Safety concerns regarding a possible increased risk of stroke, cardiovascular death, and myocardial infarction (MI) associated with inhaled anticholinergic use have been raised following a meta-analysis of 17 clinical trials in COPD.[1] These concerns are echoed in the experience with an alternate tiotropium formulation delivered by the Respimat device, which is not approved in the US. 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. However, interpretation of these results is limited by the lack of pre-specification of safety endpoints and retrospective vital status assessment. At the time of this memorandum, the manufacturer of tiotropium Respimat is conducting a large, prospective safety trial to further evaluate the risk.

In contrast with the meta-analysis and the tiotropium Respimat trials, 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.[2] With 17,721 patient-years of exposure, the UPLIFT study doubled the size of the tiotropium safety database. The UPLIFT results were discussed at a previous PADAC meeting held on November 19, 2009. Given the strength of the UPLIFT study design and findings, the committee members and the Agency subsequently concluded that the current data do not support an increased risk of stroke, myocardial infarction, or death associated with

[1] Singh S, Loke YK, Furberg CD. JAMA 2008; 300: 1439-50.
[2] Tashkin DP, Celli B, Senn S, et al. N Engl J Med 2008; 359: 1543-54.

Spiriva Handihaler.[3] However, the safety signal for the tiotropium Respimat formulation remains unresolved at this time. More recently, another LAMA, aclidinium bromide (Tudorza Pressair) was approved for COPD.[4] The approval letter dated July 23, 2012, identified major cardiovascular adverse events as a potential safety signal and noted a postmarketing requirement to conduct a randomized, controlled trial to evaluace the risk of these events in patients with COPD. Therefore, cardiovascular adverse events and stroke remain safety issues of interest for this class of drugs.

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).[5] 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.[6, 7, 8, 9, 10] The issue has been discussed at previous FDA Advisory Committee meetings[11] and in the literature,[12, 13, 14] and is the subject of a safe use strategy outlined by the Agency.[15] 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.[16] While the underlying pathophysiology for these asthma-related severe adverse events

[3] Michele TM, Pinheiro S, Iyasu S. N Engl J Med 2010; 363:1097-99.
[4] July 23, 2012, Approval Letter, accessed from http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202450Orig1s000Approv.pdf
[5] *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/.
[6] Benson RL, Perlman F. J Allergy 1948; 19:129-140.
[7] Lowell FC, Curry JJ, Schiller IW. N Eng J Med 1949; 240:45-51.
[8] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Thorax 1991; 46:105-111.
[9] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al. N Eng J Med 1992; 326:501-506.
[10] US Product Labels of salmeterol and formoterol containing products
[11] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[12] Martinez FD. New Eng J Med 2005; 353:2637-2639.
[13] Kramer JM. New Eng J Med 2009; 360:1952-1955.
[14] Drazen JM, O'Byrne PM. New Eng J Med 2009; 360:1671-1672.
[15] Chowdhury BA, DalPan G. New Eng J Med 2010; 362:1169-1171.
[16] Chowdhury BA, Seymour SM, Levenson MS. New Eng J Med 2011;364:2473-5

remains uncertain, studies suggest that these events may be dose-related[17]. As a result, a higher dose of inhaled formoterol was not approved in the US due to the occurrence of severe asthma-related adverse events[18]. 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.[19]

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 FF/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

[17] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Chest 2003; 124:70-74.
[18] Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. N Eng J Med 2011; 365:2247-2249.
[19] 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

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.

- **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, 2013, NDA submission for UMEC/VI 125/25 mcg and 62.5/25 mcg (NDA 203795)**
- **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)**

Product Information

Umeclidinium/vilanterol inhalation powder is a novel, fixed-dose, combination product administered by oral inhalation. The proposed dose is 62.5/25 mcg once daily. UMEC is not currently available as an inhalation monotherapy, and as mentioned above, there are currently no plans to market VI commercially. VI is available in a fixed-dose combination with fluticasone furoate (Breo Ellipta). UMEC/VI is administered by the same dry powder inhaler device 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 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.

Nonclinical Pharmacology and Toxicology

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.

Clinical Pharmacology

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.

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.

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.

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 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 *23%*
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) *55%*
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)
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) *42%*

[a] R=randomized, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, SD=single dose, XO=crossover

[b] 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 *Mar 2011 – Sep 2012*	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%*
DB2113373 *Mar 2011 – Apr 2012*	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 *Mar 2011 – Apr 2012*	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 *Mar 2011 – Apr 2012*	R, DB, DD, AC, PG	215 217 222 215	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 Tio 128	Trough FEV1	95 sites (US, E and W Europe, S. America, Australia, Canada, Mexico, S Korea, S Africa) *26%*
12-week exercise trials					
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%*
BD2114418 *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/VI 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

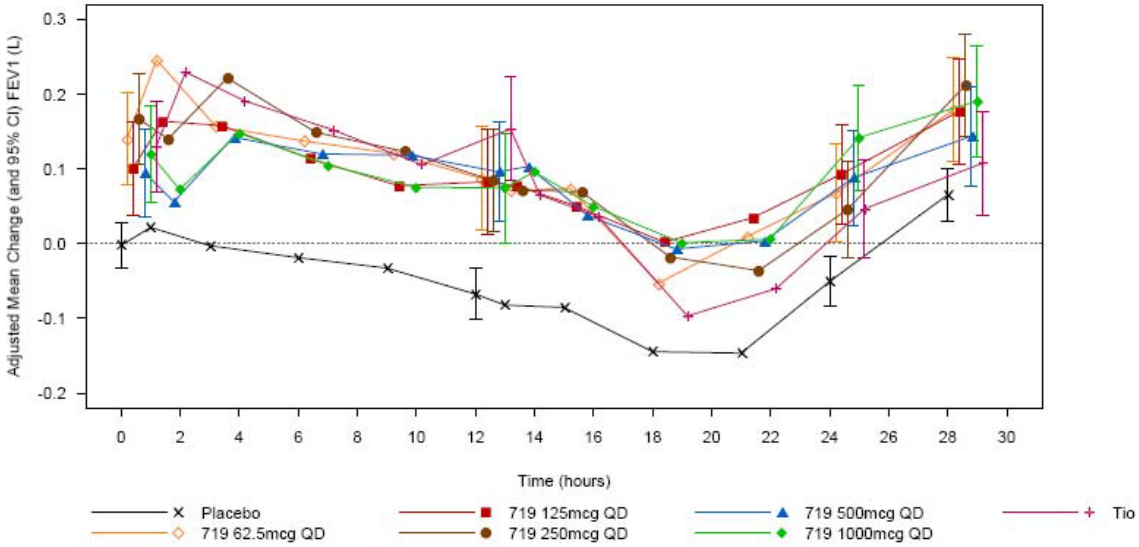
Dose selection

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.

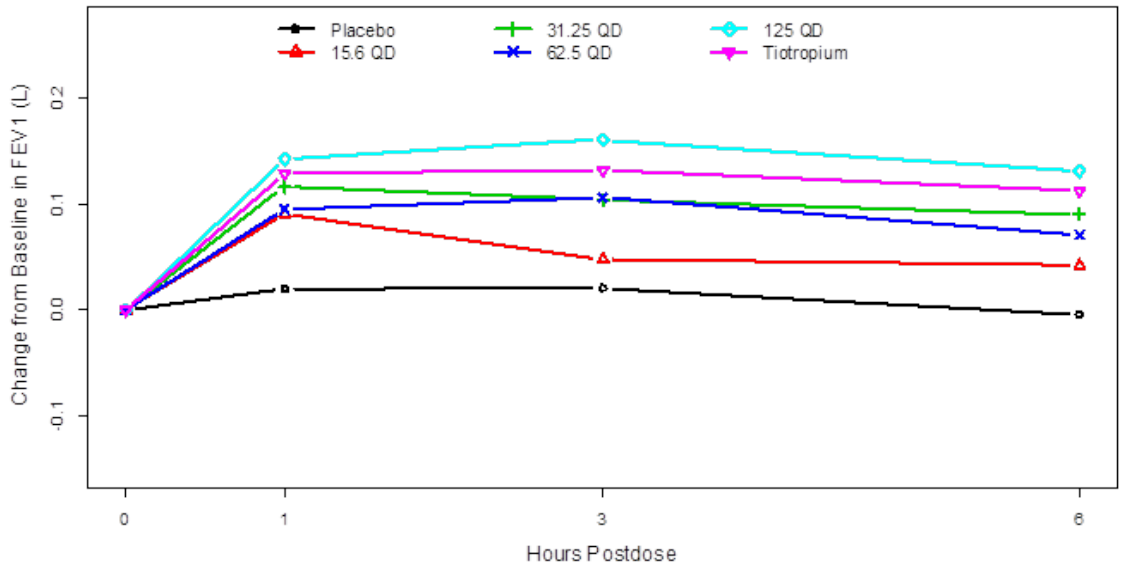
Figure 1 Trial 3073: Adjusted mean change from baseline in FEV1 (L) over 24 hours at Day14



Source: CSR AC4113073, Figure 6

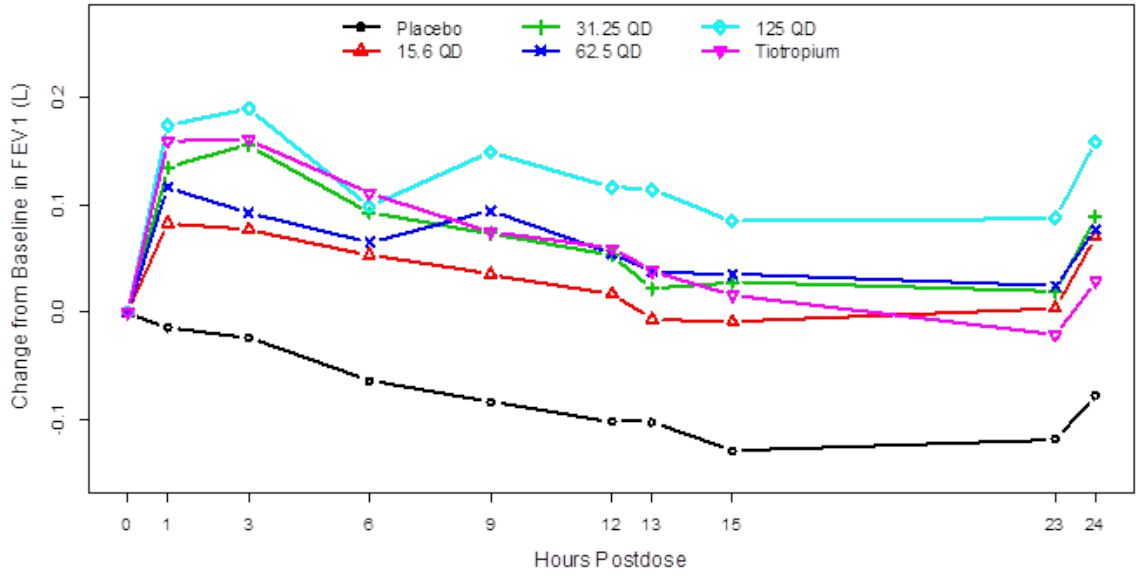
To explore the lower end of the dose range further, Trial 5321 evaluated doses ranging from 15.6 mcg to 125 mcg once daily. The serial FEV1 over 6 hours at Day 1 demonstrated a dose response, with the lowest UMEC 15.6 mcg dose overlapping with placebo at the peak 3-hour timepoint (Figure 2). While there 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 FEV_1 at Day 1 for different once-daily umeclidinium doses and tiotropium



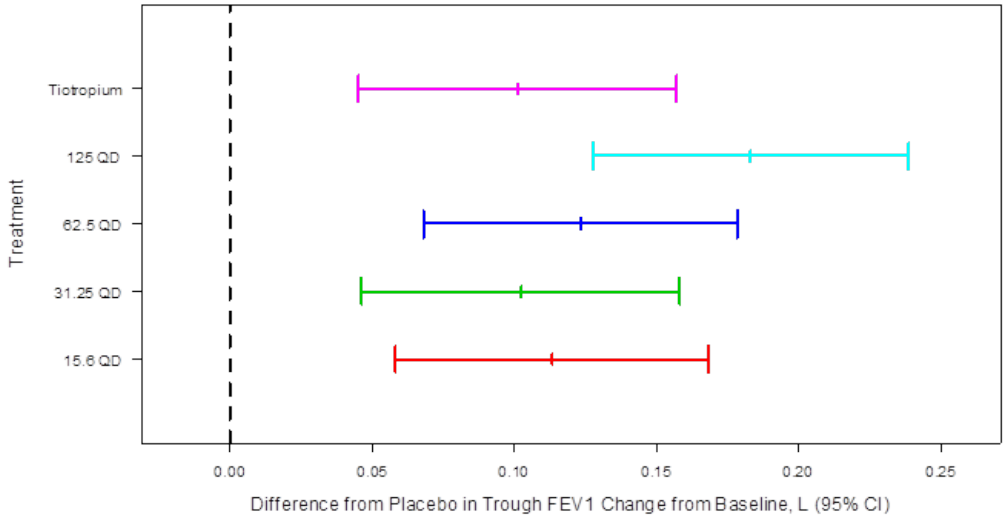
Source: FDA Statistical Review

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

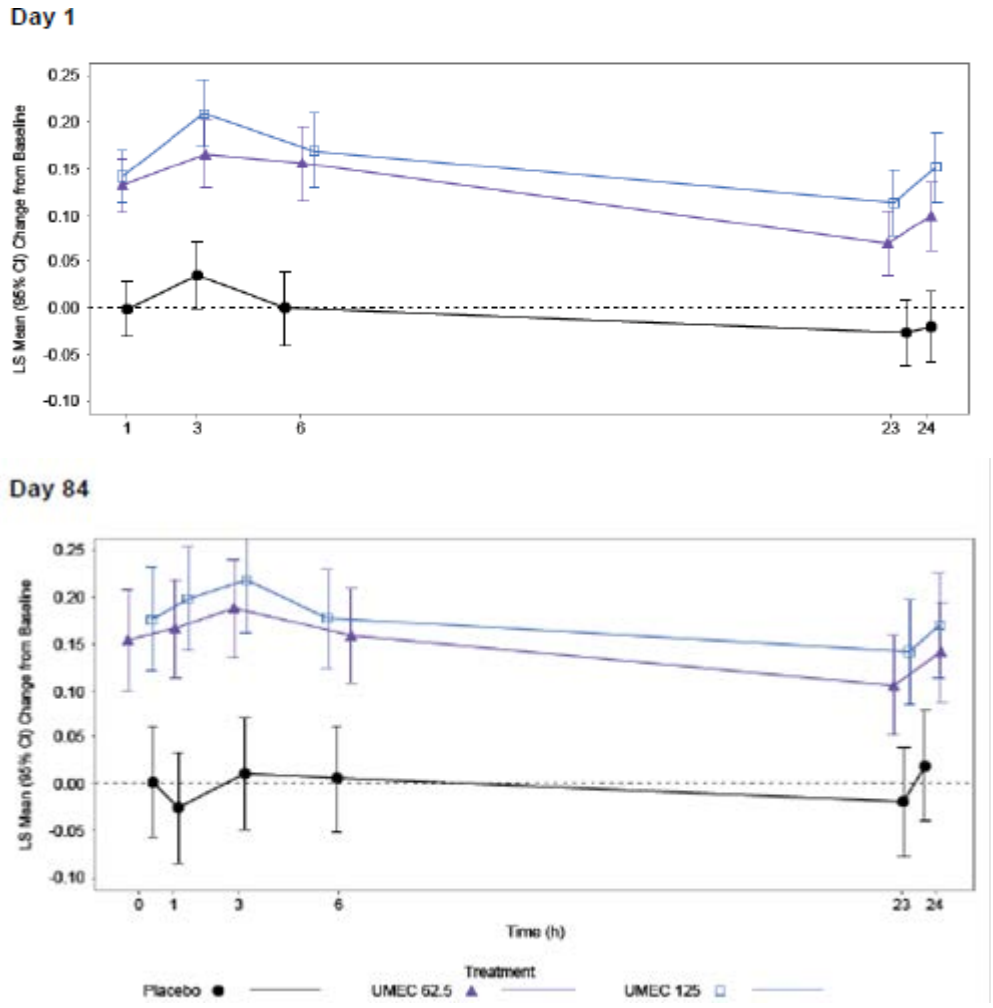
The results from Trial 5321 suggest that UMEC 15.6 is at the low end of the dose response curve and subtherapeutic with overlap with placebo on some analyses. Doses of UMEC from 31.25 through 125 separate from placebo and while the dose response was not consistent, UMEC 125 appears to have a greater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

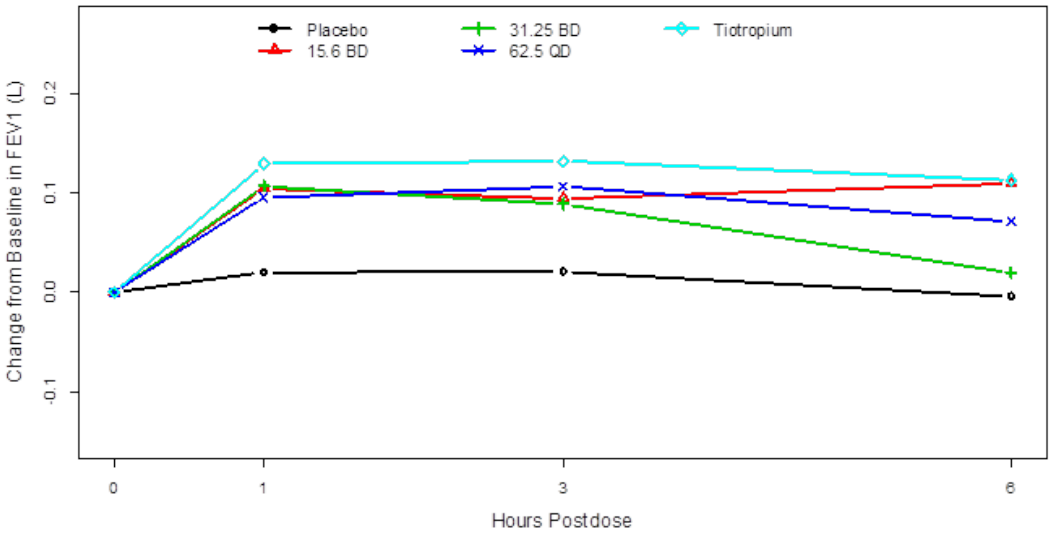


Source: Module 5.3.5.1, CSR AC4115408, Figures 6.13 and 6.17

- **Dosing frequency**

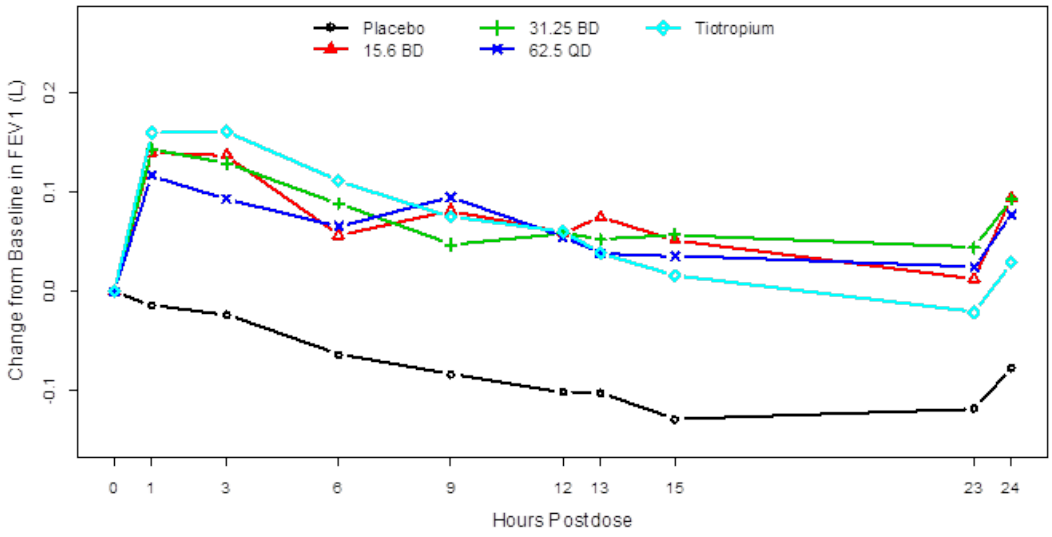
The dosing frequency of UMEC was evaluated in Trials 5321 and 3073. In Trial 5321, there was inconsistent dose separation among nominal daily doses below 125 mcg. However, the results did not suggest that twice-daily dosing was preferable to once-daily dosing for a given nominal dose at Days 1 and 7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

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, 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,[20] 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.

[20] 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.

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 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 Briefing Documents. 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)	0.002	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 discussion on the issue of missing data is located in the FDA Statistical Briefing Document included in this briefing package.

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 a clear dosing order for the UMEC 62.5 and UMEC 125 in each trial.

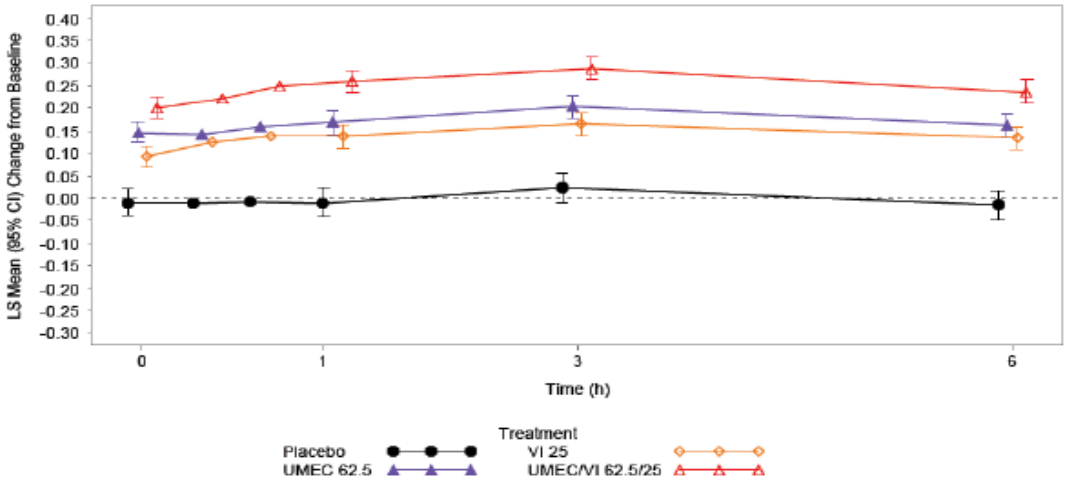
Table 6 Trials 4417 and 4418: Mean change from baseline in trough FEV1 at Week 12 (ITT)							
Treatment	**N**	**LS mean (L)**	**LS mean change**	**Difference from UMEC (95% CI)**	**P[c]**	**Difference from VI (95% CI))**	**P[c]**
4417							
UMEC 62.5/25	152	1.615	0.178	0.124[a] (0.067, 0.182)	<0.001	0.111 (0.062, 0.161)	<0.001
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
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 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	-	-	-	-

[a] UMEC/VI 62.5/25 versus UMEC 62.5
[b] UMEC/VI 125/25 versus UMEC 125
[c] nominal 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

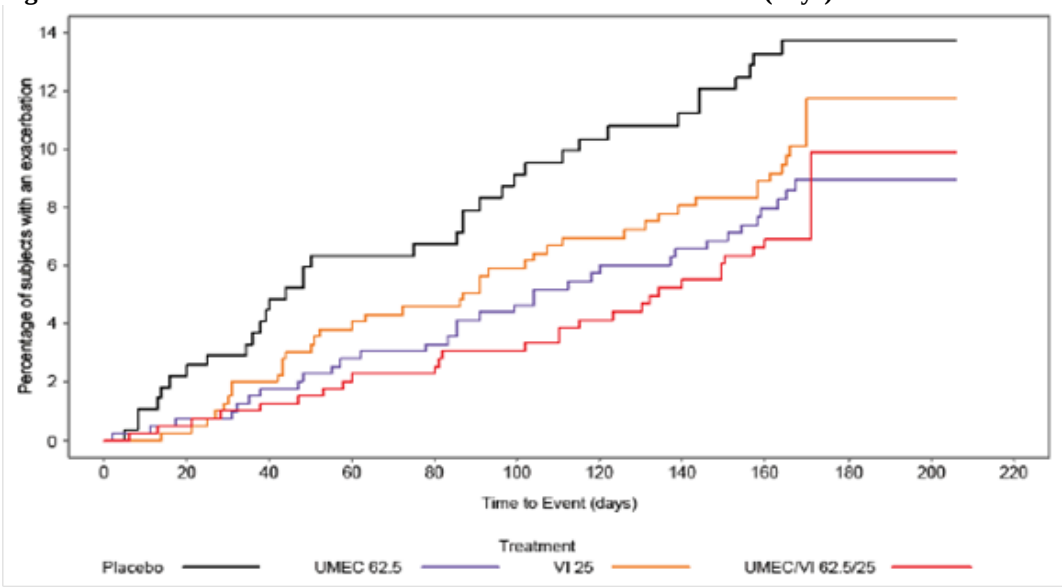


Source: Module 5.3.5.1, CSR DB213373, Figure 10

- **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 excerbation (days)



Source: Module 5.3.5.1, CSR DB2113373 Figure 17and 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, 3372, 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.

Safety findings

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 62.5/125. 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 Primacy 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 (8-10%). 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=22/2051), 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/VI or UMEC. A more detailed discussed of the individual cases can be found in the Clinical Briefing Document.

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)[21]

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, with the exception of dose-related pneumonia.

- **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

[21] 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.

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.

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 **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.

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** **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, 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 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, 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 ischemica 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. Further detailed discussion of this relative imbalance is found in the Clinical Briefing Document.

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 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 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. While the specific nature of the ECG and Holter abnormalities that resulted in early withdrawal is under review and may provide some insight, the actual outcomes for 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 ≥3% and more commonly than in placebo are summarized in Table 11 and Table 12.

Table 11 Common adverse events reported in ≥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=1034**	**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 ≥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/VI 62.5/25.

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 general 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. Whether these imbalances and discrepancies constitute a safety signal when taken in the context of the complete development program will be a topic for further discussion.

Benefit-risk 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 is fairly large but not entirely conclusive, particularly in regards to cardiovascular safety. There are some imbalances in the safety data when examining subsets of the integrated safety database, and a question remains whether the totality of the data are sufficient to address the potential concern raised by these imbalances.

In summary, GSK has conducted an extensive program to evaluate the efficacy and safety of UMEC/VI. Because UMEC is not approved as a monotherapy for COPD and a LAMA/LABA represents a novel combination, GSK was asked to provide data to support the nominal dose and dosing frequency and data to demonstrate the relative efficacy contributions of the UMEC and VI monocomponents to justify the combination for the treatment of COPD. While the submitted data are extensive, the data to support the safety of UMEC/VI is not entirely consistent. Whether the observed imbalances constitute a safety signal when taken in the context of the complete development program will be a major topic for discussion.

Summary

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by GSK to support the approval of umeclidinium/vilanterol 62.5/25 mcg once daily for the long-term, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. The major issues for discussion are: 1) the adequacy of the efficacy data to support the proposed dose of UMEC/VI 62.5/25 for the long-term, maintenance treatment of airflow obstruction; 2) the adequacy of the safety data to support long-term use of UMEC/VI 62.5/25 in COPD patients; and 3) the benefit-risk assessment for UMEC/VI 62.5/25 for the proposed indication.

At the meeting, GSK will present an overview of the clinical program and the efficacy and safety data. The Agency will follow with its own presentation of the efficacy and safety data. Please consider the questions listed in the following section that will be discussed after you listen to the presentations. Some of the questions are intended for discussions only, while others will be accompanied by a vote.

Draft Topics for Discussion

1. **DISCUSSION:** Discuss the data for umeclidinium/vilanterol (UMEC/VI) 62.5/25 mcg once daily in support of the proposed indication, 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. Consider the following issues in the discussion:
    - *Dose selection for umeclidinium*
    - *Comparison of efficacy for UMEC/VI 62.5/25 versus UMEC 62.5 mcg and VI 25 mcg alone*

2. **VOTE:** Do the efficacy data provide substantial evidence of a clinically meaningful benefit for UMEC/VI 62.5/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction in COPD?
    - *If not, what further data should be obtained?*

3. **DISCUSSION:** Discuss the safety profile of UMEC/VI 62.5/25 mcg once daily, particularly in regards to dose selection and cardiovascular safety.

4. **VOTE:** Has the safety of UMEC/VI 62.5/25 mcg once daily in COPD been adequately demonstrated for the proposed indication?
    - *If not, what further data should be obtained?*

5. **VOTE:** Do the efficacy and safety data provide substantial evidence to support approval of UMEC/VI 62.5/25 mcg once daily for the long-term, maintenance treatment of airflow obstruction in COPD?
    - *If not, what further data should be obtained?*

Clinical Review for the Pulmonary-Allergy Drugs Advisory Committee Meeting

September 10, 2013

umeclidinium/vilanterol inhalation powder NDA 203-975

Dose: 62.5 mcg/25 mcg (1 inhalation) once daily

Proposed indication:
Maintenance bronchodilator treatment of airflow obstruction in patients with COPD

Clinical Reviewer: Jennifer Rodriguez Pippins, MD, MPH

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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List of Commonly Used Abbreviations

AE	Adverse Event
AESI	Adverse Event of Special Interest
ATS/ERS	American Thoracic Society/European Respiratory Society
BDI	Baseline Dyspnea Index
BMI	Body Mass Index
CAT	COPD Assessment Test
CK	Creatine Kinase
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CT	Computed Tomography
CXR	Chest X-ray
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
EMA	European Medicines Agency
EOP2	End of Phase 2
ESWT	Endurance Shuttle Walk Test
ETT	Exercise Endurance Time
FEV1	Forced Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GSK	GlaxoSmithKline
HLT	Higher Level Term
IC	Inspiratory Capacity
ICS	Inhaled Corticosteroid
IND	Investigational New Drug
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
ISWT	Incremental Shuttle Walk Test
ITT	Intent-to-Treat
LABA	Long-acting Beta Agonist
LAMA	Long-acting Muscarinic Antagonist
LRTI	Lower Respiratory Tract Infection
MACE	Major Adverse Cardiac Events
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
mITT	Modified Intent-to-Treat
mMRC	Modified Medical Research Council Dyspnea Scale
MMRM	Mixed Model Repeated Measures

NDA	New Drug Application
NME	New Molecular Entity
PD	Pharmacodynamic
PK	Pharmacokinetic
PRO	Patient-reported Outcome
PT	Preferred Term
RV	Residual Volume
SAE	Serious Adverse Event
SGRQ	St. George's Respiratory Questionnaire (SGRQ)
SMQ	Standardized MedDRA Query
SOBDA	Shortness of Breath with Daily Activities Questionnaire
SOC	System Organ Class
TDI	Transition Dyspnea Index
TIO	Tiotropium
UMEC	Umeclidinium
VI	Vilanterol

1 Executive Summary

1.1 Brief Overview of the Clinical Development Program

GlaxoSmithKline (GSK) has submitted a New Drug Application (NDA) for a once-daily, fixed-dose, long-acting muscarinic antagonist (LAMA) and long-acting beta agonist (LABA) combination inhalation dry powder administered by a dry powder inhaler. The combination device contains umeclidinium bromide (a new molecular entity) as the LAMA and vilanterol trifenatate as the LABA in two double-foil blister strips. Within the foil packs, one strip contains 62.5 mcg of umeclidinium (UMEC) and the second 25 mcg of vilanterol (VI). A single UMEC/VI dose is proposed: 62.5 mcg/25 mcg administered as one inhalation once daily. The proposed trade name is Anoro™ Ellipta™.

The proposed indication is "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." Dose-ranging for each of the monocomponents was conducted as part of this application; particular attention is paid is this review to the dose-ranging for UMEC, as it is an NME. Dose-ranging for VI has been previously discussed at a Pulmonary-Allergy Drugs Advisory Committee meeting held on April 17, 2013, for a related product (fluticasone furoate and vilanterol inhalation power, NDA 204-275).

The core Phase 3 program consists of four primary efficacy trials (two placebo-controlled and two active-controlled), two exercise endurance trials, and one long-term safety trial. Evidence for efficacy comes from the four primary efficacy trials, with additional support from the exercise endurance trials. The core Phase 3 program also serves as the primary source of safety data.

1.2 Efficacy

The proposed indication for UMEC/VI 62.5 mcg/25 mcg once daily is the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD.

Evidence of efficacy comes from the core Phase 3 program, which consists of four primary efficacy trials and two exercise endurance trials. The four primary efficacy trials include two placebo-controlled trials and two active-comparator trials. The placebo-controlled trials were replicate in design and each compared UMEC/VI (either 62.5 mcg/25 mcg or 125 mcg/25 mcg) to placebo and to the monotherapies making up the combination. The active-controlled trials were also replicate in design and each

compared both doses of UMEC/VI (62.5 mcg/25 mcg and 125 mcg/25 mcg) to tiotropium, and also included either of the monotherapies as a comparator. These four trials included patients with moderate to very severe COPD (GOLD stages II-IV), and the duration of the double-blind treatment period was 24 weeks. The two exercise endurance trials were replicate in design and each evaluated both doses of UMEC/VI, both doses of UMEC, VI, and placebo. In contrast to the primary efficacy trials, the duration of double-blind treatment period in the exercise endurance trials was 12 weeks. The primary efficacy endpoint was trough FEV1 on treatment Day 169 (Week 24) for the four primary efficacy trials; trough FEV1 on treatment Day 85 (Week 12) was pre-specified as a co-primary endpoint in the exercise endurance trials.

Overall, the clinical development program provides replicate, statistically significant results for the primary endpoint for the comparison between both doses of the fixed combination product and placebo. Replicate, statistically significant results for the comparisons between the monotherapy components and placebo are also observed. As UMEC is a new molecular entity (NME), the replicate, statistically significant results for the comparison between the UMEC monotherapy and placebo are a critical element of the UMEC/VI development program. The effect of VI compared to placebo has been previously established by the development program for fluticasone furoate and vilanterol inhalation power (NDA 204-275).

Comparable results for the 62.5 mcg/25 mcg and 125 mcg/25 mcg doses of UMEC/VI were observed in trials that included a head to head comparison; the totality of the phase 3 data do not suggest a clear efficacy advantage for doses higher than UMEC/VI 62.5 mcg/25 mcg. Focusing on the UMEC/VI 62.5 mcg/25 mcg dose, which is the dose proposed for approval, the magnitude of the treatment effect compared to placebo ranges from 167 mL to 243 mL, which represents an outcome that is likely to be clinically meaningful. In addition, the placebo- and active-controlled trials provide evidence of persistence of efficacy for up to 6 months. With regard to the contribution of each of the components to the trough FEV1 effect of the combination, there is replicate, statistically significant evidence of the contribution of UMEC for both doses of the fixed combination, and adequate support for the contribution of VI to UMEC/VI 62.5 mcg/25 mcg.

Results for secondary and other endpoints, including weighted mean FEV1 over 0 to 6 hours post-dose at Week 24, trough FEV1 at additional time points, serial FEV1, and peak FEV1, were supportive of the primary analysis.

1.3 Safety

The safety database for the proposed product consists of 17 completed trials in patients with COPD, and includes 2,454 patients treated with either UMEC/VI 62.5 mcg/25 mcg or 125 mcg/25 mcg, 1,851 patients treated with either UMEC 62.5 mcg or 125 mcg, and

2,501 patients treated with VI. Fourteen of these 17 trials had treatment periods of at least 4 weeks and a relevant UMEC/VI, UMEC, or VI arm; these 14 trials are collectively referred to as the "All COPD Clinical Studies" by the Applicant. Across the "All COPD Clinical Studies," 788 patients were treated with either UMEC/VI 62.5 mcg/25 mcg or 125 mcg/25 mcg for at least 24 weeks, and 146 treated with UMEC/VI 125 mcg/25 for at least 48 weeks. In addition, 524 patients were treated with either UMEC 62.5 mcg or 125 mcg for at least 24 weeks, and 133 for at least 48 weeks. The extent of exposure was adequate for review.

The clinical development program prospectively identified adverse events of special interest, which included cardiovascular events, based largely on the known pharmacological effects of the two classes of drugs (LAMA and LABA) making up the combination. The Applicant's approach to evaluating cardiovascular adverse events was two-fold: an analysis of Major Adverse Cardiac Events (MACE) was conducted, along with an evaluation of cardiovascular adverse events of special interest (AESIs); these analyses represent different approaches to assessing the same safety data. In both the MACE and cardiovascular AESI analyses a numerical imbalance favoring placebo is demonstrated for events related to cardiovascular ischemia. In the MACE analysis, the imbalance is noted for narrow category of non-fatal myocardial infarction, but not the broader category of non-fatal cardiac ischemia; the imbalance in non-fatal myocardial infarction is seen across all UMEC/VI, UMEC, and VI treatment arms. In the cardiovascular AESI analysis, imbalances are noted in the primary efficacy trials, but not the long-term safety trial; these include an imbalance in the cardiac ischemia subgroup of the overall category of cardiovascular AESIs, and an imbalance in the overall category of serious cardiovascular AESIs, which appears be largely driven by events in cardiac ischemia subgroup. While these imbalances are noted, several features of the observed data decrease concern. The imbalances identified in the cardiovascular AESI analysis are for the primary efficacy trials; similar patterns are not demonstrated for the long-term safety trial. It is reasonable to expect that a signal for increased cardiac ischemia, if it represents a true risk, ought to be observed not just in the primary efficacy trials, but also in the long-term safety trial which evaluated the higher UMEC/VI dose for a longer duration. This argument is tempered somewhat, however, by the fact that a greater percentage of patients in the UMEC/VI and UMEC treatment arms of the long-term safety trial withdrew due to abnormalities on ECGs and on 24-hour Holter monitoring compared to placebo; the safety profile of these patients after withdrawal cannot be known. Nevertheless, while small numerical imbalances were observed between the active treatment arms and placebo in the primary efficacy trials, the most notable feature of these analyses is the overall low number of events observed in the clinical development program, which is reassuring.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed product is a fixed-dose, long-acting muscarinic antagonist (LAMA) and long-acting beta agonist (LABA) combination inhalation dry powder administered by a dry powder inhaler. The combination device contains umeclidinium bromide (a new molecular entity) as the LAMA and vilanterol trifenatate as the LABA in two double-foil blister strips. Within the foil packs, one strip contains 62.5 mcg of umeclidinium (UMEC) and the second 25 mcg of vilanterol (VI). A single UMEC/VI dose is proposed: 62.5 mcg/25 mcg administered as one inhalation once daily. The proposed trade name is Anoro™ Ellipta™.

The Applicant proposes a single indication for this new drug product:

> *Anoro Ellipta is indicated 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.*

This is consistent with the indications of other products approved for use as bronchodilators in COPD.

2.2 Tables of Currently Available Treatments for Proposed Indications

A summary of treatments available for the relief of airflow obstruction in patients with COPD is provided in Table 1.

Table 1. Treatments available for the relief of airflow obstruction in COPD

Pharmacologic Class		Established Name	Trade Name
Beta-adrenergic agonists	Long-acting (LABA)	Salmeterol xinafoate	Serevent Diskus
		Formoterol fumarate	Foradil Aerolizer Perforomist
		Arformoterol tartrate	Brovana
		Indacaterol maleate	Arcapta Neohaler
Anti-cholinergics	Short-acting	Ipratropium bromide	Atrovent HFA
	Long-acting (LAMA)	Tiotropium bromide	Spiriva HandiHaler
		Aclidinium bromide	Tudorza Pressair
Combination	Short-acting anti-	Ipratropium	Combivent

	cholinergic/ Short-acting beta-adrenergic agonist	bromide/Albuterol sulfate	Combivent respimat Duoneb
	Corticosteroid/LABA	Fluticasone propionate /Salmeterol xinafoate	Advair Diskus
		Budesonide/Formoterol fumarate	Symbicort
		Fluticasone furoate/Vilanterol	Breo Ellipta
Methylxanthines		Theophylline	Multiple

In addition to the products listed above, short-acting beta-adrenergic agents are often used in the management of COPD. While not specifically indicated for COPD, this class of drugs carries a general bronchodilator claim.

With the exception of methylxanthines, all of the products listed in Table 1 are inhalation products.

2.3 Availability of Proposed Active Ingredient in the United States

Vilanterol is a component of the fixed-dose combination product fluticasone furoate and vilanterol inhalation powder (Breo Ellipta), which received United States approval on May 10, 2013. Umeclidinium is a new molecular entity and is not currently marketed in the United States.

2.4 Important Safety Issues With Consideration to Related Drugs

This new proposed combination product comprises both LAMA and LABA monocomponents. Safety issues have been raised for both of these pharmacologic classes, and are pertinent to the review of UMEC/VI.

LAMA Safety Issues

Class effects of long-acting muscarinic antagonists include the worsening of narrow-angle glaucoma and worsening of urinary retention.

The cardiovascular safety and stroke risk of inhaled anticholinergics have been discussed extensively both in the medical literature[1-2] and in open public forums.[3] In

[1] Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. *JAMA* 2008; 300(12):1439-1450.
[2] Lee TA, Pickard S, Au DH et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. *Annals of Internal Medicine* 2008;149:380-390.
[3] November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting.

January 2010 FDA provided a Follow-Up[4] to an Early Communication regarding the safety of tiotropium marketed as Spiriva Handihaler. In this update, FDA communicated its conclusion that the available data, including results from the UPLIFT trial, do not support an association between the use of Spirva HandiHaler (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. A summary of the FDA's conclusions regarding the safety of tiotropium may also be found in the medical literature.[5]

The July 23, 2012, approval letter for another LAMA, Tudorza Pressair (aclidinium bromide inhalation powder), includes a postmarketing requirement for a clinical trial to evaluate the risk of major adverse cardiac events (MACE) in patients with COPD. The Summary Review for aclidinium concluded that the data for did not raise any specific safety concerns including no increase in the overall MACE score; however, it noted that the MACE analysis was limited by a relatively small sample size and low event rate. The required postmarketing trial will enlarge the safety database for aclidinium.

LABA Safety Issues

Class effects of LABAs include hypokalemia, hyperglycemia, and cardiovascular effects (i.e., increases in pulse rate, blood pressure, ECG changes of unclear clinical significance, and symptoms).

Drugs belonging to the LABA pharmacologic class are inhaled medications used in both the treatment of asthma and of COPD. LABAs are associated with an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, as well as death in some patients using LABAs for the treatment of asthma.[6] FDA announced in February 2010[7] that the they would require manufacturers to revise their drug labels to include updated guidelines for the use of LABA in asthma, and in April 2011[8] announced that they would require manufacturers of LABAs to conduct five randomized,

[4] Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler), January 14, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm197429.htm; accessed August 3, 2013.
[5] Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.
[6] FDA Drug Safety Communication: Drug labels now contain updated recommendations on the appropriate use of long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), June 2, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213836.htm; accessed August 3, 2013.
[7] FDA Drug Safety Communication: New safety requirements for long-acting inhaled asthma medications called Long-Acting Beta-Agonists (LABAs), February 18, 2010. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm; accessed August 3, 2013.
[8] FDA Drug Safety Communication: FDA requires post-market safety trials for Long-Acting Beta-Agonists, April 15, 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm251512.htm; accessed August 3, 2013.

double-blind, controlled clinical trials comparing the addition of LABAs to inhaled corticosteroids versus inhaled corticosteroids alone. These risks identified for LABAs are believed to be restricted to the asthma population and have not been observed in COPD.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of key interactions that took place between the Agency and the Applicant during the development of UMEC/VI is provided in Table 2. These include interactions that were conducted for other, related investigational products or instruments.

Table 2. Regulatory History

Product or Instrument	IND	Interaction/Date/Topic
VI	74,696	• preIND January 31, 2007 • Teleconference March 24, 2010: dose and dosing interval in COPD discussed
UMEC	104,479	• preIND May 26, 2009
UMEC/VI	106,616	• EOP2 October 29, 2010: dose and dosing interval discussed • preNDA January 18, 2012
FF/VI	77,955	• EOP2 March 31, 2009 (asthma program), June 17,2009 (COPD program), June 8, 2010 (asthma program)
SOBDA*		• Meetings on August 29, 2006, June 16, 2008, May 10, 2010, July 27, 2010 • Written feedback provided by Agency on June 30, 2010: concerns raised about the content validity of the instrument

***SOBDA=Shortness of Breath with Daily Activities Questionnaire**

3 Dose Ranging

As it is important to determine if appropriate doses and an appropriate dosing regimen were evaluated in the phase 3 program, data pertinent to dose selection are reviewed first in this clinical briefing document.

Traditionally, approval for a combination inhalation product for COPD follows the approval of the constituent monocomponents. In this case, neither umeclidinium nor

vilanterol are approved as monotherapy products. Vilanterol, however, is a component of the fixed-dose combination fluticasone furoate and vilanterol inhalation powder (Breo Ellipta, NDA 204-275) which recently received approval for use in COPD.

Given the absence of an approved umeclidinium monotherapy product, this NDA review includes an analysis of the dose-ranging and dosing-interval selection data for the umeclidinium component. Dose selection for the vilanterol monocomponent has been previously reviewed under NDA 204-275, and so is only briefly discussed here.

3.1 Umeclidinium Dose and Dosing Regimen Selection

UMEC dose selection trials included three phase 2b trials evaluating dose-ranging and dosing interval for UMEC (15.6 mcg to 1000 mcg once-daily and 15.6 mcg to 250 twice-daily mcg), along with a 12-week phase 3 trial evaluating 62.5 mcg and 125 mcg once-daily, which were identified by the Applicant as the best candidates to carry forward into phase 3.

A summary of key UMEC trials pertinent to dose-ranging and dosing interval selection is provided in Table 3.

Table 3. Key UMEC Dose-Ranging and Dosing-Interval trials

Trial *Year completed*	Objective	Design	N	Treatments	Duration	Primary Endpoint
AC4113589 2010	Dose-ranging	R, DB, PC, PG	 72 72 72 72	Once-daily: UMEC 125 UMEC 250 UMEC 500 P	28 days	Trough FEV1
AC4113073	Dose-ranging, dosing interval, PK	R, DB, PC, CO, incomplete block	179	Once-daily: UMEC 62.5 UMEC 125 UMEC 250 UMEC 500 UMEC 1000 Tio 18 (OL) P Twice-daily: UMEC 62.5 UMEC 125	3 periods per subject, 14 days per period	Trough FEV1

2010				UMEC 250 P		
AC4115321 2011	Dose-ranging, dosing interval	R, DB, PC, CO, incomplete block	163	Once-daily: UMEC 15.6 UMEC 31.25 UMEC 62.5 UMEC 125 Tio 18 (OL) P Twice-daily: UMEC 15.6 UMEC 31.25 P	3 periods per subject, 7 days per period	Trough FEV1
AC4115408 2012	Efficacy, safety	R, DB, PC, PG	 69 69 68	Once-daily: UMEC 62.5 UMEC 125 P	12 weeks	Trough FEV1

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 26-27 (Table 1); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113589); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115408)
Note: N=number randomized
Key: CO=cross-over, DB=double-blind, PC=placebo-controlled, PG=parallel group, R=randomized

Trial AC4113589

Trial AC4113589 was a randomized, double-blind, placebo-controlled, parallel group trial in COPD patients focused on dose-ranging. It evaluated doses ranging from 125 mcg to 500 mcg administered once-daily, for a duration of 28 days. Results for the primary endpoint, trough FEV1, are provided in Table 4.

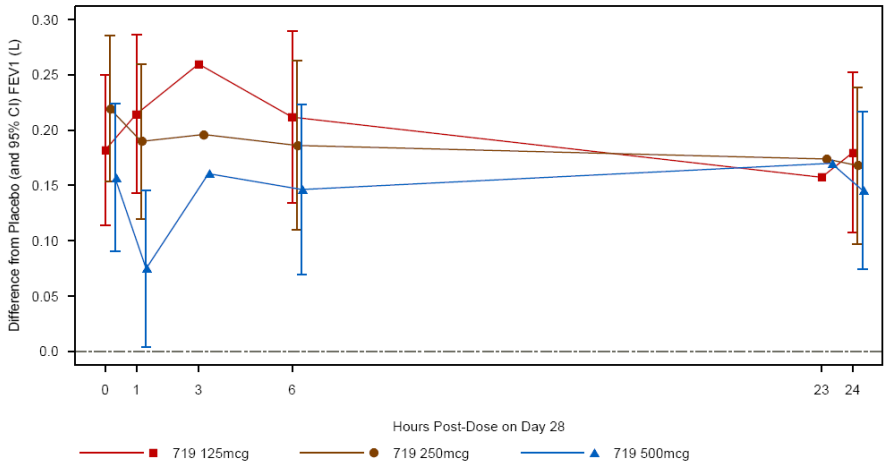
Table 4. Change in Trough FEV1 (L) at Day 29, Trial AC4113589, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		Mean (SD)	LS Mean (SE)	Difference	95% CI	p-value
UMEC 500	71	1.320 (0.4242)	0.163 (0.025)	0.150	0.080, 0.220	<0.001
UMEC 250	72	1.480 (0.5772)	0.181 (0.025)	0.168	0.099, 0.238	<0.001
UMEC 125	71	1.466 (0.4737)	0.171 (0.025)	0.159	0.088, 0.229	<0.001
P	71	1.349 (0.4438)	0.013 (0.025)			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113589), pg. 51 (Table 10)

Statistically significant results were observed for the primary endpoint at all doses. No clear dose response was demonstrated at this range of doses, as the effect size was comparable across the 125 mcg and 250 mcg doses and lower at the highest dose of 500 mcg. Results for an additional efficacy endpoint, 0-6 hour weighted mean FEV1, and for 24-hour serial spirometry (shown in Figure 1) similarly did not demonstrate a dose response.

Figure 1. Adjusted Mean Difference from Placebo (95% CI) in Change from Baseline in FEV1 (L), 0-24 hours on Day 28, Trial AC4113589, ITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113589), pg. 60 (Figure 8)

The percentage of patients experiencing any adverse event was comparable across the placebo, 125 mcg, and 250 mcg treatment arms, but substantially higher for the 500 mcg treatment arm (34% versus 23-25%).

Trial AC4113073

Trial AC4113073 was a randomized, double-blind, placebo-controlled, cross-over, incomplete block trial in COPD patients focused on dose-ranging, dosing-interval selection, and PK. It evaluated once-daily doses ranging from 62.5 mcg to 1000 mcg, and twice-daily doses ranging from 62.5 mcg to 250 mcg. Patients participated in three dosing periods, each with a duration of 14 days. Results for the primary endpoint, trough FEV1, are provided in Table 5.

Table 5. Change in Trough FEV1 (L) at Day 15, Trial AC4113073, mITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
Once-daily						

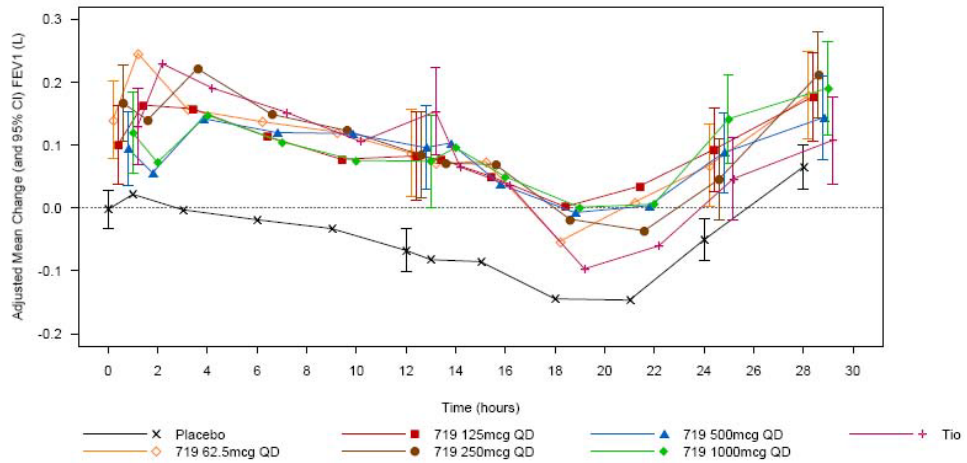
UMEC 1000	32	1.581 (0.036)	0.138 (0.036)	0.186	0.113, 0.259	<0.001
UMEC 500	38	1.535 (0.032)	0.092 (0.032)	0.140	0.074, 0.205	<0.001
UMEC 250	36	1.490 (0.033)	0.048 (0.033)	0.095	0.027, 0.162	0.006
UMEC 125	34	1.542 (0.034)	0.099 (0.034)	0.147	0.077, 0.216	<0.001
UMEC 62.5	35	1.524 (0.033)	0.081 (0.033)	0.128	0.060, 0.196	<0.001
Tio 18	35	1.500 (0.033)	0.058 (0.033)	0.105	0.037, 0.173	0.003
Twice-daily						
UMEC 250	33	1.567 (0.034)	0.124 (0.034)	0.172	0.101, 0.242	<0.001
UMEC 125	37	1.529 (0.034)	0.087 (0.034)	0.134	0.064, 0.204	<0.001
UMEC 62.5	34	1.475 (0.035)	0.032 (0.035)	0.079	0.008, 0.151	0.03
P	158	1.395 (0.017)	-0.047 (0.017)			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073), pg. 64 (Table 12)
Note: modified ITT (mITT) population=all patients randomized who received at least one dose of study medication

Statistically significant results were observed for the primary endpoint with all of the treatment regimens. For the once-daily regimens, while the largest effect size was observed for the highest dose (0.186 ml at 1000 mcg), there was no clear dose-response across the range of doses, with the effect sizes for the 125 mcg and 500 mcg doses being comparable (0.147 L and 0.140 L, respectively) and greater than the effect size for the 250 mcg dose (0.095 L). The effect size for the lowest dose (0.128 L for 62.5 mcg) was only slightly smaller than that observed for the 125 mcg and 500 mcg doses. For the twice-daily regimens, there does seem to be some dose-ordering, with the effect size increasing as the dose is increased. The comparison of the twice-daily regimens to the once-daily regimens yields variable results, with the effect size being considerable smaller for the 62.5 mcg twice-daily regimen compared to the 125 mcg once-daily regimen, and somewhat larger for the other comparisons of the twice-daily and once-daily regimens (i.e., 125 mcg twice-daily to 250 mcg once-daily, and 250 mcg twice-daily to 500 once-daily).

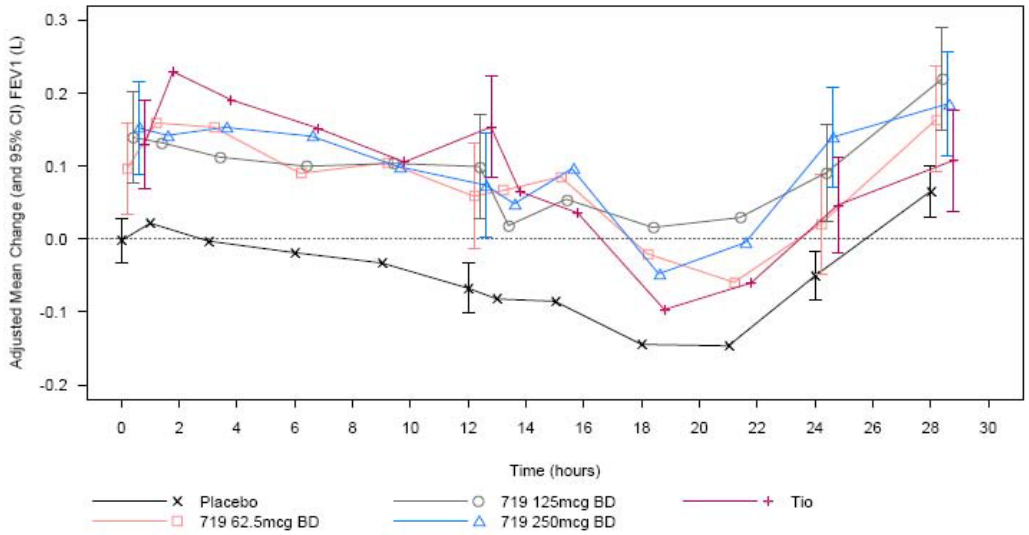
Results for an additional efficacy endpoint, 0-24 hour weighted mean FEV1 on Day 14, are supportive of the findings of the primary endpoint, with statistically significant results for each treatment group compared to placebo, and no clear dose ordering. Also consistent with the results for the primary endpoint were the results of serial spirometry, which are presented in Figure 2 and Figure 3 (the reader should note that these figures present adjusted *mean change from baseline* in FEV1 over *28 hours*, in contrast to Figure 1 which presents *mean difference from placebo in change from baseline* FEV1 over *24 hours*).

Figure 2. Adjusted Mean Change from Baseline (95% CI) in FEV1 (L), 0-28 hours on Day 14, Once-Daily Doses, Trial AC4113073, mITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073), pg. 70 (Figure 6)

Figure 3. Adjusted Mean Change from Baseline (95% CI) in FEV1 (L), 0-28 hours on Day 14, Twice-Daily Doses and Tiotropium, Trial AC4113073, mITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073), pg. 71 (Figure 7)

The percentage of patients experiencing any adverse event generally increased with dose across each of the two dosing regimens.

Trial AC4115321

Trial AC4115321 was a randomized, double-blind, placebo-controlled, cross-over, incomplete block trial in COPD patients focused on dose-ranging and dosing interval selection. It evaluated once-daily doses ranging from 15.6 mcg to 125 mcg, and twice-daily doses from 15.6 mcg to 31.25 mcg. Patients participated in three dosing periods, each with a duration of 7 days. Results for the primary endpoint, trough FEV1, are provided in Table 6.

Table 6. Change in Trough FEV1 (L) on Day 8, Trial AC4115321, mITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
Once-daily						
UMEC 125	60	1.525 (0.022)	0.109 (0.022)	0.183	0.127, 0.239	<0.001
UMEC 62.5	59	1.466 (0.022)	0.049 (0.022)	0.124	0.068, 0.179	<0.001
UMEC 31.25	57	1.443 (0.023)	0.027 (0.023)	0.101	0.045, 0.158	<0.001
UMEC 15.6	60	1.455 (0.022)	0.038 (0.022)	0.113	0.058, 0.168	<0.001
Tio 18	56	1.443 (0.023)	0.027 (0.023)	0.101	0.045, 0.157	<0.001
Twice-daily						
UMEC 31.25	58	1.481 (0.023)	0.065 (0.023)	0.139	0.083, 0.196	<0.001
UMEC 15.6	56	1.467 (0.023)	0.051 (0.023)	0.125	0.069, 0.182	<0.001
P	60	1.342 (0.022)	-0.074 (0.022)			

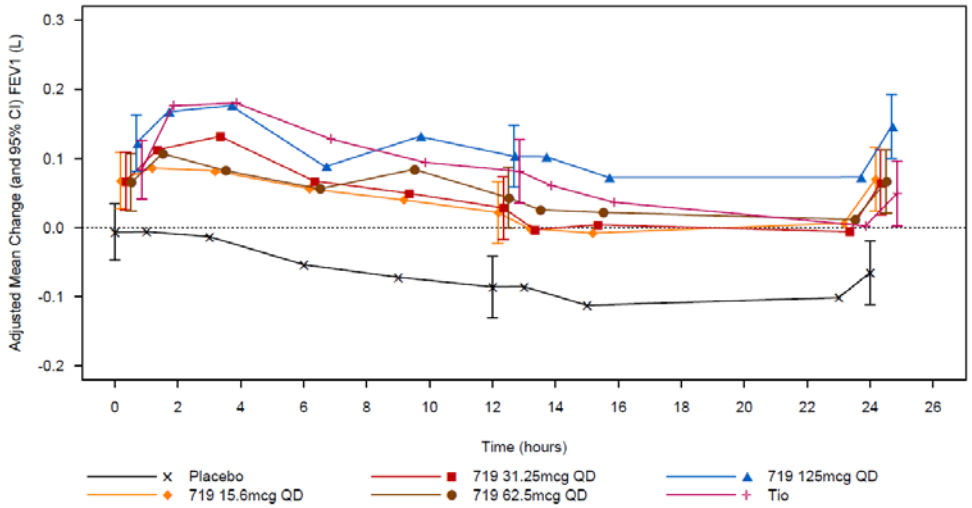
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 78 (Table 24)
Note: modified ITT (mITT) population=all patients randomized who received at least one dose of study medication

Statistically significant results were observed for the primary endpoint at all doses. With regard to the once-daily regimens, the magnitude of the treatment effect was comparable across the tiotropium, 15.6 mcg and 31.25 mcg treatment arms (0.101L – 0.113 L), greater for the 62.5 mcg arm (0.124 L), and greatest for the 125 mcg arm (0.183 L). The treatment effects for the twice-daily regimens were generally comparable to those for their corresponding (i.e., same total daily dose) once-daily regimens (e.g., 0.125 L for 15.6 mcg twice-daily versus 0.101 L for 31.25 once-daily, and 0.139 L for 31.25 twice-daily versus 0.124 L for 62.5 once-daily). Results for an additional efficacy endpoint, 0-24 weighted mean FEV1, were generally consistent with the results for trough FEV1.

Results for 24-hour serial spirometry are shown below. In Figure 4, the once-daily regimens are compared to both placebo and tiotropium; all active arms demonstrate an effect over placebo, and the 125 mcg and 62.5 mcg curves straddle the curve for

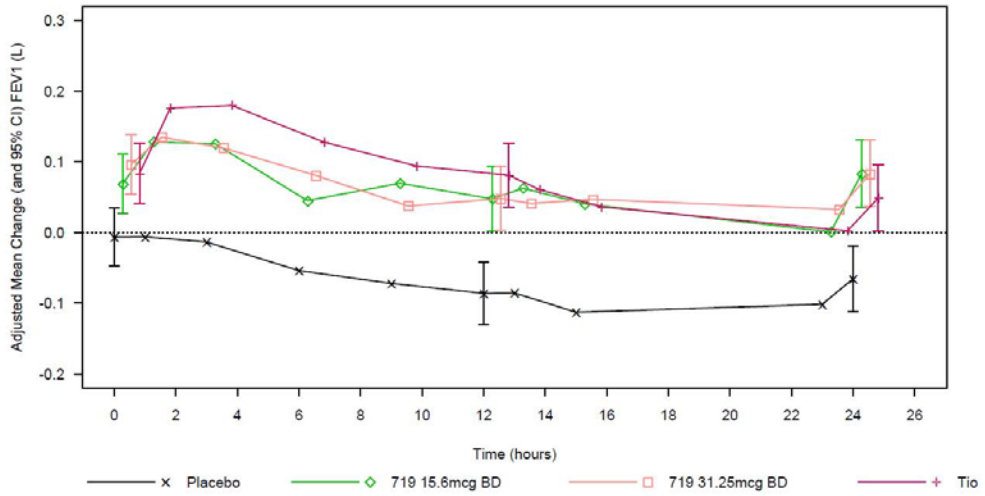
tiotropium. In Figure 5 the twice-daily regimens are compared to both placebo and tiotropium; all active arms demonstrate an effect over placebo, and the 31.25 mcg and 15.6 mcg twice-daily regimens approximate the curve for tiotropium, albeit with a somewhat lesser effect in the first 12 hours. In Figure 6 the once-daily and twice-daily regimens are compared to placebo (but not tiotropium); the largest effect is observed for the 125 mcg once-daily regimen; results for the 62.5 mcg once-daily, the 31.25 mcg twice-daily, and 15.6 mcg twice-daily regimens all appear similar.

Figure 4. Adjusted Mean Change from Baseline (95% CI) in FEV1 (L), 0-24 hours on Day 7, Once-Daily Doses, Trial AC4115321, mITT Population



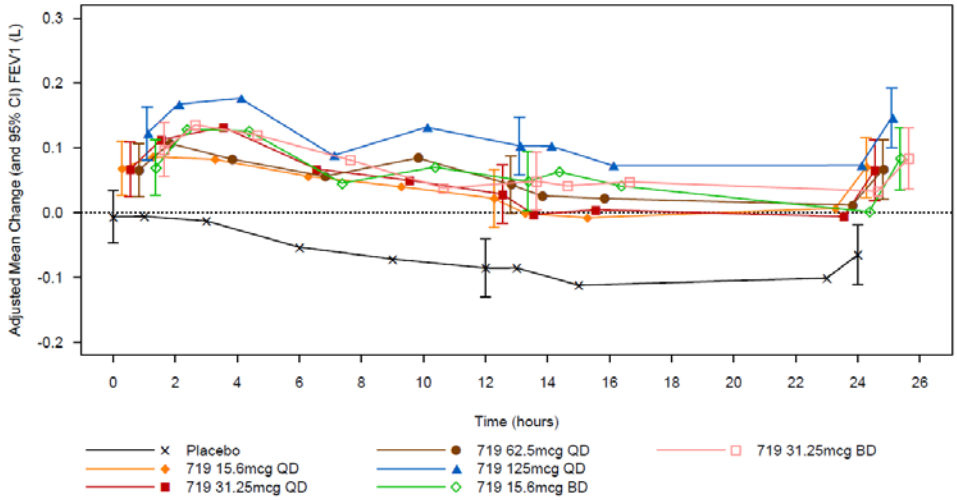
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 93 (Figure 16)

Figure 5. Adjusted Mean Change from Baseline (95% CI) in FEV1 (L), 0-24 hours on Day 7, Twice-Daily Doses and Tiotropium, Trial AC4115321, mITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 94 (Figure 17)

Figure 6. Adjusted Mean Change from Baseline (95% CI) in FEV1 (L), 0-24 hours on Day 7, Once-Daily and Twice-Daily Doses, Trial AC4115321, mITT Population



A notable imbalance between active and placebo in any adverse event was observed with only the highest doses for both the once-daily (18% for 125 mcg once-daily versus 8% for placebo) and twice-daily regimens (12% for 31.25 mcg twice-daily versus 8% for placebo).

Trial AC4115408

Trial AC4115408 was a randomized, double-blind, placebo-controlled, parallel group trial in COPD patients focused efficacy and safety. It evaluated UMEC 62.5 mcg and 125 mcg, each administered once daily for 12 weeks. Results for the primary endpoint, trough FEV1, are provided in Table 7.

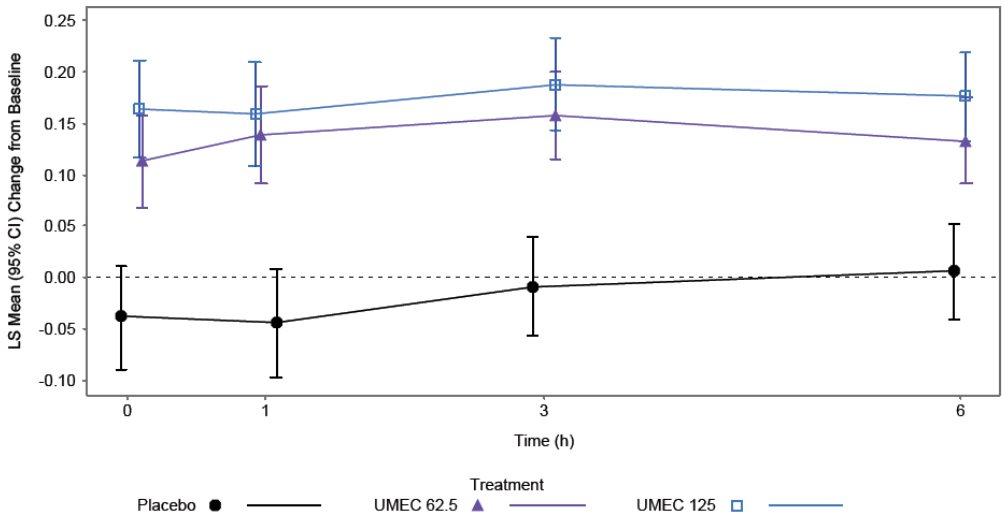
Table 7. Change in Trough FEV1 (L) on Day 85, Trial AC4115408, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
UMEC 125	69	1.388 (0.0268)	0.145 (0.0268)	0.152	0.076, 0.229	<0.001
UMEC 62.5	69	1.363 (0.0257)	0.120 (0.0257)	0.127	0.052, 0.202	<0.001
P	68	1.235 (0.0280)	-0.007 (0.0280)			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115408), pg. 70 (Table 22)

Statistically significant results were observed for the primary endpoint at both the 62.5 mcg and 125 mcg doses. The magnitude of the treatment effect was somewhat larger for the 125 mcg dose (0.152 L versus 0.127 L). Results for an additional efficacy endpoint, 0-6 hour weighted mean FEV1, were consistent with the results for the primary endpoint, as were results for 6-hour serial spirometry, which are shown in Figure 7.

Figure 7. Least Squares Mean Change from Baseline (95% CI) in FEV1 (L), 0-6 hours on Day 28, Trial AC4115408, ITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115408), pg. 81 (Figure 8)

The percentage of patients experiencing any adverse event was comparable between the two active treatment arms.

Summary of UMEC Dose Selection

A summary of the results for trough FEV1 across the four dose selection trials described above is provided in Table 8.

Table 8. Difference from Placebo for Change from Baseline in Trough FEV1 (L), UMEC dose selection trials: AC4113589, AC4113073, AC4115321, AC4115408

Trial	UMEC 15.6 QD	UMEC 15.6 BID	UMEC 31.25 QD	UMEC 31.25 BID	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
AC4115321*, Day 8	0.113 (0.058, 0.168)	0.125 (0.069, 0.182)	0.101 (0.045, 0.158)	0.139 (0.083, 0.196)	0.124 (0.068, 0.179)	--	0.183 (0.027, 0.239)	--	--	--	--	--
AC4113073*, Day 15	--	--	--	--	0.128 (0.060, 0.196)	0.079 (0.008, 0.151)	0.147 (0.077, 0.216)	0.134 (0.064, 0.204)	0.095 (0.027, 0.162)	0.172 (0.101, 0.242)	0.140 (0.074, 0.205)	0.186 (0.113, 0.259)
AC4113589#, Day 29	--	--	--	--	--	--	0.159 (0.088, 0.229)	--	0.168 (0.099, 0.238)	--	0.150 (0.080, 0.220)	--
AC4115408#, Day 85	--	--	--	--	0.127 (0.052, 0.202)	--	0.152 (0.076, 0.229)	--	--	--	--	--

Source:

Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 78 (Table 24)
Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073), pg. 64 (Table 12)
Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4113589), pg. 51 (Table 10)
Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115408), pg. 70 (Table 22)
*modified ITT (mITT) population= all patients randomized who received at least one dose of study medication
#ITT population

Taking the results of these four trials together, there appears to be an increased treatment effect for trough FEV1 with the 62.5 mcg and 125 mcg once-daily doses compared to lower once-daily doses; the relationship between dose and the magnitude of treatment effect is variable in the 250 mcg to 500 mcg dose range. While an increased effect size is apparent with the 1000 once-daily dose, this dose was also associated with a greater number of adverse events. Data for additional endpoints, including weighted mean FEV1 and serial spirometry, were consistent with the findings for trough FEV1. Moreover, the results of serial spirometry do not suggest an advantage for twice-daily dosing compared to once-daily dosing for the same nominal dose. Given the totality of the data, the Applicant's decision to carry forward the 62.5 mcg and 125 mcg once-daily regimens into phase 3 appears reasonable.

3.2 Vilanterol Dose and Dosing Regimen Selection

Dose and dosing regimen selection for Vilanterol has been previously reviewed in detail for the recently approved fluticasone furoate and vilanterol inhalation powder (see NDA 204-275 review by Dr. Sofia Chaudhry, March 18, 2013). The data to support the 25 mcg once daily vilanterol dose was also discussed by the Agency at the April 17, 2013, Advisory Committee meeting for NDA 204-275. A brief overview of this topic is provided here.

Historically, dose selection for beta-agonists has relied on information from clinical trials in asthma, as this population is typically more bronchodilator-sensitive than the COPD population. In keeping with this, VI dose selection was based on data derived from evaluation in both asthma and COPD patients. A summary of key VI dose and dosing regimen selection trials is provided in Table 9.

Table 9. Key VI Dose-Ranging and Dosing-Interval trials

Trial *Year completed*	Objective	Design/ Population	N	Treatments	Duration	Primary Endpoint
B2C111045	Dose-ranging	R, DB, PC, PG	 101 101 101 101 100	Once-daily: VI 3 VI 6.25 VI 12.5 VI 25 VI 50	28 days	Trough FEV1

2008		COPD	101	P		
B2C109575 2008	Dose-ranging	R, DB, PC, PG Asthma	 102 102 102 103 102 103	Once-daily: VI 3 VI 6.25 VI 12.5 VI 25 VI 50 P	28 days	Trough FEV1
HZA113310 2010	Dose-ranging, dosing interval	R, DB, PC, CO Asthma	75	Once-daily: VI 6.25 VI 12.5 VI 25 Twice-daily: VI 6.25 P	5 periods per subject, 7 days per period	Trough FEV1

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 28-29 (Table 1); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (B2C111045), pg. 60 (Table 6); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (B2C109575), pg. 55 (Table 4); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (HZA113310), pg. 64 (Table 5.1)
Note: N=number randomized
Key: CO=cross-over, DB=double-blind, PC=placebo-controlled, PG=parallel group, R=randomized

Trial B2C111045

Trial B2C111045 was a randomized, double-blind, placebo-controlled, parallel group trial in COPD patients focused on dose-ranging. It evaluated doses ranging from 3 mcg to 50 mcg once-daily, for a duration of 28 days. Results for the primary endpoint, trough FEV1, are provided in Table 10.

Table 10. Change in Trough FEV1 (L) at Day 29, Trial B2C111045, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		Mean (SD)	LS Mean (SE)	Difference	95% CI	p-value
VI 50	99	1.330 (0.4873)	0.194 (0.0190)	0.165	0.112, 0.217	<0.001
VI 25	101	1.182 (0.4832)	0.166 (0.0190)	0.137	0.085, 0.190	<0.001
VI 12.5	101	1.222 (0.4265)	0.138 (0.0190)	0.110	0.057, 0.162	<0.001
VI 6.25	101	1.242 (0.4307)	0.127 (0.0188)	0.098	0.046, 0.150	<0.001
VI 3	99	1.299 (0.4591)	0.120 (0.0190)	0.092	0.039, 0.144	<0.001
P	101	1.255	0.029			

		(0.4672)	(0.0188)			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (B2C111045), pg. 67 (Table 14)

Statistically significant results were observed for the primary endpoint at all doses. The magnitude of the treatment effect was comparable across the three lowest doses (0.092 L – 0.110 L), higher for the 25 mcg dose (0.137 L), and highest for the 50 mcg dose (0.165 L).

Trial B2C109575

Trial B2C109575 was a randomized, double-blind, placebo-controlled, parallel group trial in asthma patients focused on dose-ranging. It evaluated doses ranging from 3 mcg to 50 mcg once-daily, for a duration of 28 days. The primary endpoint was mean change from baseline in trough FEV1 at Day 28. The primary treatment comparison for the primary endpoint was a test of linear dose response, which was statistically significant. Additional analyses of the primary endpoint included pair-wise tests of each dose versus placebo, and their results are provided in Table 11.

Table 11. Change in Trough FEV1 (L) at Day 28, Trial B2C109575, ITT Population

Treatment Arm	N	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	Difference	95% CI	p-value
VI 50	102	0.309 (0.035)	0.162	0.062, 0.261	0.001
VI 25	101	0.269 (0.035)	0.121	0.023, 0.220	0.016
VI 12.5	100	0.278 (0.036)	0.130	0.030, 0.230	0.011
VI 6.25	101	0.217 (0.035)	0.069	-0.029, 0.168	0.169
VI 3	101	0.212 (0.036)	0.064	-0.036, 0.164	0.208
P	102	0.147 (0.036)			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (B2C109575), pg. 65 (Table 12)

Statistically significant results were observed only for doses 12.5 mcg and higher. The magnitude of the treatment effect was comparable between the 12.5 mcg and 25 mcg doses (0.121-130 L), and higher for the 50 mcg dose. These results are supportive of the dose-ranging conducted in COPD patients (i.e., Trial B2C111045).

Trial HZA113310

Trial HZA113310 was a randomized, double-blind, placebo-controlled, crossover trial in asthma patients focused on dose-ranging dosing interval selection. It evaluated once daily doses ranging from 6.25 mcg to 25 mcg, and a twice-daily dose of 6.25 mcg.

Each patient participated in 5 periods, and each period was 7 days in duration. Results for the primary endpoint, trough FEV1, are provided in Table 12.

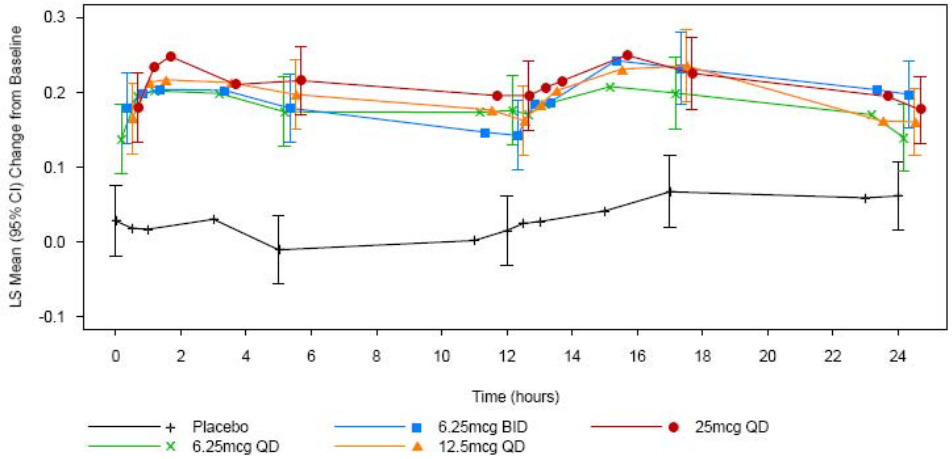
Table 12. Change in Trough FEV1 (L) at Day 7, Trial HZA113310, ITT Population

Treatment Arm	N	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	Difference	95% CI	p-value
Once-daily					
VI 25	73	0.184 (0.0221)	0.125	0.080, 0.170	<0.001
VI 12.5	73	0.161 (0.0221)	0.102	0.057, 0.147	<0.001
VI 6.25	73	0.153 (0.0222)	0.094	0.049, 0.140	<0.001
Twice-daily					
VI 6.25	74	0.198 (0.0221)	0.140	0.095, 0.185	<0.001
P	74	0.059 (0.0221)			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (HZA113310), pg. 45 (Table 13)

Statistically significant results were observed with all treatments. For the once-daily treatments, the magnitude of the treatment effect was comparable between the 6.25 mcg and 12.5 mcg doses (0.094-0.102 L), and greater for the 25 mcg dose (0.125 L). The treatment effect for the 6.25 mcg twice-daily regimen was the largest observed across the trial (0.140 L). While this may suggest a benefit of the 6.25 mcg twice-daily dose over the once-daily regimens, an examination of serial FEV1 data, as seen in Figure 8, suggests otherwise.

Figure 8. Adjusted Mean Change from Baseline (95% CI) in FEV1 (L), 0-24 hours on Day 7, Trial HZA113310, ITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (HZA113310), pg. 50 (Figure 3)

As is seen in the above figure, the 12.5 mcg regimen, and, in particular, the 25 mcg once-daily regimen, had a more consistent effect on FEV1 throughout the 24-hour period, while the 6.25 mcg twice-daily regimen was associated with a smaller treatment effect in the first 12 hours after dosing compared all the twice-daily regimens except for the 6.25 mcg once-daily dose.

Summary of VI Dose Selection

In summary, data from dose-ranging trials in both COPD and asthma demonstrated dose-related increases in trough FEV1, and in a single trial evaluating dosing interval, the 25 mcg once-daily regimen demonstrated the most consistency in FEV1 treatment effect across the entire 24 hours period following dosing. These results, taken together, support the Applicant's choice of carrying forward the VI 25 mcg once-daily dose into the phase 3 trials.

4 Sources of Clinical Data

4.1 Tables of Studies/Clinical Trials

Summaries of the trials conducted in support of UMEC and VI dose selection are provided in Sections 3.1 and 3.2 of this review. The core phase 3 development program[9] conducted in support of UMEC/VI includes two placebo-controlled efficacy

[9] An additional phase 3 trial, AC4115408, is described by the Applicant as providing additional support for

and safety trials (DB2113361 and DB2113373), two active-comparator (tiotropium) efficacy and safety trials (DB113360 and DB2113374), one long-term safety trial (DB2113359), and two exercise trials (DB2114417 and DB2114418); a summary of these trials is provided in Table 13.

Table 13. Core Phase 3 Clinical Development Program

Trial *Year completed*	Design	N	Treatments	Duration	Primary Endpoint	Number of Sites *n (%) of patients from US*
Placebo-controlled efficacy and safety trials						
DB2113361 2012	R, DB, PC, PG	403 409 404 277	UMEC/VI 125/25 UMEC 125 VI 25 P	24 weeks	Trough FEV1	153 *316 (21)*
DB2113373 2012	R, DB, PC, PG	414 421 421 280	UMEC/VI 62.5/25 UMEC 62.5 VI 25 P	24 weeks	Trough FEV1	163 *428 (28)*
Active-comparator efficacy and safety trials						
DB2113360 2012	R, DB, DD, AC, PG	216 212 209 209	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 Tio 18	24 weeks	Trough FEV1	91 *227 (27)*
DB2113374 2012	R, DB, DD, AC, PG	217 218 222 215	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 Tio 18	24 weeks	Trough FEV1	95 *225 (26)*
Long-term Safety						
DB2113359 2012	R, DB, PC, PG	227 227 109	UMEC/VI 125/25 UMEC 125 P	52 weeks	Safety Assessments	53 *156 (28)*
Exercise Endurance Trials						
DB2114417 2012	R, DB, PC, CO Incomplete block	145 152 50 49 76 170	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 P	12 weeks per period	Co-primary: EET post dose, Trough FEV1	31 *196 (56)*
DB2114418	R, DB, PC, CO	128	UMEC/VI 125/25	12 weeks	Co-primary:	42

UMEC dose selection, and so is discussed in Section 3.1.

2012	Incomplete block	130 41 41 64 151	UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 P	per period	EET post dose, Trough FEV1	*139 (45)*

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 25-26 (Table 1), pg. 93 (Table 28), pg. 94 (Table 29); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361), pg. 376 (Table 5.06); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373), pg. 323 (Table 5.06); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360), pg. 68 (Table 11), pg. 238 (Table 5.06); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113374), pg. 274 (Table 5.06); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 195 (Table 5.01), pg. 202 (Table 5.06); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2114417), pg. 246 (Table 5.08); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2114418), pg. 221 (Table 5.08)
Note: N=number randomized, however, the calculation of the percent of patients from the United States utilizes the ITT population.
Key: AC=active-controlled, CO=cross-over, DB=double-blind, DD=double-dummy, PC=placebo-controlled, PG=parallel group, R=randomized

4.2 Review Strategy

The focus of this review is on the clinical development program conducted in support of UMEC/VI 62.5 mcg/25 mcg once daily, which is proposed for use as a bronchodilator in patients with COPD. Data to support the selection of dose and dosing interval carried into the phase 3 program have already been reviewed in Sections 3.1 and 3.2. The remainder of this clinical review addresses first the data presented in support of efficacy, and then the data in support of safety.

The review of efficacy focuses on the four primary efficacy trials, which include two placebo-controlled (DB2113361 and DB2113373) and two active-comparator (DB113360 and DB2113374) trials, and on the two exercise endurance trials (DB2114417 and DB2114418). The general design of these trials is presented in Section 4.3 of this review; a discussion of the efficacy data generated by these trials is provided in Section 5.

The review of safety focuses on safety data from the four primary efficacy trials, as well as safety data from the long-term safety trial (DB2113359). A summary of the safety evaluations conducted in the clinical development program is included in Section 6.1.1, and a discussion of the safety findings follows in the rest of Section 6. Any supportive efficacy and safety data generated from other trials are reviewed in the applicable efficacy or safety section.

4.3 Discussion of Individual Studies/Clinical Trials

A summary of the protocols for the four primary efficacy trials, i.e., the two placebo-controlled trials (DB2113361 and DB2113373) and the two active-comparator trials (DB113360 and DB2113374), and for the two exercise endurance trials (DB2114417 and DB2114418) is provided here; the long-term safety trial and the dose-ranging trials are discussed in Sections 5.1.1 and 4.4.2, respectively.

Placebo-controlled Trials

The administrative information and protocol for the two placebo-controlled trials are presented below. These trials each compared UMEC/VI (125 mcg/25 mcg in Trial DB2113361 and 62.5 mcg/25 mcg in Trial DB2113373) to placebo and to the UMEC (125 mcg in Trial DB2113361 and 62.5 mcg in Trial DB2113373) and VI monotherapies.

The use of a placebo control arm in the UMEC/VI development program is acceptable given the following: 1) patients in the placebo arms were not untreated, since they were allowed to use short-acting beta agonists as needed; 2) inhaled corticosteroids at stable doses were also permitted; 3) patients who experienced a COPD exacerbation were withdrawn from the trial; 4) there was close clinical monitoring for COPD exacerbations; and 5) the informed consent documents clearly described the presence of a placebo arm, the possibility of no direct benefit with trial participation, and the availability of alternative treatment choices.

As Trials DB2113361 and DB2113373 were replicate in design (with the exception of the UMEC/VI and UMEC dose evaluated), a single protocol summary pertinent to both trials is provided. The protocol for these trials was amended twice; the summary below is based on the final version of the protocol. A description of the changes provided by the two protocol amendments follows the summary.

Administrative Information

DB2113361

- Study Title: "A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW632444 Inhalation Power and the Individual Components Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease."
- Study Dates: March 22, 2011 – April 19, 2012
- Study Sites: A total of 153 centers in the United States, Belgium, Denmark, Estonia, France, Germany, Hungary, Japan, The Netherlands, Norway, Philippines, Slovakia, Sweden, and Ukraine
- Study Report Date: September 11, 2012

DB2113373

- Study Title: "A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease."
- Study Dates: March 30, 2011 – April 5, 2012
- Study Sites: A total of 163 centers in the United States, Bulgaria, Canada, Chile, Czech Republic, Greece, Japan, Mexico, Poland, Russia, South Africa, Spain, and Thailand

- Study Report Date: November 20, 2012

Objectives

Primary:

- To evaluate the efficacy and safety of UMEC/VI, UMEC, and VI when administered once-daily via a novel DPI over 24 weeks in patients with COPD

Secondary:

- To characterize the pharmacokinetics (PK) of UMEC and VI administered in combination and individually
- To explore the effects of covariates on PK parameters using population PK methodology
- To evaluate PK-pharmacodynamic (PD) relationships, if any, between UMEC or VI systemic exposure and systemic PD endpoints following administration of UMEC/VI and the individual treatments

Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial.

Treatments

Patients were randomized 3:3:3:2 to receive one of the following treatments:

- UMEC/VI 125 mcg/25 mcg once daily (Trial DB2113361) or
  UMEC/VI 62.5 mcg/25 mcg once daily (Trial DB2113373)
- UMEC 125 mcg once daily (Trial DB2113361) or
  UMEC 62.5 mcg once daily (Trial DB2113373)
- VI 25 mcg once daily
- Placebo once daily

In addition, patients were provided albuterol/salbutamol for “as-needed” use.

Population

Key Inclusion Criteria:

- Outpatient
- 40 years of age or older
- Females:
  - Of non-child bearing potential – OR –
  - Of children bearing potential, with a negative pregnancy test at screening, and agreed to use contraception as per the protocol
- Diagnosis of COPD consistent the American Thoracic Society (ATS)/ European Respiratory Society (ERS) guidelines
- Current or former cigarette smokers with a history of ≥ 10 pack-years
- A post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and a post-albuterol/salbutamol FEV1 of ≤70% of predicted normal values using NHANES III reference equations at Visit 1

- A score of ≥ 2 on the Modified Medical Research Council Dyspnea Scale (mMRC) at visit 1

Key Exclusion Criteria:

- Pregnancy or lactation, either current or planned
- Current diagnosis of asthma
- Known respiratory disorders other than COPD including (but not limited to): α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or computed tomography (CT) scan[10] with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, $beta_2$-agonist, lactose/milk protein or magnesium stearate
- History of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicated use of an inhaled anticholinergic
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- Lung volume reduction surgery within 12 months prior to Visit 1
- A significant abnormal ECG finding on the 12-lead ECG obtained at Visit 1
- A significant abnormal finding on the 24-hour Holter monitoring conducted at Visit 1 (applicable to a subset of patients)
- Significantly abnormal screening laboratory test results at Visit 1
- Unable to go without albuterol/salbutamol for the 4 hour period prior to spirometry testing at each trial visit
- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 14

Table 14. Prohibited medications and associated washout intervals

Prohibited Medication	Washout Interval (prior to Visit 1)
Corticosteroids, depot	12 weeks
Corticosteroids, systemic oral or parenteral	6 weeks
Antibiotics for lower respiratory tract infection	6 weeks
Cytochrome P450 3A4 strong inhibitors	6 weeks
LABA/ICS combination products, if to be discontinued completely	30 days
ICS at a dose > 1000 mcg of fluticasone propionate or equivalent*	30 days

[10] If no chest X-ray or CT scan was available from the 6 months prior to Visit 1, then a chest X-ray had to be obtained at Visit 1 (except for Germany, where such patients were ineligible).

Phosphodiesterase 4 Inhibitor	14 days
Tiotropium	14 days
Theophyllines	48 hours
Oral leukotriene inhibitors	48 hours
Oral beta$_2$-agonists, long-acting	48 hours
Inhaled LABA	48 hours
LABA/ICS combination products, if discontinuing LABA and switching to ICS only[#]	48 hours for the LABA component
Inhaled sodium cromoglycate or nedrocromil sodium	24 hours
Oral beta$_2$-agonists, short-acting	12 hours
Inhaled short-acting beta$_2$-agonists[@]	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting beta$_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1.4 (DB2113361), pg. 223 (unnumbered table)
*Consistent use of an ICS at a dose ≤ 1000 mcg of fluticasone propionate is permitted; ICS use may not be initiated or discontinued within 30 days prior to Visit 1
[#]The dose of ICS must be consistent with that of the ICS/LABA combination product
[@]Use of trial provided albuterol/salbutamol is permitted during the trial, except in the 4 hours prior to spirometry testing

- Use of oxygen therapy for greater than 12 hours a day
- Daily, prescribed use of short-acting bronchodilators via nebulizer
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1
- A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1
- Previous use of UMEC, VI, UMEC/VI or fluticasone furoate/VI

Key Randomization Criteria:

- No evidence of a significantly abnormal 12-lead ECG pre-dose at Visit 2
- No COPD exacerbation or lower respiratory tract infection during run-in or at Visit 2
- For patients on ICS, regular use of a stable dose during the run-in period (dose ≤ 1000 mcg/day of fluticasone propionate or equivalent)
- Completion of the eDiary on at least 4 of the last 7 days of the run-in period

Withdrawal Criteria:

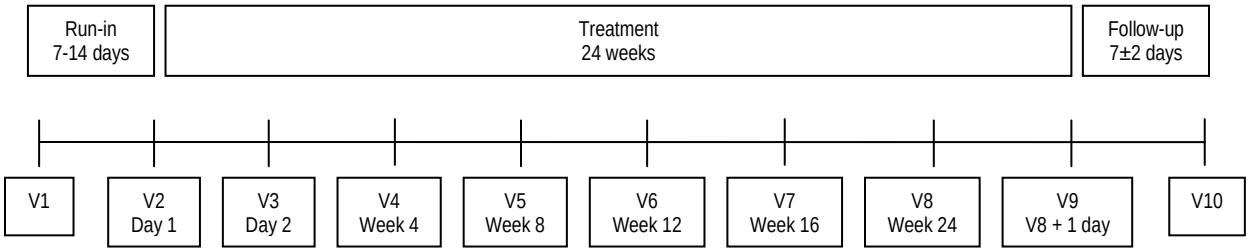
- COPD exacerbation
  The protocol defined COPD exacerbation as an acute worsening of symptoms of COPD requiring treatment beyond trial medication or rescue albuterol/salbutamol, including the use of systemic corticosteroids, antibiotics,

and/or emergency treatment or hospitalization. COPD exacerbations were considered to be associated with the underlying disease and were not recorded as AEs unless the event met criteria necessary to be classified as a serious adverse reaction (see Section 6.1.2 of this review).

- Clinically relevant changes in laboratory assessments, per the Investigator's discretion
- Significant abnormal ECG finding
- Significant abnormal finding from 24-hour Holter monitoring (applicable to a subset of patients)
- Protocol-defined liver chemistry stopping criteria
- Positive urine pregnancy test

Trial Conduct
The trials consisted of a 7 to 14-day run-in period, a 24-week treatment period, and a follow-up period (approximately 7 days), with a total of 10 clinic visits over the entire trial duration of approximately 27 weeks. A trial schematic is presented in Figure 9.

Figure 9. Schematic, Placebo-controlled Trials



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Protocol or Amendment), pg. 217 (Figure 1)

Spirometry:
As the Applicant is seeking an indication for the maintenance bronchodilator treatment of airflow obstruction, particular focus on the trials' spirometric assessments is warranted.

Both pre- and post-bronchodilator spirometry was conducted at screening; post-bronchodilator results were used to determine patient eligibility. Spirometry was also conducted at each post-randomization clinic visit. Trough spirometry, measured at 23 and 24 hours after the previous day's dose, was measured at Visits 3 through 9. Six-hour serial spirometry was performed for all patients at Visits 2, 4, 6, and 8. In addition, at selected sites, 24-hour serial spirometry was performed for a subset of patients (approximately 200 from each trial, equivalent to 13% of the ITT population) at Visits 2, 6, and 8.

Spirometry was to be conducted using equipment meeting or exceeding ATS minimal performance recommendations, with all sites using standardized equipment provided by an external vendor. For FEV1 and FVC, at least 3 (and no more than 8) acceptable efforts were to be obtained; the largest FEV1 and FVC from the 3 acceptable efforts were to be recorded, regardless of whether they were obtained from the same effort. Except for that occurring at Visit 10, spirometric assessments were to be initiated between 6:00 AM and 10:00 AM. Albuterol/salbutamol was to be withheld for at least 4 hours; at Visit 1, COPD medications had to be withheld as specified in the exclusion criteria; at Visits 3 through 8, the morning dose of blinded trial drug was to be withheld. In addition, patients were to refrain from smoking and from drinking caffeinated beverages for 1 hour and 2 hours prior to testing, respectively.

The full schedule of trial events is provided in Table 15.

Table 15. Schedule of Trial Events, Placebo-controlled Trials

	Run-in	Treatment Period									Follow-up
	Visit 1 (Screening)	Visit 2 (Randomization)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	EW	Visit 10
	Day -7 to -14	Day 1	Day 2	Day 28 (±2)	Day 56 (-4 to +2)	Day 84 (-4 to +2)	Day 112 (-4 to +2)	Day 168 (±4)	Visit 8 +1 day		7±2 days after Visit 9 or EW
Informed Consent	X										
Demographics/ Medical and COPD history	X										
Physical Examination	X							X		X	
Smoking Status	X					X		X		X	
Smoking Cessation Counseling	X								X	X	
Chest X-ray[1]	X										
Verify Inclusion/Exclusion Criteria	X										
Verify Randomization Criteria		X									
Screening spirometry[2]	X										
mMRC	X										
Issue eDiary	X										
Collect eDiary									X	X	
Review eDiary		X	X	X	X	X	X	X	X	X	
Issue paper diary	X	X		X	X	X	X				
Review and/or collect paper diary		X	X	X	X	X	X	X	X	X	
Post-treatment spirometry											X
Trough spirometry[3]			X	X	X	X	X	X	X		
6-hour serial spirometry[4]		X		X		X		X			
24-hour serial spirometry (subset)[5]		X				X		X			
COPD exacerbation assessment		X	X	X	X	X	X	X	X	X	X

BDI		X									
TDI				X		X		X			
SOBDA	X	X	X	X	X	X	X	X	X		
SGRQ		X		X		X		X			
Healthcare resource utilization		X	X	X	X	X	X	X	X		
12-lead ECG[6]	X	X				X		X		X	
Vital Signs[7]	X	X	X	X	X	X	X	X	X	X	
24-hour Holter monitoring (subset)	X	X				X		X			
AE assessment		X	X	X	X	X	X	X	X	X	X
Pharmacogenetics						X					
Urine pregnancy	X	X				X		X		X	
Clinical laboratory[8]	X					X		X		X	
Plasma PK[9]		X			X			X			
Plasma PK 24 hours (subset)[10]		X				X		X			
Concurrent medications	X	X	X	X	X	X	X	X	X	X	
Dispense/collect rescue medication	X	X	X	X	X	X	X	X	X		
Dispense double-blind medication		X		X	X	X	X				
Collect double-blind medication				X	X	X	X	X		X	
Assess compliance[11]				X	X	X	X	X		X	

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Protocol or Amendment), pg. 235-237(Table 6)
[1] Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1
[2] Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing
[3] Obtained at 23 and 24 hours after the previous day's morning dose
[4] Performed pre-dose and post-dose at 15 and 30 minutes and at 1, 3, and 6 hours
[5] Performed pre-dose and post dose at 15 and 30 minutes, and at 1, 3, 6, 12, 15, 21, 23, and 24 hours
[6] On Visits 2, 6, and 8 performed pre-dose and 10 and 45 minutes post-dose
[7] On Visits 2, 6, and 8 performed pre-dose and 10 and 45 minutes post-dose; on Visits 3, 4, 5, 7, and 9 performed at 23 hours after the previous day's dose
[8] Hematology and chemistry
[9] Performed pre-dose and at 1 to 15 minutes post-dose
[10] Performed pre-dose and at 1 to 15 minutes, 20 minutes to 4 hours, 4.5 hours to 15 hours, and 23 to 24 hours post-dose
[11] Assessed by reviewing device dose counter

Endpoints

Primary Endpoint:

- Pre-dose trough FEV1[11] on Treatment Day 169

Secondary Endpoint:

- Weighted mean FEV1 over 0 to 6 hours post-dose at Week 24

Other Endpoints:

- Trough FEV1 and weighted mean FEV1 over 0-6 hours post-dose at other time points
- Time to onset (defined as an increase of 100 mL above baseline FEV1) during 0-6 hours post-dose on Treatment Day 1

[11] Trough FEV1 on Day 169 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 168.

- Proportion of patients achieving an increase in FEV1 of ≥ 12% and ≥ 200 mL above baseline at any time during 0-6 hours post-dose on Treatment Day 1
- Proportion of patients achieving an increase of ≥ 100 mL above baseline in trough FEV1
- Serial FEV1 over 0 to 6 hours post-dose (at each time point)
- Serial and trough FVC
- Weighted mean and serial FEV1 over 0 to 24 hours post-dose obtained in a subset of patients
- Rescue albuterol/salbutamol use (percentage of rescue-free days and puffs/day)
- Mean TDI focal score at Week 24[12]
- Mean TDI focal score at other time points
- Proportion of responders to TDI
- Mean SOBDA score
- Proportion of responders to SOBDA
- Time to first COPD exacerbation

Health-Related Quality of Life/Health Outcomes:

- St. George's Respiratory Questionnaire (SGRQ)

Population PK:

- Plasma concentrations and derived PK parameters for UMEC and VI

Statistical Considerations

Sample Size:

The protocol states that the sample size calculation was performed with the goal of providing sufficient power to detect a difference for both the primary and secondary endpoints (including TDI, which was designated as a secondary endpoint for the EMA).

A sample size of 273 evaluable patients in each active treatment arm and 182 evaluable patients in the placebo arm was estimated to have 90% power to detect a 1 unit difference between treatments in TDI, and >99% power to detect a 100 mL difference between UMEC/VI and either UMEC or VI, or between an active treatment and placebo, assuming a standard deviation of 210 mL for trough FEV1 and a two-sided 5% significance level. This sample size would provide 90% power to detect a 58 mL difference between UMEC/VI and either UMEC or VI, and a 68 mL difference between an active treatment and placebo.

The Applicant anticipated a 30% withdrawal rate; as a result, it was estimated that 399 randomized patients were needed per active treatment arm and 266 randomized patients per placebo arm in order to obtain the desired number of evaluable patients.

[12] Mean TDI focal score was included as a secondary endpoint for submission to EMA; for the FDA submission, mean TDI focal score was categorized as an "other endpoint."

Analysis Population:
The primary population for all data analyses was specified to be the Intent-to-Treat (ITT) Population, defined as all patients randomized to treatment who received at least one dose of randomized trial medication in the treatment period; patients were to be included in an analysis of a particular outcome if they provided at least one on-treatment assessment of that outcome.

Primary Efficacy Analysis:
The analysis of the primary endpoint, trough FEV1 on Day 169, was prespecified to be a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of Days 2, 28, 56, 84, 112, 168, and 169, and performed for the ITT Population.

Multiplicity:
In order to account for multiplicity, the protocol specified a step-down closed testing procedure, using the following hierarchy: UMEC/VI vs. placebo, UMEC vs. placebo, VI vs. placebo, UMEC/VI vs. VI, UMEC/VI vs. UMEC, for the primary and secondary endpoints.

Interim Analysis:
No interim analysis was planned.

Protocol Amendments
The original protocol was submitted on January 17, 2011. Two protocol amendments were submitted[13] and are summarized below. The changes provided by these amendments are reflected in the protocol description above.

Protocol Amendment #1:
This protocol amendment replaced the originally planned follow-up phone contact with a follow-up clinic visit (Visit 10). The amendment also provided for clarifications in the ECG exclusion and withdrawal criteria, permitted medications, duration of reporting of COPD exacerbations, pharmacogenetic analyses, and BDI/TDI administration procedures.

Protocol Amendment #2:
This protocol amendment reclassified mean SOBDA score from a secondary endpoint to an "other" endpoint. The amendment also revised the list of trial medical monitors.

[13] For Trial DB2113361 the original protocol was submitted on January 17, 2011, the first amendment was submitted on April 12, 2011, and the second amendment was submitted on October 14, 2011. For Trial DB2113373 the original protocol was submitted on January 17, 2011, the first amendment was submitted on April 12, 2011, and the second amendment was submitted on November 7, 2011.

The changes outlined in these amendments do not alter the study design or conduct in a major fashion.

Active-comparator Trials

The administrative information and protocol for the two active-controlled trials are presented below. These trials each compared both doses of UMEC/VI to tiotropium; in addition, Trial DB2113360 included VI as a comparator, while Trial DB2113374 included UMEC 125 mcg. As these trials were replicate in design (with the exception of the choice of monotherapy comparator), a single protocol summary pertinent to both trials is provided below.

The protocol for these trials was amended once; the summary below is based on the final version of the protocol. A description of the changes provided by the single protocol amendment follows the summary.

Administrative Information

DB2113360

- Study Title: "A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 with GW642444 and with Tiotropium over 24 weeks in Subjects with COPD."
- Study Dates: March 21, 2011 – April 24, 2012
- Study Sites: A total of 91 centers in the United States, Germany, Italy, Mexico, Peru, Poland, Romania, Russian Federation, and Ukraine
- Study Report Date: September 14, 2012

DB2113374

- Study Title: "A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 with GSK57319 and with Tiotropium over 24 Weeks in Subjects with COPD."
- Study Dates: March 21, 2011 – April 10, 2012
- Study Sites: A total of 95 centers in the United States, Argentina, Australia, Canada, Chile, Germany, South Korea, Mexico, Romania, and South Africa
- Study Report Date: November 27, 2012

Objectives

Primary:

- To compare the efficacy of UMEC/VI with VI (Trial DB2113360) or with UMEC 125 mcg (Trial DB2113374) and with tiotropium over 24 weeks for the treatment of patients with COPD

Secondary:

- To compare effects of UMEC/VI with VI (Trial DB2113360) or with UMEC (Trial DB2113374) and with tiotropium on safety and quality of life assessments over 24 weeks in patients with COPD

Design
This was a randomized, double-blind, double-dummy, parallel-group, multicenter trial.

Treatments
Patients were randomized 1:1:1:1 to one of the following treatment arms:

- UMEC/VI 125 mcg/25 mcg via DPI + placebo via HandiHaler, once daily
- UMEC/VI 62.5 mcg/25 mcg via DPI + placebo via HandiHaler, once daily
- VI 25 mcg once daily via DPI (Trial DB2113360) or UMEC 125 mcg (Trial DB2113374) + placebo via HandiHaler, once daily
- Tiotropium 18 mcg once daily via HandiHaler + placebo via DPI, once daily

In addition, patients were provided albuterol/salbutamol for "as-needed" use.

Population
Key Inclusion Criteria:

- Outpatient
- 40 years of age or older
- Females:
  - Of non-child bearing potential – OR –
  - Of children bearing potential, with a negative pregnancy test at screening, and agreed to use contraception as per the protocol
- Diagnosis of COPD consistent ATS/ERS guidelines
- Current or former cigarette smokers with a history of ≥ 10 pack-years
- A post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and a post-albuterol/salbutamol FEV1 of ≤70% of predicted normal values using NHANES III reference equations at Visit 1
- A score of ≥ 2 on the mMRC at Visit 1

Key Exclusion Criteria:

- Pregnancy or lactation, either current or planned
- Current diagnosis of asthma
- Known respiratory disorders other than COPD including (but not limited to): α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or CT scan[14] with clinically significant abnormalities not attributable to COPD

[14] If no chest X-ray or CT scan was available from the 6 months prior to Visit 1, then a chest X-ray had to be obtained at Visit 1 (except for Germany, where such patients would be ineligible).

- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta$_2$-agonist, lactose/milk protein or magnesium stearate
- History of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicated use of an inhaled anticholinergic
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- Lung volume reduction surgery within 12 months prior to Visit 1
- A significant abnormal ECG finding on the 12-lead ECG obtained at Visit 1
- Significantly abnormal screening laboratory test results at Visit 1
- Unable to go without albuterol/salbutamol for the 4 hour period prior to spirometry testing at each trial visit
- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 14 (same guidelines as those for the placebo-controlled trials)
- Use of oxygen therapy for greater than 12 hours a day
- Daily, prescribed use of short-acting bronchodilators via nebulizer
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1
- A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1
- Previous use of UMEC, VI, UMEC/VI or fluticasone furoate/VI

Key Randomization Criteria:

- No evidence of a significantly abnormal 12-lead ECG pre-dose at Visit 2
- No COPD exacerbation or lower respiratory tract infection during run-in or at Visit 2
- For patients on ICS, regular use of a stable dose during the run-in period (dose ≤ 1000 mcg/day of fluticasone propionate or equivalent)
- Completion of the eDiary on at least 4 of the last 7 days of the run-in period

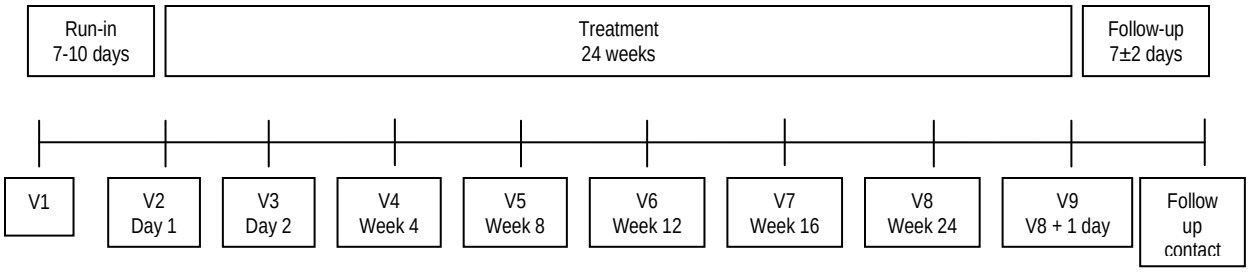
Withdrawal Criteria:

- COPD exacerbation
  The protocol defined COPD exacerbation as an acute worsening of symptoms of COPD requiring treatment beyond trial medication or rescue albuterol/salbutamol, including the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization. COPD exacerbations were considered to be associated with the underlying disease and were not recorded as AEs unless the event met criteria necessary to be classified as a serious adverse reaction (see Section 6.1.2 of this review).
- Clinically relevant changes in laboratory assessments, per the Investigator's discretion
- Significant abnormal ECG finding
- Protocol-defined liver chemistry stopping criteria

- Positive urine pregnancy test

Trial Conduct
The trials consisted of a 7 to 10-day run-in period, a 24-week treatment period, and a follow-up period (approximately 7 days), with a total of 9 clinic visits and one follow-up contact by phone[15] over the entire trial duration of approximately 26 weeks. A trial schematic is presented in Figure 10.

Figure 10. Schematic, Active-comparator Trials



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Protocol Amendment 1), pg. 17 (Figure 1)

Spirometry:
As the Applicant is seeking an indication for the maintenance bronchodilator treatment of airflow obstruction, particular focus on the trials' spirometric assessments is warranted.

Both pre- and post-bronchodilator spirometry was conducted at screening for determination of eligibility and calculation of reversibility. Baseline spirometry was conducted at Visit 2 prior to randomization. Pre-dose trough spirometry was conducted at every on-treatment clinic visit after randomization. In addition, six-hour post-dose serial spirometry was conducted at Visit 2 (Day 1), Visit 6 (Week 12), and Visit 8 (Week 24).

Spirometry was to be conducted using equipment meeting or exceeding ATS minimal performance recommendations, with all sites using standardized equipment provided by an external vendor. For FEV1 and FVC, at least 3 (and no more than 8) acceptable efforts were to be obtained; the largest FEV1 and FVC from the 3 acceptable efforts were to be recorded, regardless of whether they were obtained from the same effort. Spirometric assessments were to be initiated between 6:00 AM and 10:00 AM. Albuterol/salbutamol was to be withheld for at least 4 hours; at Visit 1, COPD medications had to be withheld as specified in the exclusion criteria; at Visits 3 through 8, the morning dose of blinded trial drug was to be withheld. In addition, patients were

[15] Except for patients in Germany, who had a follow-up clinic visit.

to refrain from smoking and from drinking caffeinated beverages for 1 hour and 2 hours prior to testing, respectively.

The full schedule of trial events is provided in Table 16.

Table 16. Schedule of Trial Events, Active-comparator Trials

	Run-in	Treatment Period									Follow-up
	Visit 1 (Screening)	Visit 2 (Randomization)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	EW	Follow up Contact
	Day -7 to -10	Day 1	Day 2	Day 28 (±2) Week 4	Day 56 (-4 to +2) Week 8	Day 84 (-4 to +2) Week 12	Day 112 (-4 to +2) Week 16	Day 168 (±4) Week 24	Visit 8 +1 day		7±2 days after Visit 9 or EW
Informed Consent	X										
Demographics/ Medical and COPD history	X										
Smoking Status	X					X			X		
Smoking Cessation Counseling	X								X	X	
Verify Inclusion/Exclusion Criteria	X										
Verify Randomization Criteria		X									
Chest X-ray[1]	X										
Physical Examination	X							X		X	
Screening spirometry[2]	X										
mMRC	X										
Trough spirometry[3]			X	X	X		X		X		
Serial spirometry[4]		X				X		X			
BDI		X									
TDI				X		X		X			
COPD exacerbation assessment	X	X	X	X	X	X	X	X	X	X	X
Vital Signs[5]	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[6]	X	X				X		X		X	
AE assessment		X	X	X	X	X	X	X	X	X	X
Pharmacogenetics						X				X	
Urine pregnancy	X	X				X		X		X	
Clinical laboratory[7]	X					X		X		X	
SOBDA	X	X	X	X	X	X	X	X			
SGRQ		X		X		X		X			
EQ-5D		X		X		X		X			
CAT		X				X		X			
Healthcare resource utilization		X	x	X	X	X	X	X			
Device preference questionnaire								X		X	
Concurrent medications	X	X	X	X	X	X	X	X	X	X	
Dispense rescue medication	X	X	X	X	X	X	X	X			
Collect rescue medication		X	X	X	X	X	X	X	X	X	
Dispense double-blind medication		X		X	X	X	X				
Collect double-				X	X	X	X	X		X	

blind medication											
Assess compliance[8]				X	X	X	X	X		X	
Issue eDiary	X										
Review eDiary		X	X	X	X	X	X	X	X	X	
Collect eDiary									X	X	
Assess eDiary compliance		X	X	X	X	X	X	X	X	X	
Dispense peak flow meter	X										
Collect peak flow meter									X	X	
Issue paper diary	X	X		X	X	X	X				
Review paper diary		X	X	X	X	X	X	X	X	X	
Collect paper diary		X		X	X	X	X		X	X	

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Protocol Amendment 1), pg. 37-39 (Table 5)
[1] Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1
[2] Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing
[3] Obtained at 23 and 24 hours after the previous day's morning dose
[4] Performed pre-dose and post-dose at 15 and 30 minutes and at 1, 3, and 6 hours
[5] On Visits 2, 6, and 8 performed pre-dose and 10 and 45 minutes post-dose; on Visits 3, 4, 5, 7, and 9 performed at 23 hours after the previous day's dose
[6] On Visits 2, 6, and 8 performed pre-dose and 10 and 45 minutes post-dose
[7] Hematology and chemistry
[8] Assessed by reviewing device dose counter for novel DPI, and by reviewing remaining blister doses for tiotropium

Endpoints

Primary Endpoint:

- Pre-dose trough FEV1[16] on Treatment Day 169

Secondary Endpoint:

- Weighted mean FEV1 over 0 to 6 hours post-dose at Week 24

Other Endpoints:

- Mean SOBDA score
- Mean TDI focal score
- Trough FEV1 and weighted mean FEV1 over 0-6 hours post-dose at other time points
- Rescue albuterol/salbutamol use
- Time to onset during 0 to 6 hours post-dose on Treatment Day 1
- Proportion of patients achieving an increase in FEV1 of ≥ 12% and ≥ 200 mL above baseline at any time during 0-6 hours post-dose on Treatment Day 1
- Proportion of patients achieving an increase of ≥ 100 mL above baseline in trough FEV1
- Serial FEV1 over 0 to 6 hours post-dose (at each time point)
- Serial and trough FVC
- Proportion of responders to SOBDA

[16] Trough FEV1 on Day 169 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 168.

- Proportion of responders to TDI
- Morning PEF
- Time to first COPD exacerbation
- Patient device preference

Health-Related Quality of Life/Health Outcomes:

- St. George's Respiratory Questionnaire (SGRQ)
- EQ-5D health outcome assessment
- COPD Assessment Test (CAT)
- Healthcare resource utilization

Statistical Considerations

Sample Size:

The protocol states that the sample size calculation was performed with the goal of providing sufficient power to detect a difference in the comparisons conducted for the primary endpoint (trough FEV1) within each trial, as well as to detect a difference between UMEC/VI and tiotropium for TDI in a meta-analysis using both trials; the latter analysis is intended to support EMA registration.

A sample size of 94 evaluable patients per arm was estimated to have 90% power to detect a 100 mL difference in trough FEV1 between treatments, assuming a standard deviation of 210 mL for trough FEV1 and a 2-sided 5% significance level. In order to provide additional safety data, the planned number of evaluable patients was set at 146 per treatment arm; this sample size would yield 98% power to detect a 100mL difference in trough FEV1.

The Applicant anticipated a 30% withdrawal rate; as a result, it was estimated that 208 randomized patients were needed per treatment arm in order to obtain the desired number of evaluable patients.

Analysis Population:

The primary population for all data analyses was specified to be the ITT Population, defined as all patients randomized to treatment who received at least one dose of randomized trial medication in the treatment period; patients were to be included in an analysis of a particular outcome if they provided at least one on-treatment assessment of that outcome.

Primary Efficacy Analysis:

The analysis of the primary endpoint, trough FEV1 on Day 169, was prespecified to be a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of Days 2, 28, 56, 84, 112, 168, and 169, and performed for the ITT Population.

Multiplicity:
In order to account for multiplicity, the protocol specified a step-down closed testing procedure, using the following hierarchy:

- Primary endpoint:
  - UMEC/VI 125 mcg/25 mcg vs. tiotropium
  - UMEC/VI 125 mcg/25 mcg vs. VI (Trial DB2113360) or vs. UMEC 125 mcg (Trial DBD2113374)
- Secondary endpoint, weighted mean FEV1 over 0 to 6 hours at Week 24
  - UMEC/VI 125 mcg/25 mcg vs. tiotropium
  - UMEC/VI 125 mcg/25 mcg vs. VI (Trial DB2113360) or vs. UMEC 125 mcg (Trial DBD2113374)
- Primary endpoint:
  - UMEC/VI 62.5 mcg/25 mcg vs. tiotropium
  - UMEC/VI 62.5 mcg/25 mcg vs. VI (Trial DB2113360) or vs. UMEC 125 mcg (Trial DBD2113374)
- Secondary endpoint, weighted mean FEV1 over 0 to 6 hours at Week 24
  - UMEC/VI 62.5 mcg/25 mcg vs. tiotropium
  - UMEC/VI 62.5 mcg/25 mcg vs. VI (Trial DB2113360) or vs. UMEC 125 mcg (Trial DBD2113374)

Interim Analysis:
No interim analysis was planned.

Protocol Amendments
The original protocol was submitted on January 17, 2011. One protocol amendment was submitted on July 5, 2011, and is summarized below. The changes provided by this amendment are reflected in the protocol description above.

Protocol Amendment #1:
This protocol amendment provided the option of a clinic visit for the follow-up contact in countries where required (i.e. Germany). This amendment also reclassified mean SOBDA score from a secondary endpoint to an "other" endpoint, and modified the statistical testing hierarchy. In addition, the amendment also provided for clarifications in the ECG exclusion and withdrawal criteria, permitted medications, duration of reporting of COPD exacerbations, dosing of tiotropium and placebo capsules, eDiary compliance notification, and BDI/TDI administration procedures. The changes outlined in this amendment do not alter the study design or conduct in a major fashion.

Exercise Endurance Trials
The administrative information and protocol for the two exercise endurance trials are presented below. These trials each evaluated both doses of UMEC/VI, both doses of UMEC, VI, and placebo. As these trials were replicate in design (except for minor

exceptions which are noted), a single protocol summary pertinent to both trials is provided below.

The protocol for these trials was amended once; the summary below is based on the final version of the protocol. A description of the changes provided by the single protocol amendment follows the summary.

Administrative Information

DB2114417

- Study Title: "An exercise endurance study to evaluate the effects of treatment of COPD patients with a dual bronchodilator: GSK573719/GW642444"
- Study Dates: March 16, 2011 – June 14, 2012
- Study Sites: A total of 31 centers in the United States, Germany, United Kingdom, Bulgaria, Estonia, and Russia
- Study Report Date: October 17, 2012

DB2114418

- Study Title: "An exercise endurance study to evaluate the effects of treatment of COPD patients with a dual bronchodilator: GSK573719/GW642444"
- Study Dates: March 16, 2011 – July 16, 2012
- Study Sites: A total of 42 centers in the United States, Czech Republic, South Africa, Denmark, Canada, Ukraine, and the United Kingdom
- Study Report Date: October 2012

Objectives

Primary:

- To evaluate the effect of UMEC/VI on pre-dose FEV1 and exercise endurance over 12 weeks in patients with COPD

Secondary:

- To evaluate the effect of UMEC/VI, its components, and placebo on measures of hyperinflation and post-dose lung function over 12 weeks in patients with COPD

Design

This was a randomized, double-blind, placebo-controlled, 2-period, incomplete block, cross-over trial.

Treatments

Patients were randomized to one of 26 sequences which included two of the following treatments:

- UMEC/VI 125 mcg/25 mcg once daily
- UMEC/VI 62.5 mcg/25 mcg once daily
- UMEC 125 mcg once daily
- UMEC 62.5 mcg once daily

- VI 25 mcg once daily
- Placebo once daily

Each treatment was delivered via DPI for a duration of 12 weeks.

In addition, patients were provided albuterol/salbutamol for "as-needed" use throughout the trial. Short-acting anticholinergics, while prohibited for the 4 hours prior to Visit 1, were permitted during the run-in and washout periods

Population

Key Inclusion Criteria:

- Outpatient
- 40 years of age or older
- Females:
  - Of non-child bearing potential – OR –
  - Of children bearing potential, with a negative pregnancy test at screening, and agreed to use contraception as per the protocol
- Diagnosis of COPD consistent ATS/ERS guidelines
- Current or former cigarette smokers with a history of ≥ 10 pack-years
- A post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and a post-albuterol/salbutamol FEV1 of ≥35% and ≤70% of predicted normal values using NHANES III reference equations at Visit 1
- A score of ≥ 2 on the mMRC at Visit 1
- A resting functional residual capacity (FRC) of ≥120% of predicted normal at Visit 1

Key Exclusion Criteria:

- Pregnancy or lactation, either current or planned
- Current diagnosis of asthma
- Known respiratory disorders other than COPD including (but not limited to): α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or CT scan[17] with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, $beta_2$-agonist, lactose/milk protein or magnesium stearate

[17] If no chest X-ray or CT scan was available from the 6 months prior to Visit 1, then a chest X-ray had to be obtained at Visit 1 (except for Germany, where such patients would be ineligible).

- History of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicated use of an inhaled anticholinergic
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- Lung volume reduction surgery within 12 months prior to Visit 1
- A significant abnormal ECG finding on the 12-lead ECG obtained at Visit 1
- Significantly abnormal screening laboratory test results at Visit 1
- Unable to go without albuterol/salbutamol for the 4 hour period prior to spirometry testing at each trial visit
- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 14 (same guidelines as those for the placebo-controlled trials)
- Use of oxygen therapy for greater than 12 hours a day
- Daily, prescribed use of short-acting bronchodilators via nebulizer
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1
- A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1

Key Randomization Criteria:

- No evidence of a significantly abnormal 12-lead ECG pre-dose at Visit 4
- No COPD exacerbation or lower respiratory tract infection during run-in or at Visit 4
- For patients on ICS, regular use of a stable dose during the run-in period (dose ≤ 1000 mcg/day of fluticasone propionate or equivalent)
- Demonstrated ability to properly perform the Endurance Shuttle Walk Test (ESWT) at Visit 3 or 4
- ESWT exercise endurance time ≤ 15 minutes, and with variability no greater than > 2 minutes, at visit 3 or 4
- SpO2 of ≥ 85% during the ESWT at Visit 3, with no need for supplemental oxygen
- Ability to properly use inhaler after 3 demonstrations

Withdrawal Criteria:

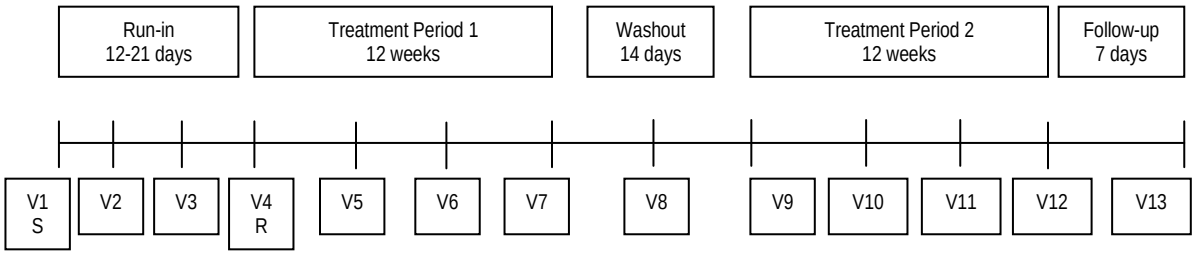
- Significant abnormal ECG finding
- Protocol-defined liver chemistry stopping criteria
- Positive pregnancy test

The protocol for these trials also stated that patients experiencing a COPD exacerbation during the treatment periods would be withdrawn from the trial.

Trial Conduct

The trials consisted of a 12 to 21-day run-in period, two 12-week treatment periods separated by a 14 day washout period, and a safety follow-up visit 7 days after the end of treatment period two. A trial schematic is presented in Figure 11.

Figure 11. Schematic, Exercise Endurance Trials



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2114417, Protocol Amendment 1), pg. 17 (Unnumbered Figure)
Key: S=screening; R=randomization

ISWT and ESWT:

Given the trials' stated objective, description of the trials' assessment of exercise endurance is warranted; however, it should be noted that the Applicant is not seeking an exercise claim. As will be discussed in Section 6, these trials provide additional trough FEV1 data, and also allow for a direct comparison of UMEC/VI 62.5 mcg/25 mcg and 125 mcg/25 mcg.

The incremental shuttle walk test (ISWT) was demonstrated at Visit 1 and performed at Visits 2 and 8. The ISWT was conducted on a flat 10-meter long course, with monitoring of heart rate and arterial oxygen saturation (via pulse oximeter). Patients were instructed to walk at a predetermined rhythm, as dictated by an audio signal, with an initial speed of 0.5 m/sec. Speed was increased by 0.17 m/sec every minute until patient reached maximal capacity.

The endurance shuttle walk test (ESWT) was performed at Visits 3-7 and 9-12 on the same course as that used for the ISWT. Speed was set to correspond to 85% of maximal oxygen uptake. Observers recorded a patient's reason for halting. In addition, the exercise dyspnea scale was used to assess the degree of dyspnea experienced by a patient at two minute intervals during the ESWT.

The full schedule of trial events is provided in Table 17.

Table 17. Schedule of Trial Events, Exercise Endurance Trials

	Screen	Run-in		R	Treatment Period 1			Wash-out	Treatment Period 2				EW	Follow-up
Visit	1	2	3	4	5	6	7	8	9	10	11	12		13
Day	-21 to -12	-20 to -5	-9 to -1 (after V2)	1	2	43±3	85±3	V7 + 10-12	1 (V7 +12-16)	2	43±3	85±3		V12 + 5-9

Week	-2 to -3	-2	-1	1	1+1d	6	12	V7 + 1-2	1 (V7 + 2)	1 + 1d	6	12		V12 + 1
Informed Consent	X													
Demographics/ Medical and COPD history	X													
BMI	X			X			X		X			X	X	
Smoking Status	X													
Smoking Cessation Counseling	X											X	X	
Verify Inclusion/Exclusion Criteria	X													
Verify Randomization Criteria				X										
Chest X-ray[1]	X													
Physical Examination	X											X	X	
Screening VS	X												X	
Screening ECG	X													
Screening spirometry[2]	X													
Screening lung volume	X													
mMRC	X													
AE assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vitals pre & post dose				X	X	X	X		X	X	X	X		
Vitals pre & post shuttle walk		X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[3] pre & post dose				X			X		X			X	X	
COPD exacerbation assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry pre and post-dose				X	X	X	X		X	X	X	X		
Lung volumes pre & post dose				X	X	X	X		X	X	X	X		
Diffusing capacity				X					X					
ISWT	X	X						X						
ESWT			X	X	X	X	X		X	X	X	X		
Pulse Oximetry		X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory[4]	X						X					X	X	
PGx sampling							X						X	
Urine pregnancy	X			X			X		X			X	X	
Issue/collect run-in diary	X	X	X	X			X		X				X	
Issue/collect double-blind diary				X			X		X			X	X	
Exercise dyspnea scale			X	X	X	X	X		X	X	X	X		
Inhaler use assessment				X	X	X								
Ease of use assessment						X								
Concomitant medications assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exercise IC (subset, Trial DB2114417 only)			X	X	X	X	X		X	X	X	X		
Cardio-respiratory			X	X	X	X	X		X	X	X	X		

assessment (subset, Trial DB2114417 only)														
Dispense/collect rescue medication	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense trial medication				X					X					
Collect trial medications and assess compliance						X	X				X	X	X	

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2114417, Protocol Amendment 1), pg. 38-41 (Table 3)
Key: EW=early withdrawal; IC=inspiratory capacity; R=randomization
[1] Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1
[2] Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing
[3] Pre-dose and 45 minutes post-dose
[4] Hematology and chemistry

Endpoints

Primary Endpoints:

- Exercise endurance time (EET) post-dose at Week 12
- Trough FEV1 at Week 12

Secondary Endpoints:

- Inspiratory Capacity (IC) at Week 12
- Functional Residual Capacity (FRC) at Week 12
- Residual Volume (RV) at Week 12
- 3-hour post-dose FEV1 at Week 12

Other Endpoints:

- Rescue medication use
- Ease of use of Novel DPI
- Exercise Inspiratory Capacity (subset)
- Cardio-respiratory measurements (subset)
- Exercise Dyspnea Scale

Statistical Considerations

Sample Size:

A sample size of 208 evaluable patients per arm was estimated to have 94% power to detect a 70 sec difference in EET between either of the UMEC/VI doses and placebo at the two-sided 5% significance level, assuming a standard deviation of 160 seconds and a correlation of 0.5 between measurements on the same subject. This sample size was also estimated to provide 92% power to detect a 100 mL difference in trough FEV1 between either dose of UMEC/VI and placebo at the two-sided 5% significance level, assuming a standard deviation of 168 mL.

The Applicant anticipated a 30% withdrawal rate; as a result, it was estimated that 312 randomized patients were needed in order to obtain the desired number of evaluable patients.

Analysis Population:
The primary population for all data analyses was specified to be the ITT Population, defined as all patients randomized to treatment who received at least one dose of randomized trial medication in the treatment period; patients were to be included in an analysis of a particular outcome if they provided at least one on-treatment assessment of that outcome.

Primary Efficacy Analysis:
The analysis of the each of the two primary endpoints, 3-hour post EET at Week 12 and trough FEV1 at Week 12, was prespecified to be a mixed model repeated measures (MMRM) analysis, including data recorded at each of Days 2, Week 6, and Week 12.

Multiplicity:
In order to account for multiplicity, the protocol specified a step-down testing procedure, using the following hierarchy:

- 3 hour post-dose EET for UMEC/VI 125 mcg/25 mcg vs. placebo
- Trough FEV1 for UMEC/VI 125 mcg/25 mcg vs. placebo
- 3 hour post-dose EET for UMEC/VI 62.5 mcg/25 mcg vs. placebo
- Trough FEV1 for UMEC/VI 62.5 mcg/25 mcg vs. placebo

Interim Analysis:
No interim analysis was planned.

Protocol Amendments
The original protocol was submitted on January 17, 2011. One protocol amendment was submitted on June 22, 2011, and is summarized below. The changes provided by this amendment are reflected in the protocol description above.

Protocol Amendment #1:
This protocol amendment provided for the use of short-acting anticholinergics during the run-in and washout periods, as well as clarified the timing of spirometry testing and the ISWT. In addition, the amendment clarified the trial's permitted medications as well as the 12-lead ECG exclusion and withdrawal criteria. The protocol amendment for DB2114418 also omitted the inhaler use and ease of use assessment for patients in Canada.

5 Review of Efficacy

Efficacy Summary

Evidence of efficacy comes from the core Phase 3 program, which consists of four primary efficacy trials and two exercise endurance trials. The four primary efficacy trials include two placebo-controlled trials (DB2113361 and DB2113373) and two active-comparator trials (DB113360 and DB2113374). The placebo-controlled trials were replicate in design and each compared UMEC/VI (125 mcg/25 mcg in Trial DB2113361 and 62.5 mcg/25 mcg in Trial DB2113373) to placebo and to the UMEC (125 mcg in Trial DB2113361 and 62.5 mcg in Trial DB2113373) and VI monotherapies. The active-controlled trials were also replicate in design and each compared both doses of UMEC/VI to tiotropium; in addition, Trial DB2113360 included VI as a comparator, while Trial DB2113374 included UMEC 125 mcg. These four trials included patients with moderate to very severe COPD (GOLD stages II-IV), and the duration of the double-blind treatment period was 24 weeks. The two exercise endurance trials were replicate in design and each evaluated both doses of UMEC/VI, both doses of UMEC, VI, and placebo. In contrast to the primary efficacy trials, the duration of double-blind treatment period in the exercise endurance trials was 12 weeks. The primary efficacy endpoint was trough FEV1 on treatment Day 169 (Week 24) for the four primary efficacy trials; trough FEV1 on treatment Day 85 (Week 12) was pre-specified as a co-primary endpoint in the exercise endurance trials.

Results for the comparison of the primary endpoint between UMEC/VI and placebo in the primary efficacy trials are statistically significant for both doses of the fixed combination product. While only a single placebo comparison is provided for each of the two UMEC/VI doses in the primary efficacy trials, the exercise endurance trials provide additional support. Overall, then, the clinical development program provides replicate, statistically significant results for the primary endpoint for the comparison between both doses of the fixed combination product and placebo. Replicate, statistically significant results for the comparisons between the monotherapy components and placebo are also observed. As UMEC is an NME, the replicate, statistically significant results for the comparison between the UMEC monotherapy and placebo are a critical element of the UMEC/VI development program. The effect of VI compared to placebo has been previously established by the development program for fluticasone furoate and vilanterol inhalation power (NDA 204-275).

Comparable results for the 62.5 mcg/25 mcg and 125 mcg/25 mcg doses of UMEC/VI were observed in trials that included a head to head comparison; the totality of the phase 3 data do not suggest a clear efficacy advantage for doses higher than UMEC/VI 62.5 mcg/25 mcg. Focusing on the UMEC/VI 62.5 mcg/25 mcg dose, which is the dose proposed for approval, the magnitude of the treatment effect compared to placebo ranges from 167 mL to 243 mL, which represents an outcome that is likely to be clinically meaningful. In addition, the placebo- and active-controlled trials provide

evidence of persistence of efficacy for up to 6 months. With regard to the contribution of each of the components to the trough FEV1 effect of the combination, there is replicate, statistically significant evidence of the contribution of UMEC for both doses of the fixed combination, and adequate support for the contribution of VI to UMEC/VI 62.5 mcg/25 mcg.

These results were robust to analyses conducted for various subgroups based on demographic factors (age, gender, race, geography) and on disease and other characteristics (COPD severity, concomitant ICS use, bronchodilator reversibility, and smoking status).

Results for secondary and other endpoints, including weighted mean FEV1 over 0 to 6 hours post-dose at Week 24, trough FEV1 at additional time points, serial FEV1, and peak FEV1, were supportive of the primary analysis. The clinical development program does not, however, provide adequate data to support a claim for the reduction of rescue medication use or improvement in health-related quality of life (based on the SGRQ). In addition, the development program included an evaluation of shortness of breath with activity utilizing a novel patient-reported outcome, the Shortness of Breath with Daily Activities (SOBDA) questionnaire. The SOBDA was developed by the Applicant for use in this development program, and has not been previously used in a regulatory context to support a product claim. Concerns about the instrument's content validity limit its use to exploratory analyses only.

5.1 Indication

The Applicant proposes that UMEC/VI 62.5 mcg/25 mcg is indicated 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 wording of this indication is consistent with other bronchodilators approved for use in COPD.

5.1.1 Methods

Refer to Section 5.3 for a discussion of the general design of the primary efficacy trials (DB2113361, DB2113373, DB2113360, and DB2113374).

5.1.2 Demographics

Demographic and baseline characteristics for the pooled ITT population from the primary efficacy trials (DB2113361, DB2113373, DB2113360, and DB2113374) are provided in Table 18.

Table 18. Demographic and selected baseline characteristics for pooled ITT population, primary efficacy trials

	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
Age (years), n	555	837	826	418	629	1030	418
Mean	62.2	63.6	63.4	64.0	63.6	62.9	64.1
SD	8.79	8.67	8.40	9.16	8.45	8.73	8.87
Min, Max	40,86	40,86	40,84	40,93	40,86	40,88	41,88
Sex, n	555	837	826	418	629	1030	418
Male, n (%)	370 (67)	591 (71)	558 (68)	298 (71)	418 (66)	690 (67)	291 (70)
Race*, n	555	837	826	418	629	1030	418
White, n (%)	475 (86)	690 (82)	694 (84)	354 (85)	533 (85)	899 (87)	336 (80)
African America/ African heritage, n (%)	18 (3)	29 (3)	21 (3)	14 (3)	10 (2)	19 (2)	14 (3)
Asian, n (%)	49 (9)	73 (9)	77 (9)	35 (8)	77 (12)	76 (7)	38 (9)
American Indian or Alaska native, n (%)	1 (<1)	16 (2)	22 (3)	3 (<1)	0	24 (2)	19 (5)
Native Hawaiian or other Pacific Islander, n (%)	0	2 (<1)	0	0	0	0	0
Ethnicity, n	555	837	826	418	629	1030	418
Hispanic/Latino, n (%)	26 (5)	97 (12)	62 (8)	37 (9)	42 (7)	57 (6)	61 (15)
Not Hispanic/Latino, n (%)	529 (95)	740 (88)	764 (92)	381 (91)	587 (93)	973 (94)	357 (85)
Height (cm), n	555	837	826	418	629	1030	418
Mean	168.5	169.0	169.5	168.7	169.1	169.1	168.7
SD	9.12	9.73	9.17	9.34	8.82	8.94	9.02
Min, Max	139,190	144,198	138,200	138,200	142,198	142,196	146,192
Weight (kg), n	555	837	825	418	629	1029	418
Mean	76.20	77.75	76.47	75.62	75.91	77.47	76.95
SD	19.386	19.283	17.858	18.643	18.754	18.923	19.104
Min, Max	34.0,170.0	34.3, 160.9	36.0, 170.0	36.2, 153.1	33.8, 160.1	37.0, 146.1	40.7, 157.3
BMI (kg/m^2), n	555	837	825	418	629	1029	418
Mean	26.70	27.12	26.48	26.46	26.42	26.99	26.89
SD	6.003	5.994	5.291	5.595	5.791	5.917	5.696
Min, Max	12.3, 50.7	14.5, 54.6	13.9, 52.5	14.5, 47.1	14.4, 56.7	13.3, 48.3	15.1, 53.2
Smoking status at Screening, n	555	837	826	418	629	1030	418
Current smoker, n (%)	293 (53)	390 (47)	415 (50)	207 (50)	314 (50)	511 (50)	196 (47)
Former smoker, n (%)	262 (47)	447 (53)	411 (50)	211 (50)	315 (50)	519 (50)	222 (53)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 98-99 (Table 32), pg. 104 (Table 35)
*Applicant's table includes additional subcategories for race

Demographic and baseline characteristics were generally well balanced across treatment arms. Patients of African American or African heritage accounted for 3% of the overall ITT population in the primary efficacy trials and 10% of patients at U.S. sites; the prevalence of COPD among non-Hispanic black adults in the United States in 2007-2009 (annual average) was 4.4%.[18] There was a slight imbalance in the percentage of current smokers between the placebo arm (53%) and active treatment arms (47-50%).

[18] Akinbami LJ, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998-2009. NCHS Data Brief. 2011; 63:1-8.

Disease characteristics are presented for the pooled ITT population from the primary efficacy trials in Table 19.

Table 19. COPD disease characteristics for pooled ITT population, primary efficacy trials

	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
GOLD stage, n	554	834	821	417	627	1024	415
I: FEV ≥80% predicted	0	0	0	0	0	0	0
II: 50%≤FEV1<80% predicted	240 (43)	409 (49)	362 (44)	191 (46)	280 (45)	498 (49)	195 (47)
III: 30%≤FEV1<50% predicted	265 (48)	331 (40)	375 (46)	172 (41)	286 (46)	425 (42)	169 (41)
IV: FEV1<30% predicted	49 (9)	94 (11)	84 (10)	54 (13)	61 (10)	101 (10)	51 (12)
ICS use at Screening, n	555	837	826	418	629	1030	418
ICS user, n (%)	275 (50)	408 (49)	389 (47)	219 (52)	317 (50)	485 (47)	208 (50)
ICS non-user, n (%)	280 (50)	429 (51)	437 (53)	199 (48)	312 (50)	545 (53)	210 (50)
Pre-bronchodilator FEV1 (L), n	554	837	824	417	626	1026	413
Mean	1.234	1.256	1.246	1.211	1.243	1.276	1.231
SD	0.4595	0.4996	0.4680	0.4764	0.4800	0.4906	0.4693
Median	1.165	1.180	1.190	1.140	1.160	1.220	1.160
Min, Max	0.38, 2.81	0.30, 3.07	0.24, 3.00	0.31, 2.80	0.35, 3.09	0.34, 3.17	0.36, 2.79
Reversibility to Salbutamol, n	553	834	821	415	625	1022	412
Not reversible, n (%)	385 (70)	586 (70)	549 (67)	294 (71)	418 (67)	697 (68)	306 (74)
Reversible, n (%)	168 (30)	248 (30)	272 (33)	121 (29)	207 (33)	325 (32)	106 (26)
Reversibility to Salbutamol and Ipratropium, n	543	827	819	411	618	1014	410
Not reversible, n (%)	255 (47)	380 (46)	381 (47)	188 (46)	263 (43)	489 (48)	205 (50)
Reversible, n (%)	288 (53)	447 (54)	438 (53)	223 (54)	355 (57)	525 (52)	205 (50)
COPD Type*, n	552	836	825	418	625	1029	417
Chronic bronchitis, n (%)	381 (69)	561 (67)	550 (67)	274 (66)	386 (62)	678 (66)	266 (64)
Emphysema, n (%)	333 (60)	487 (58)	487 (59)	271 (65)	393 (63)	617 (60)	257 (62)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 107-108 (Table 38), pg. 111 (Table 39), pg. 103 (Table 34)
*Patients could select "chronic bronchitis," "emphysema," or both

COPD disease characteristics were generally well balanced across treatment arms. The numbers of patients with Gold Stage II and Stage III disease were approximately equivalent and together accounted for about 90% of patients; the balance of the population was identified as having Stage IV disease. ICS use at screening was evenly split across the patient population. Pre-bronchodilator FEV1 was balanced across treatment groups (1.2-1.3 L). Approximately one-third of the patient population demonstrated reversibility to salbutamol, and approximately one-half demonstrated reversibility to both salbutamol and ipratropium. Both chronic bronchitis and emphysema were represented in a substantial proportion of the population (58% or more); the percent of patients reporting each subtype was balanced across treatment arms.

Past and current cormorbid conditions are presented for the pooled ITT population from the primary efficacy trials in Table 20.

Table 20. Comorbid conditions for pooled ITT population, 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=1034	TIO N=423
Common Current Medical Conditions							
Any condition	443 (80)	683 (81)	657 (79)	328 (78)	498 (79)	840 (81)	341 (81)
Cardiovascular risk factors	324 (58)	525 (62)	484 (58)	242 (58)	347 (55)	632 (61)	251 (59)
Musculoskeletal and connective tissue disorders	176 (32)	288 (34)	269 (32)	134 (32)	215 (34)	347 (34)	146 (35)
Cardiac disorders	100 (18)	189 (22)	165 (20)	100 (24)	119 (19)	216 (21)	89 (21)
Psychiatric disorders	79 (14)	127 (15)	118 (14)	57 (14)	93 (15)	159 (15)	57 (13)
Nervous system disorders	72 (13)	119 (14)	87 (10)	55 (13)	85 (14)	138 (13)	50 (12)
Endocrine disorders	61 (11)	126 (15)	95 (11)	45 (11)	75 (12)	114 (11)	57 (13)
Metabolism and nutrition disorders	60 (11)	104 (12)	74 (9)	51 (12)	65 (10)	117 (11)	54 (13)
Respiratory, thoracic, and mediastinal disorders	67 (12)	113 (13)	78 (9)	44 (11)	56 (9)	113 (11)	51 (12)
Vascular disorders	63 (11)	95 (11)	86 (10)	52 (12)	71 (11)	114 (11)	54 (13)
Skin and subcutaneous tissue disorders	65 (12)	74 (9)	70 (8)	42 (10)	40 (6)	96 (9)	36 (9)
Common Past Medical Conditions							
Any condition	260 (47)	407 (48)	430 (52)	211 (50)	362 (58)	514 (50)	223 (53)
Respiratory, thoracic, and mediastinal disorders	67 (12)	96 (11)	108 (13)	50 (12)	96 (15)	129 (12)	59 (14)
Cardiovascular risk factors	57 (10)	93 (11)	106 (13)	44 (11)	83 (13)	128 (12)	61 (14)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	48 (9)	70 (8)	78 (9)	43 (10)	61 (10)	83 (8)	47 (11)
Reproductive system and breast disorders	45 (8)	83 (10)	70 (8)	32 (8)	57 (9)	83 (8)	40 (9)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 113 (Table 54), pg. 114 (Table 55)
Note: "Common" condit**ions are defined as those reported in ≥ 10% of patients in any treatment group**
Note: The values for N listed in this table differ from those listed in Tables 18 and 19, which exclude patients from Investigator 040688 (Center 085663) in Trial DB2113360. This is further clarified in the footnotes and text associated with Table 21.

Particular attention to the distribution of cardiovascular risk factors and cardiac disorders is warranted, as cardiovascular adverse events are discussed in detail in Section 6.3.5. A small imbalance between UMEC/VI 62.5 mcg/25 mcg and placebo is noted for current cardiovascular risk factors and cardiac disorders. A small imbalance between UMEC/VI 125 mcg/25 mcg and placebo is noted for past cardiovascular risk factors.

5.1.3 Subject Disposition

The disposition of the patients participating in the four primary efficacy trials (DB2113361, DB2113373, DB2113360, and DB2113374) is provided in Table 21.

Table 21. Subject Disposition for the Primary Efficacy Trials

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Randomized	Number of Patients						
All Primary Efficacy Trials	557	839	830	421	631	1030	419
DB2113361	277	0	403	0	409	404	0
DB2113373	280	414	0	421	0	421	0
DB2113360*	0	207	210	0	0	205	204
DB2113374	0	218	217	0	222	0	215
Intent-To-Treat	Number of Patients (% of Randomized)						
All Primary Efficacy Trials	555 (>99)	837 (>99)	826 (>99)	418 (>99)	629 (>99)	1030 (100)	418 (>99)
DB2113361	275 (>99)	--	403 (100)	--	407 (>99)	404 (100)	--
DB2113373	280 (100)	413 (>99)	--	418 (>99)	--	421 (100)	--
DB2113360#	--	207 (100)	208 (>99)	--	--	205 (100)	203 (>99)
DB2113374	--	217 (>99)	215 (>99)	--	222 (100)	--	215 (100)
Disposition	Number of Patients (% of ITT)						
Completion Status							
Completed@	387 (70)	672 (80)	659 (80)	324 (78)	477 (76)	779 (76)	349 (83)
Withdrawn	168 (30)	165 (20)	167 (20)	94 (22)	152 (24)	251 (24)	69 (17)
Primary Reason/Subreason for Withdrawal%							
Adverse event	26 (5)	53 (6)	47 (6)	34 (8)	41 (7)	59 (6)	20 (5)
Lack of Efficacy	81 (15)	41 (5)	38 (5)	20 (5)	60 (10)	85 (8)	19 (5)
Exacerbation	60 (11)	35 (4)	33 (4)	18 (4)	46 (7)	70 (7)	15 (4)
Protocol deviation	8 (1)	11 (1)	13 (2)	7 (2)	4 (<1)	22 (2)	1 (<1)
Met protocol-defined stopping criteria	25 (5)	26 (3)	34 (4)	13 (3)	22 (3)	40 (4)	11 (3)
ECG abnormality	16 (3)	23 (3)	32 (4)	7 (2)	14 (2)	30 (3)	11 (3)
Lab abnormality	0	0	0	2 (<1)	0	2 (<1)	0
Holter abnormality	9 (2)	3 (<1)	2 (<1)	4 (<1)	8 (1)	9 (<1)	0
Lost to follow-up	1 (<1)	3 (<1)	4 (<1)	0	2 (<1)	5 (<1)	3 (<1)
Withdrew consent	27 (5)	31 (4)	31 (4)	20 (5)	23 (4)	40 (4)	15 (4)
Patient relocated	3 (<1)	3 (<1)	5 (<1)	2 (<1)	1 (<1)	6 (<1)	0
Frequency of visits	5 (<1)	3 (<1)	6 (<1)	1 (<1)	0	7 (<1)	2 (<1)
Burden of procedures	4 (<1)	4 (<1)	4 (<1)	4 (<1)	4 (<1)	4 (<1)	5 (1)
Other	8 (1)	19 (2)	14 (2)	10 (2)	15 (2)	16 (2)	8 (2)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 93 (Table 28), pg. 95 (Table 30)
* While not explicitly stated in the Applicant's submission, the number listed for the DB2113360 Randomization population appears to exclude patients (n=20) from Investigator 040688 (Center 085663). These patients are also excluded from the overall pooled Randomization population.
#The Applicant's submission indicates that the ITT population for Trial DB2113360 excludes patients (n=20) from Investigator 040688 (Center 085663).
@A patient was considered to have completed the trial if they completed the last clinic visit (Visit 9) and did not withdraw at that visit
%Patients recorded only a single primary reason for withdrawal; patients were not required to indicate a sub-reason, and were allowed to mark more than one sub-reason, if applicable

ITT Population

The ITT population was defined as all patients randomized to treatment who received at least 1 dose of trial medication in the treatment period, with the exception of the ITT for

Trial DB2113360, which excluded twenty patients from a single site (Investigator 040688, Center 085663) for which significant deviations from GCP were identified.

Withdrawals
The percentage of patients who withdrew from the trials was higher for the placebo arm (30%) compared to the active treatment arms (17-24%). The most commonly reported primary reason for withdrawal was "lack of efficacy," which was also higher for the placebo arm (15%) compared to the active treatment arms (5-10%), as was the most commonly reported sub-reason "exacerbation" (11% versus 4-7% for the placebo and active treatment arms, respectively). The percentage of patients reporting "adverse event" as the primary reason for withdrawal is somewhat higher for the UMEC 62.5 mcg (8%) and 125 mcg (7%) treatment arms compared to the other arms (5-6%). Withdrawal due to Holter abnormalities meeting protocol-defined stopping criteria was more commonly reported for the placebo arm (2%) compared to the active treatment arms (<1-1%). The other primary reasons and sub-reasons reported for withdrawal were generally balanced across treatment arms.

5.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for each of the four primary efficacy trials was pre-dose trough FEV1 on treatment Day 169 (Week 24). Spirometry is an appropriate choice of endpoint for a purported bronchodilator. The UMEC/VI clinical development program specified trough FEV1 as the primary endpoint, which is in contrast to the Agency's recommendation to use post-dose FEV1 as described in the Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment,"[19] but is consistent with the clinical development programs of several other drug products approved for use in COPD. While not specified as the primary endpoint, the UMEC/VI program included weighted mean FEV1 over 0 to 6 hours post-dose as a secondary endpoint, as well as the peak FEV1 and serial post-dose FEV1 as additional endpoints. These spirometric measurements are important for providing a more complete assessment of UMEC/VI's bronchodilatory action.

Results for the analysis of the primary efficacy endpoint are provided in Table 22 for the placebo-controlled trials (DB2113361 and DB2113373), and in Table 23 for the active-controlled trials (DB2113360 and DB2113374). In addition, results for trough FEV1 from the two exercise endurance trials (DB2114417 and DB2114418), which was pre-specified as a co-primary endpoint, are provided in Table 24. It should be noted that the primary efficacy trials evaluated trough FEV1 at the end of a 24 week treatment period,

[19] Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," November 2007. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf. Accessed August 5, 2013.

whereas the exercise endurance trials evaluated FEV1 at the end of 12 weeks of treatment.

Table 22. Trough FEV1 (L) at Day 169, Placebo-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2113361												
UMEC 125/25	403	1.484 (0.012)	0.207 (0.012)	0.238	(0.200, 0.276)	<0.001	0.079	(0.046, 0.112)	<0.001	0.114	(0.081, 0.148)	<0.001
UMEC 125	407	1.405 (0.012)	0.129 (0.012)	0.160	(0.122, 0.198)	<0.001						
VI 25	404	1.370 (0.012)	0.093 (0.012)	0.124	(0.086, 0.162)	<0.001						
Placebo	275	1.245 (0.015)	-0.031 (0.015)									
DB2113373												
UMEC 62.5/25	413	1.406 (0.013)	0.171 (0.013)	0.167	(0.128, 0.207)	<0.001	0.052	(0.017, 0.087)	0.004	0.095	(0.060, 0.130)	<0.001
UMEC 62.5	418	1.354 (0.013)	0.119 (0.013)	0.115	(0.076, 0.155)	<0.001						
VI	421	1.311 (0.013)	0.076 (0.013)	0.072	(0.032, 0.112)	<0.001						
Placebo	280	1.239 (0.016)	0.004 (0.016)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 90 (Table 25), pg. 863 (Table 6.05); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 88 (Table 25), pg. 793 (Table 6.05)
Key: BL=baseline
Note: N= ITT Population

Table 23. Trough FEV1 (L) at Day 169, Active-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2113360												
UMEC 125/25	208	1.519 (0.019)	0.209 (0.019)	0.088	(0.036, 0.140)	<0.001				0.088	(0.036, 0.140)	<0.001
UMEC 62.5/25	207	1.521 (0.018)	0.211 (0.018)	0.090	(0.039, 0.141)	<0.001				0.090	(0.039, 0.142)	<0.001
VI 25	205	1.431 (0.019)	0.121 (0.019)									
TIO	203	1.431 (0.019)	0.121 (0.019)									
DB2113374												
UMEC 125/25	215	1.369 (0.018)	0.223 (0.018)	0.074	(0.025, 0.123)	0.003	0.037	(-0.012, 0.087)	0.142			
UMEC 62.5/25	217	1.355 (0.018)	0.208 (0.018)	0.060	(0.010, 0.109)	0.018	0.022	(-0.027, 0.072)	0.377			
UMEC 125	222	1.332	0.186									

		(0.018)	(0.018)									
TIO	215	1.295 (0.018)	0.149 (0.018)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 83 (Table 27), pg. 580 (Table 6.05); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 80 (Table 27), pg. 674 (Table 6.05)
Key: BL=baseline
Note: N= ITT population (excluding data from Investigator 040688 in Trial DB2113360)

Table 24. Trough FEV1 (L) at Week 12, Exercise Endurance Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC*			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2114417												
UMEC 125/25	144	1.573 (0.016)	0.136 (0.016)	0.169	0.129, 0.209	<0.001	0.029	-0.028, 0.086	0.320	0.070	0.019, 0.120	0.007
UMEC 62.5/25	152	1.615 (0.016)	0.178 (0.016)	0.211	0.172, 0.249	<0.001	0.124	0.067, 0.181	<0.001	0.111	0.062, 0.161	<0.001
UMEC 125	50	1.544 (0.026)	0.108 (0.026)	0.140	0.084, 0.196	<0.001						
UMEC 62.5	49	1.491 (0.026)	0.054 (0.026)	0.087	0.030, 0.143	0.003						
VI 25	76	1.503 (0.022)	0.067 (0.022)	0.099	0.050, 0.148	<0.001						
Placebo	170	1.404 (0.015)	-0.032 (0.015)									
DB2114418												
UMEC 125/25	128	1.538 (0.016)	0.218 (0.016)	0.261	0.220, 0.303	<0.001	0.006	-0.055, 0.067	0.849	0.150	0.098, 0.201	<0.001
UMEC 62.5/25	130	1.520 (0.016)	0.200 (0.016)	0.243	0.202, 0.284	<0.001	0.099	0.041, 0.157	<0.001	0.132	0.081, 0.183	<0.001
UMEC 125	41	1.532 (0.029)	0.212 (0.029)	0.255	0.193, 0.318	<0.001						
UMEC 62.5	40	1.421 (0.027)	0.101 (0.027)	0.144	0.086, 0.203	<0.001						
VI 25	64	1.388 (0.022)	0.069 (0.022)	0.112	0.061, 0.163	<0.001						
Placebo	151	1.277 (0.016)	-0.043 (0.016)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2114417, Study Report Body), pg. 656 (Table 6.18); Section 5.3.5.1 (DB2114418, Study Report Body), pg. 545 (Table 6.18)
Key: BL=baseline
*The comparisons are for comparable UMEC doses; i.e. UMEC/VI 125 mcg/25mcg to UMEC 125 mcg, and UMEC/VI 62.5 mcg/25 mcg to UMEC 62.5 mcg
Note: N= ITT population

Comparison to Placebo

Results for the comparison between UMEC/VI and placebo in the primary efficacy trials are statistically significant for both doses of the fixed combination product, with an effect size of 238 mL for the higher 125 mcg/25 mcg dose, and an effect size of 167 mL for the lower 62.5 mcg/25 mcg dose. In addition, results for the comparisons between the monotherapies and placebo in the primary efficacy trials are all statistically significant.

It is noted that only a single placebo comparison is provided for each of the two UMEC/VI doses in the primary efficacy trials. The results for the lower dose may be construed as supporting the higher dose, as it is expected that efficacy would only be greater with an increase in dose, but reverse is not necessarily true. The exercise endurance trials, while different in design and shorter in duration, provide additional support as they also include a placebo arm (it should be noted that the results from Trial DB2114417 [see Section 6.1.10] provide descriptive evidence, due to the nature of its testing hierarchy). The effect size for the higher dose of the combination in the exercise endurance trials is quite variable (169 mL to 261 mL) but includes the point estimate observed in the primary efficacy trials (238 mL), while the effect size for the lower dose of the combination in the exercise endurance trials (211 mL to 243 mL) exceeds the point estimate observed in the primary efficacy trials (167 mL). Taken together, these trials provide replicate, statistically significant evidence of a treatment effect for both doses of the UMEC/VI combination versus placebo. Results for secondary and additional endpoints are supportive of the findings for the primary endpoint, and are discussed below.

Contribution of UMEC

The contribution of the umeclidinium monocomponent to the combination product was evaluated by comparing UMEC/VI to VI. Taken together, the primary efficacy trials provide replicate support for a statistically significant treatment effect favoring the combination over the vilanterol monotherapy. This is true for both doses of the combination product. The magnitude of the treatment effect was 88 mL to 114 mL for the UMEC/VI 125 mcg/25 to VI comparison, and 90 mL to 95 mL for the UMEC/VI 62.5 mcg/25 mcg to VI comparison. In addition, the results for the analyses of secondary and additional endpoints discussed below add further support for the contribution of UMEC to the combination.

Contribution of VI

The contribution of the vilanterol monocomponent to the combination product was evaluated by comparing UMEC/VI to UMEC. The clinical development program provides adequate support for the contribution of VI to the combination product for the 62.5 mcg/25 mcg dose. The contribution of VI to the 62.5 mcg/25 mcg combination is demonstrated in one of two the primary efficacy trials (Trial DB2113373) where the lower dose of UMEC/VI is compared to UMEC; additional support is provided in the exercise endurance trials, both of which demonstrated a treatment effect for the comparison of UMEC/VI 62.5 mcg/25 mcg to UMEC 62.5 mcg. While these analyses were not included as part of the multiple testing framework, the nominal p-values are <0.05, and the magnitude of the treatment effect (99 mL to 124 mL) is indicative of clinically meaningful results. In addition, the results for the analyses of secondary and additional endpoints discussed below add further support for the contribution of VI to the combination.

Comparison to Tiotropium

In both of the active controlled trials a statistically significant treatment effect was observed for the comparison of the combination product to tiotropium; this was true for both the 125 mcg/25 mcg and 62.5 mcg/25 mcg doses of the fixed combination. While the statistically significant results are noted, the clinical significance of the treatment effect (74-88 mL for the 125 mcg/25 mcg dose and 60-90 mL for the 62.5 mcg/25 mcg dose) are unclear. Given that the proposed product is a combination of two purported bronchodilators, and includes as one of its components a member of the same pharmacologic class as that for tiotropium, it is expected that the combination would demonstrate a treatment effect over the single-agent active comparator.

Conclusion Regarding the Primary Endpoint

Overall, the clinical development program provides replicate, statistically significant results for the primary endpoint for the comparison between both doses of the fixed combination product and placebo, and for the comparisons between the monotherapy components and placebo. Replicate, statistically significant evidence of the contribution of UMEC is also provided for both doses of the fixed combination, and adequate support is provided for the contribution of VI to UMEC/VI 62.5 mcg/25 mcg. The contribution of both of the monotherapies to the proposed UMEC/VI 62.5 mcg/25 mcg product is further supported by the results for secondary and additional endpoints described below.

Focusing on the UMEC 62.5 mcg/25 mcg dose, which is the dose proposed for approval, the magnitude of the treatment effect compared to placebo ranges from 167 mL to 243 mL, which represents an outcome that is likely to be clinically meaningful.

5.1.5 Analysis of Secondary Endpoints(s)

Weighted mean FEV1 over 0 to 6 hours post-dose at Week 24 was prespecified as a secondary endpoint in the four primary efficacy trials. Results for this secondary endpoint from the placebo-controlled and active-controlled trials are provided in Table 25 and Table 26, respectively.

Table 25. Change in 0 to 6 hours Weighted Mean FEV1 (L) at Day 168, Placebo-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
DB2113361												
UMEC 125/25	403	1.544 (0.012)	0.269 (0.012)	0.287	(0.250, 0.324)	<0.001	0.109	(0.076, 0.141)	<0.001	0.142	(0.109, 0.175)	<0.001
UMEC 125	407	1.435 (0.012)	0.160 (0.012)	0.178	(0.141, 0.216)	<0.001						

VI 25	404	1.402 (0.012)	0.127 (0.012)	0.145	(0.107, 0.182)	<0.001						
Placebo	275	1.257 (0.015)	-0.018 (0.015)									
DB2113373												
UMEC 62.5/25	413	1.479 (0.013)	0.243 (0.013)	0.242	(0.202, 0.282)	<0.001	0.092	(0.056, 0.127)	<0.001	0.120	(0.084, 0.155)	<0.001
UMEC 62.5	418	1.387 (0.013)	1.151 (0.013)	0.150	(0.110, 0.190)	<0.001						
VI	421	1.359 (0.013)	0.123 (0.013)	0.122	(0.082, 0.162)	<0.001						
Placebo	280	1.237 (0.016)	0.001 (0.016)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 107 (Table 32); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 104 (Table 32)
Key: BL=baseline
Note: N=ITT Population

Table 26. Change in 0 to 6 hours Weighted Mean FEV1 (L) at Day 168, Active-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
DB2113360												
UMEC 125/25	208	1.576 (0.019)	0.263 (0.019)	0.083	(0.031, 0.134)	0.002				0.086	(0.033, 0.138)	0.001
UMEC 62.5/25	207	1.567 (0.018)	0.254 (0.018)	0.074	(0.022, 0.125)	0.005				0.077	(0.025, 0.128)	0.004
VI 25	205	1.491 (0.019)	0.178 (0.019)									
TIO	203	1.494 (0.019)	0.181 (0.019)									
DB2113374												
UMEC 125/25	215	1.427 (0.017)	0.282 (0.017)	0.101	(0.055, 0.147)	<0.001	0.076	(0.029, 0.122)	0.001			
UMEC 62.5/25	217	1.422 (0.017)	0.276 (0.017)	0.096	(0.050, 0.142)	<0.001	0.070	(0.024, 0.117)	0.003			
UMEC 125	222	1.351 (0.017)	0.206 (0.017)									
TIO	215	1.326 (0.017)	0.180 (0.017)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg.93 (Table 32); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 90 (Table 32)
Key: BL=baseline
Note: N=ITT population (excluding data from Investigator 040688 in Trial DB2113360)

Results for the comparison between UMEC/VI and placebo in the primary efficacy trials are statistically significant for both doses of the fixed combination product. In addition, results for the comparisons between the monotherapies and placebo in the primary efficacy trials are all statistically significant. As was the case for the primary endpoint, for this secondary endpoint there is only a single placebo comparison provided for each of the two UMEC/VI doses. Unlike the situation for the primary endpoint, for this

secondary endpoint there are replicate statistically significant results to support the contribution of each monocomponent to both doses of the UMEC/VI combination. Overall, these results are supportive of the findings for the primary endpoint.

5.1.6 Other Endpoints

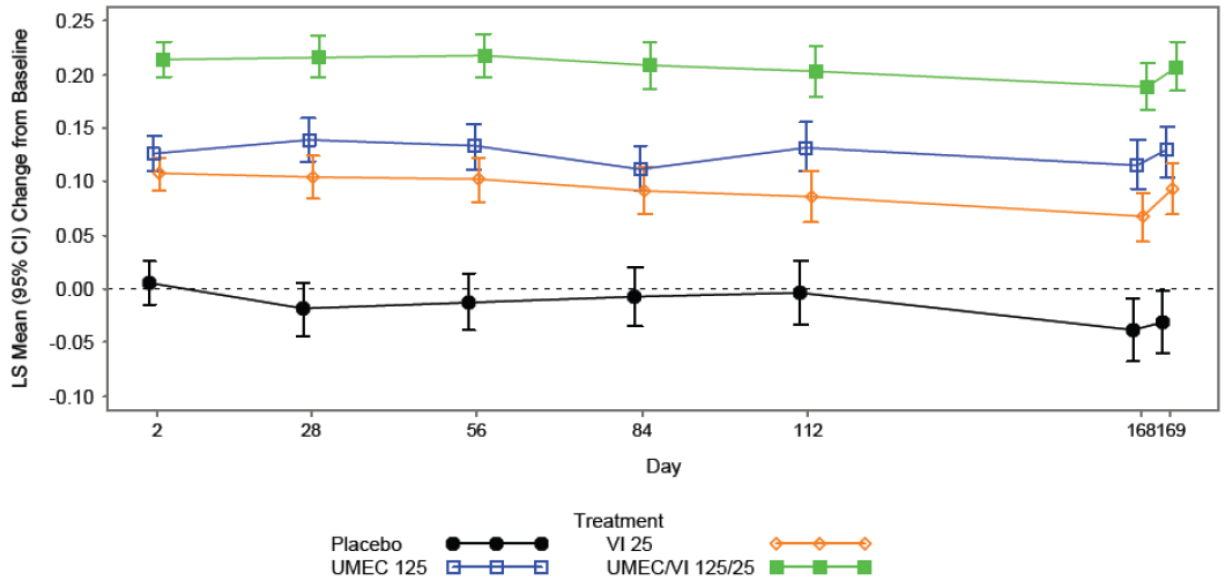
Additional Spirometric Assessments

In addition to the primary endpoint of trough FEV1 and the secondary endpoint of 0 to 6 hours weighted mean FEV1, the primary efficacy trials also included a number of additional spirometric assessments.

Trough FEV1, additional time points

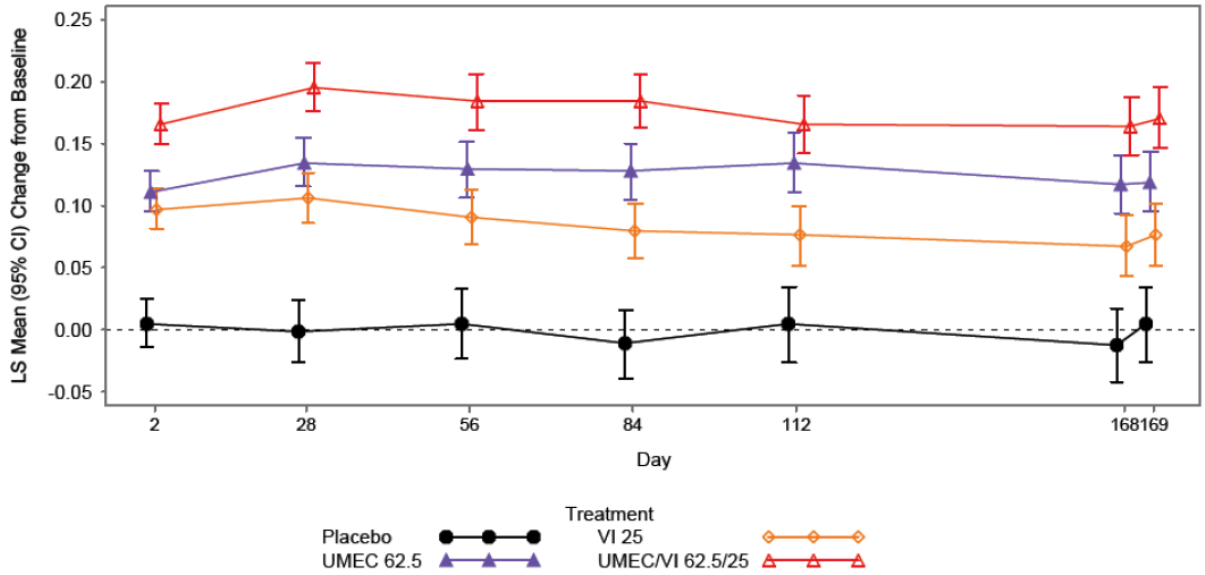
The primary analysis of trough FEV1 was conducted using data at Day 169. In addition, the primary efficacy trials analyzed trough FEV1 for other time points during the 24 week treatment period. Least squares mean change from baseline in trough FEV1 on Days 2, 28, 56, 84, 112, 168, and 169 for Trials DB2113361, DB2113373, DB2113360, and DB2113374 are presented in Figure 12, Figure 13, Figure 14, and Figure 15, respectively.

Figure 12. Least Squares Mean Change from Baseline in Trough FEV1 (L) at selected time points, Trial DB2113361, ITT Population



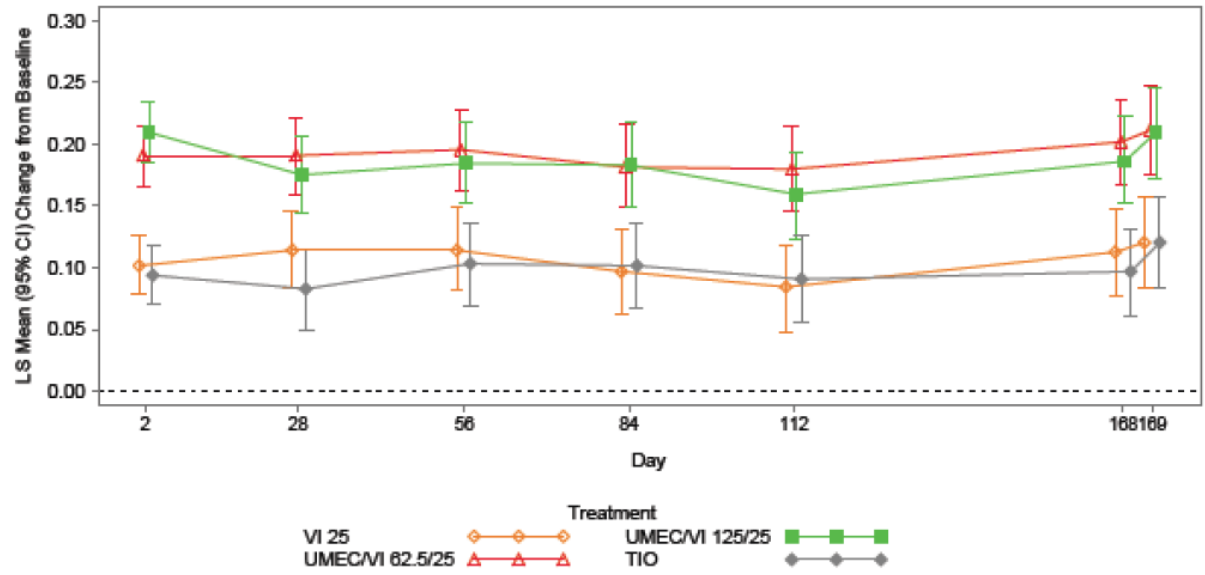
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 96 (Figure 4)

Figure 13. Least Squares Mean Change from Baseline in Trough FEV1 (L) at selected time points, Trial DB2113373, ITT Population



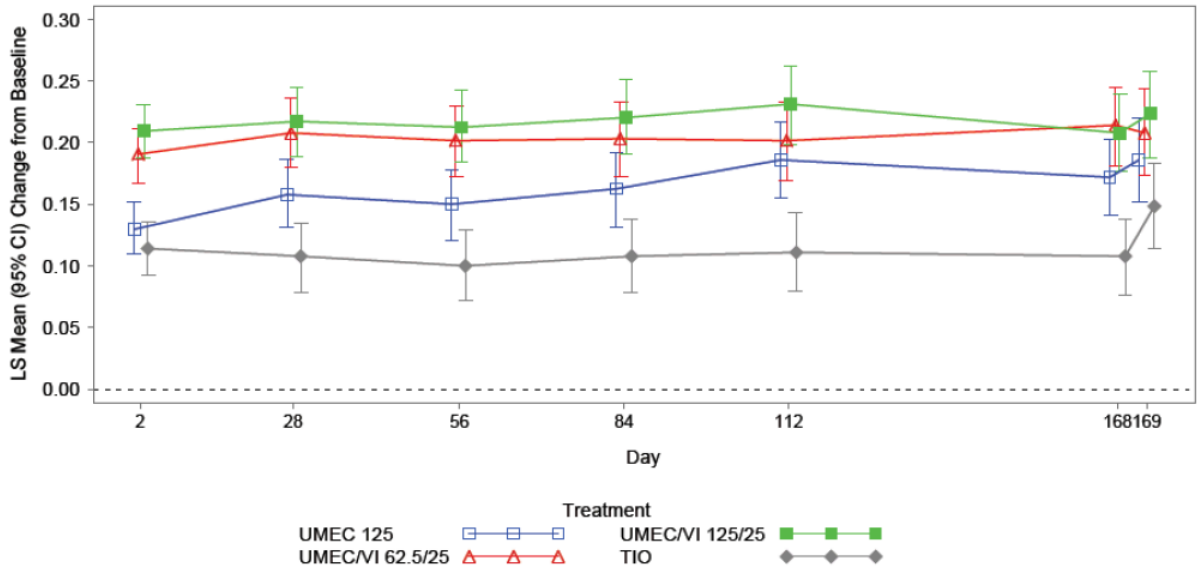
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 93 (Figure 4)

Figure 14. Least Squares Mean Change from Baseline in Trough FEV1 (L) at selected time points, Trial DB2113360, ITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 88 (Figure 4)
Note: Figure is for the ITT population, excluding data from Investigator 040688 in Trial DB2113360

Figure 15. Least Squares Mean Change from Baseline in Trough FEV1 (L) at selected time points, Trial 2113374, ITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113374, Study Report Body), pg. 85 (Figure 4)

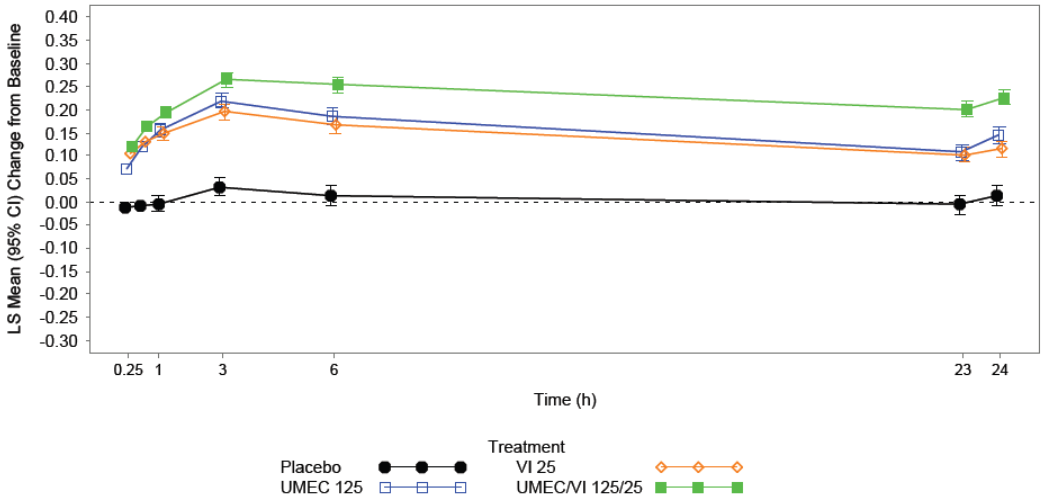
In each of the placebo-controlled trials there is separation between the curves for the combination product and placebo at all time points. In the two active-controlled trials, which each included both UMEC/VI doses, there is a high degree of overlap between the 125 mcg/25 mcg and 62.5 mcg/25 mcg doses through the 24 week treatment period. Overall, these results are supportive of the findings for the primary endpoint.

Serial FEV1, 0 to 6 hours postdose

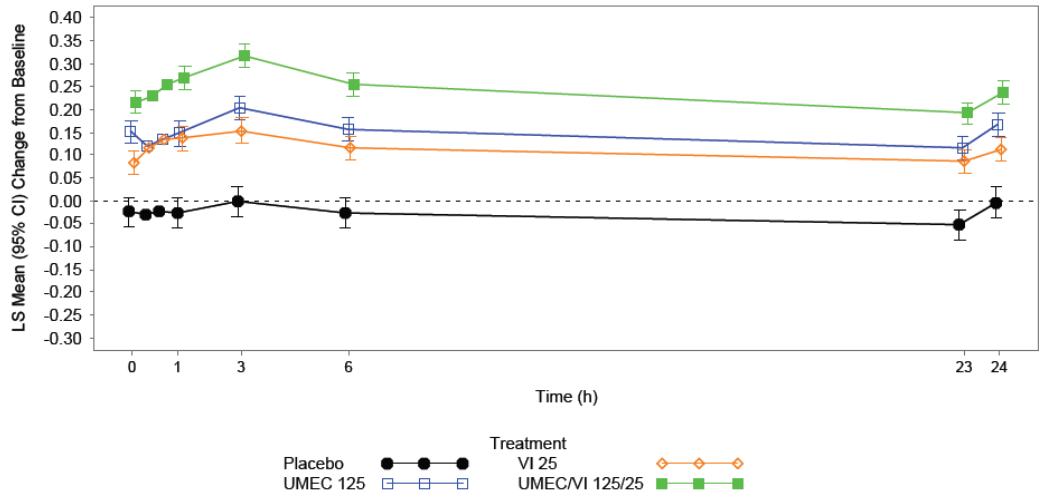
Each of the four primary efficacy trials evaluated serial FEV1 over the six hours immediately following dosing. The results for this parameter at the start of treatment (Day 1) and end of treatment (Day 168) are provided in Figures Figure 16, Figure 17, Figure 18, and Figure 19 for Trials DB2113361, DB2113373, DB2113360, and DB2113374, respectively.

Figure 16. Least Squares Mean Change from Baseline in FEV1 (L), 0-6 hours, 23, and 24 hours on Day 1 and Day 168, Trial DB2113361, ITT Population

A. Day 1



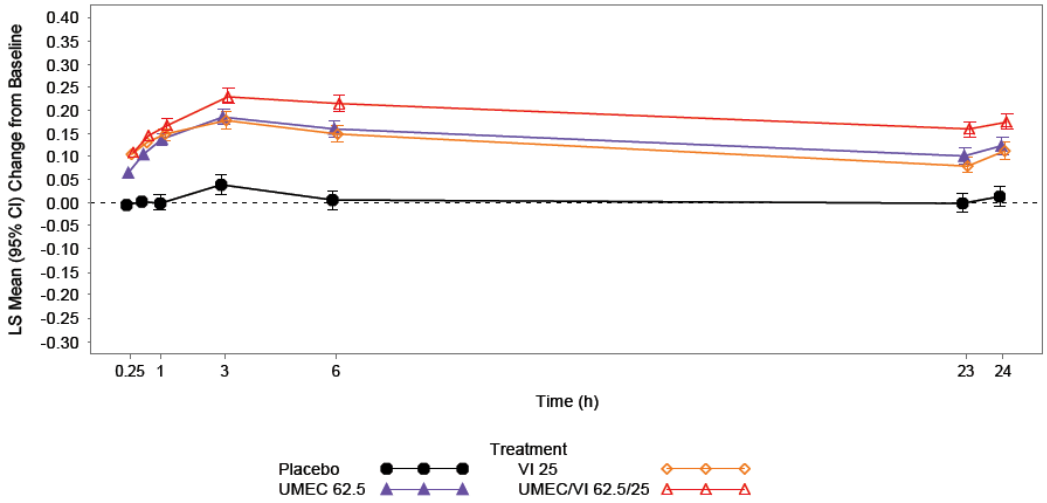
B. Day 168



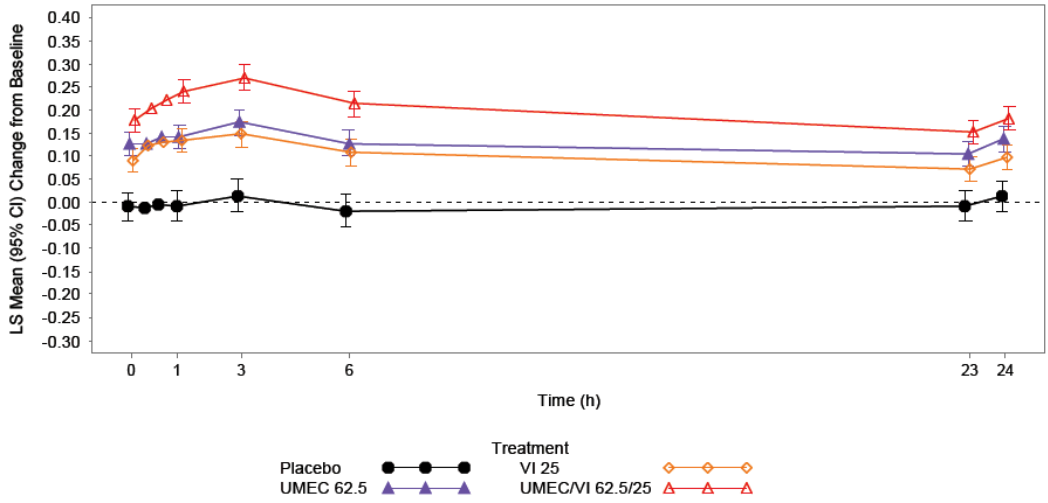
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 111, 113 (Figure 10)

Figure 17. Least Squares Mean Change from Baseline in FEV1 (L), 0-6 hours, 23, and 24 hours on Day 1 and Day 168, Trial DB2113373, ITT Population

A. Day 1



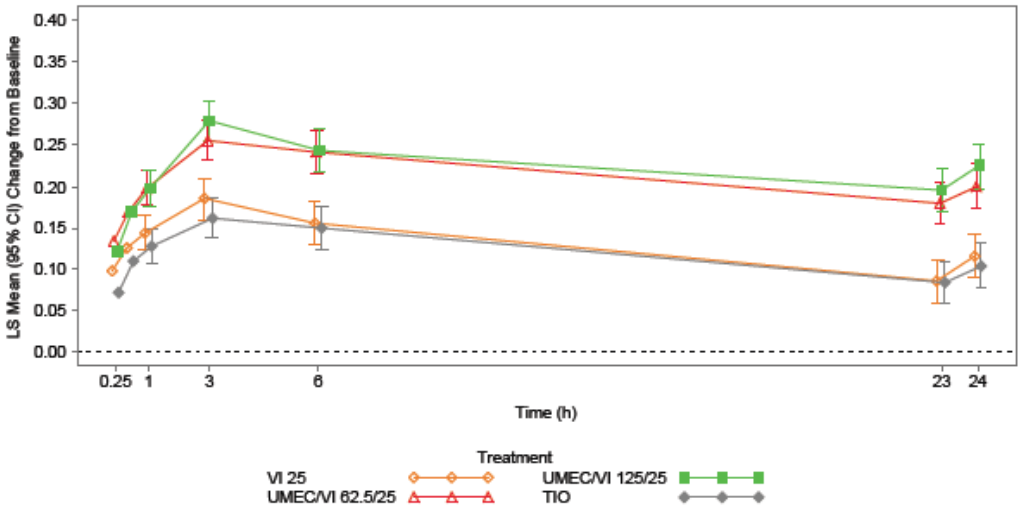
B. Day 168



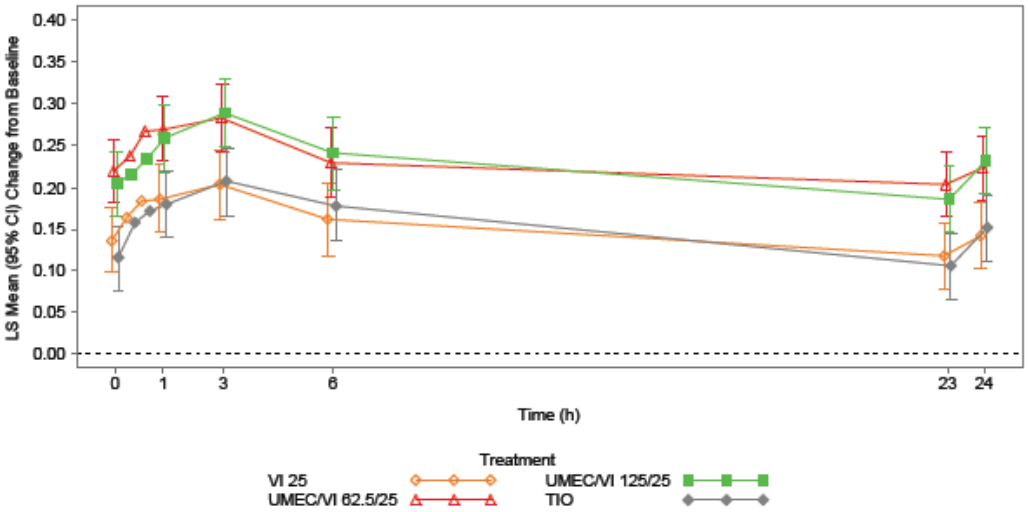
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 107,109 (Figure 10)

Figure 18. Least Squares Mean Change from Baseline in FEV1 (L), 0-6 hours, 23, and 24 hours on Day 1 and Day 168, Trial DB2113360, ITT Population

A. Day 1



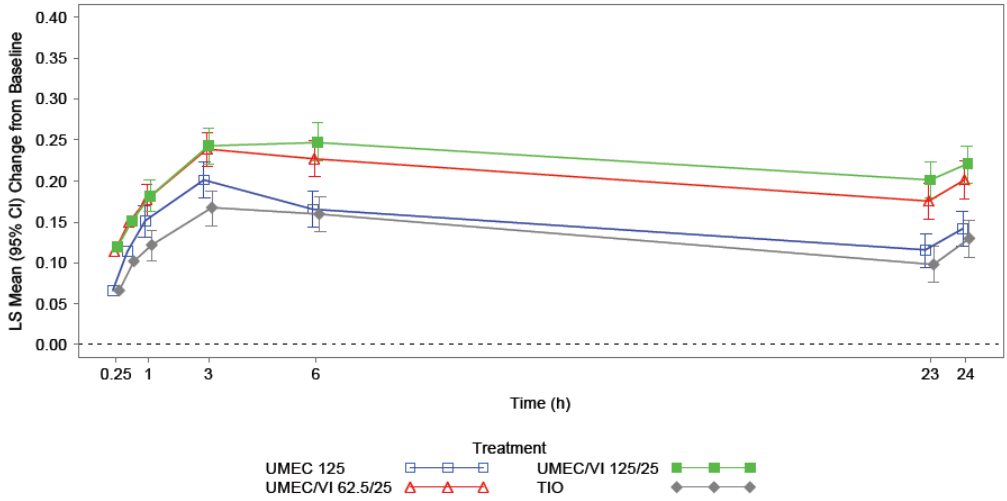
B. Day 168



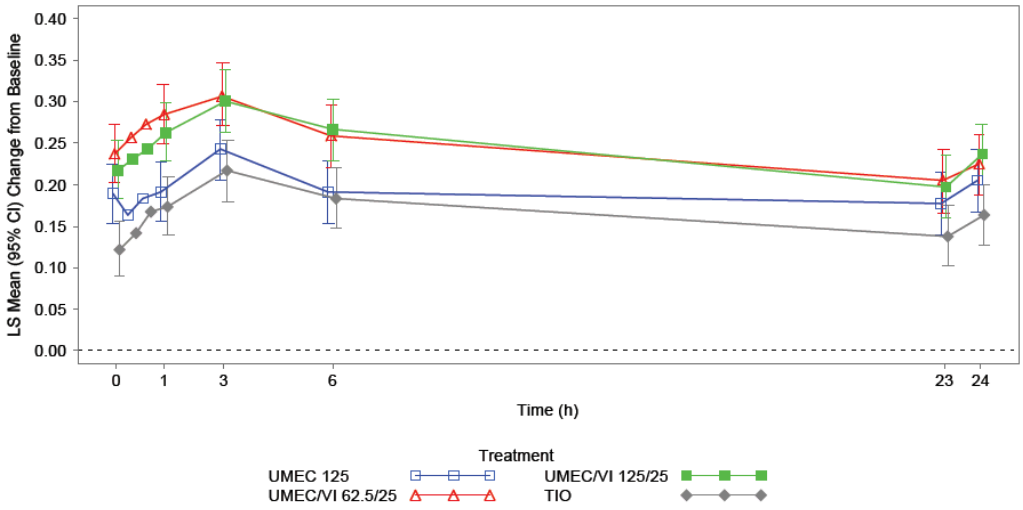
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 102 (Figure 10)
Note: Figure is for the ITT population, excluding data from Investigator 040688 in Trial DB2113360

Figure 19. Least Squares Mean Change from Baseline in FEV1 (L), 0-6 hours, 23, and 24 hours on Day 1 and Day 168, Trial DB2113374, ITT Population

A. Day 1



B. Day 168



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113374, Study Report Body), pg. 99, 100 (Figure 10)

In each of the placebo-controlled trials there is separation between the curves for the combination products and placebo at all time points on both Day 1 and Day 168. There is also a separation between the combination products and monotherapies at most time points at both the start and end of treatment. In the two active-controlled trials, which each included both the 125 mcg/25 mcg and 62.5 mcg/25 mcg doses, there is a high degree of overlap between curves for the two combination products. Separation between the curves of the combination products and the curves for the monotherapies and tiotropium is also seen, although overlap of the 95% confidence intervals is noted,

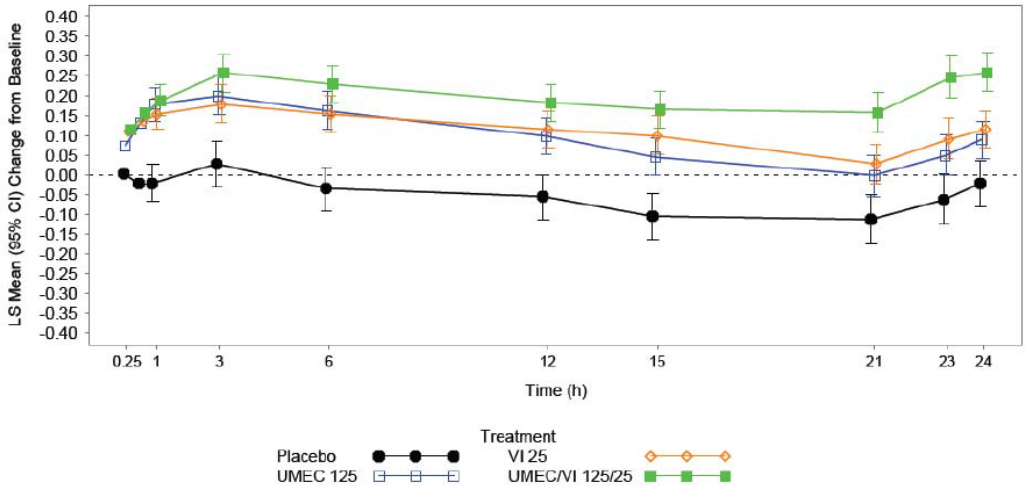
particularly for the Day 168 results. Overall, these results are supportive of the findings for the primary endpoint.

Serial FEV1, 0 to 24 hours postdose (subpopulation)

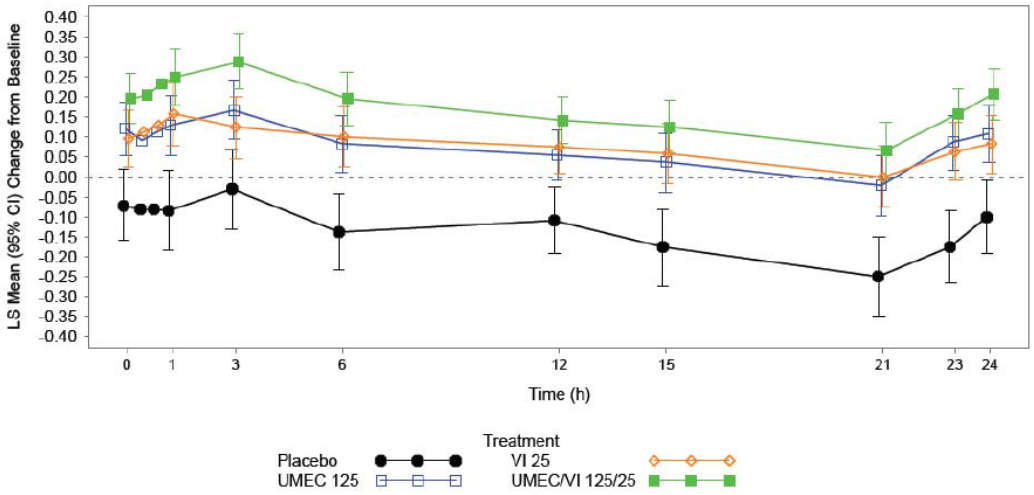
Serial FEV1 over 24 hours postdose was evaluated at selected sites for a subset of patients (approximately 200 from each trial, equivalent to 13% of the ITT population) in the two placebo-controlled trials. The results for this parameter at the start of treatment (Day 1) and end of treatment (Day 168) are provided in Figure 20 and in Figure 21 for Trials DB2113361 and DB211373, respectively.

Figure 20. Least Squares Mean Change from Baseline in FEV1 (L), 0-24 hours on Day 1 and Day 168, Trial DB2113361, Subpopulation

A. Day 1



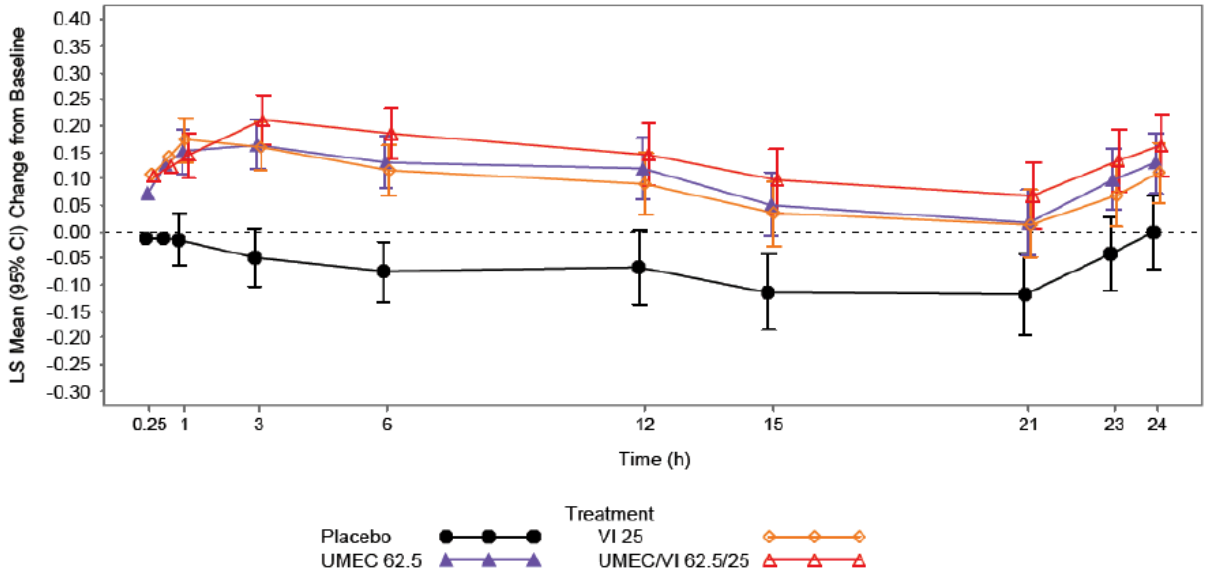
B. Day 168



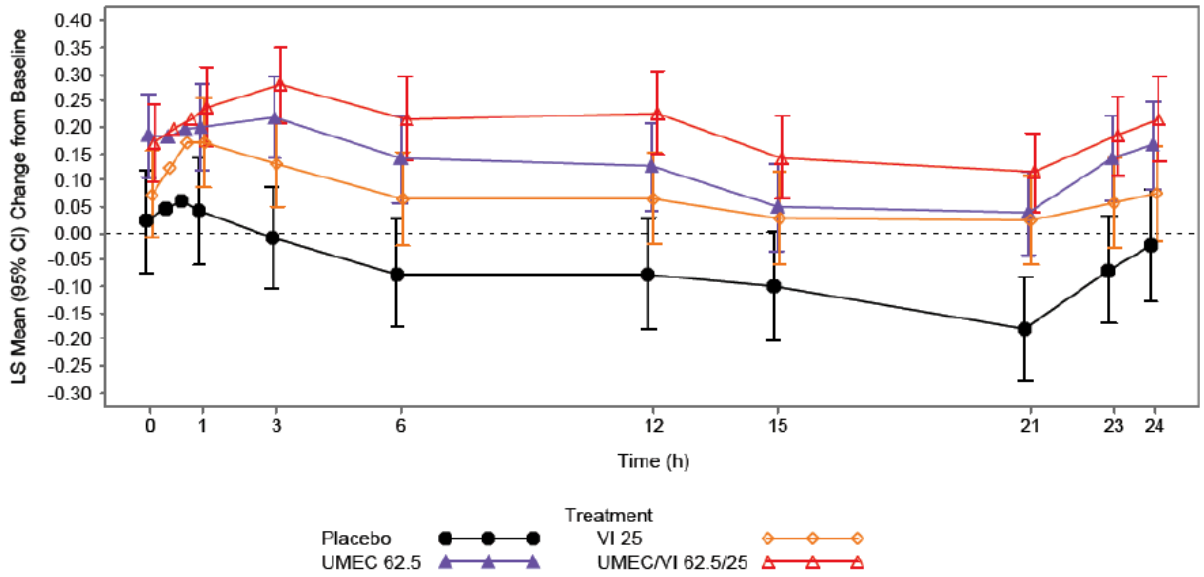
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 130-131 (Figure 15)

Figure 21. Least Squares Mean Change from Baseline in FEV1 (L), 0-24 hours on Day 1 and Day 168, Trial DB2113373, Subpopulation

A. Day 1



B. Day 168



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 125-126 (Figure 15)

In each of the placebo-controlled trials there is consistent separation between the curves for the combination products and placebo on both Day 1 and Day 168. These results are supportive of the findings for the primary endpoint.

Peak FEV1

Peak FEV1, obtained from the serial 0-6 hour FEV1 assessments, was added as an additional endpoint in the reporting and analysis plans for the primary efficacy trials. Results for this endpoint from the placebo-controlled and active-controlled trials are provided in Table 27 and Table 28, respectively.

Table 27. Change in Peak FEV1 (L) at Day 168, Placebo-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
DB2113361												
UMEC 125/25	403	1.616 (0.012)	0.341 (0.012)	0.280	(0.241, 0.319)	<0.001	0.100	(0.066, 0.134)	<0.001	0.142	(0.108, 0.176)	<0.001
UMEC 125	407	1.515 (0.012)	0.241 (0.012)	0.180	(0.141, 0.219)	<0.001						
VI 25	404	1.474 (0.012)	0.199 (0.012)	0.138	(0.099, 0.177)	<0.001						
Placebo	275	1.336 (0.016)	0.061 (0.016)									
DB2113373												
UMEC 62.5/25	413	1.555 (0.014)	0.320 (0.014)	0.224	(0.182, 0.267)	<0.001	0.094	(0.057, 0.132)	<0.001	0.116	(0.078, 0.153)	<0.001
UMEC 62.5	418	1.460 (0.014)	0.226 (0.014)	0.130	(0.088, 0.172)	<0.001						
VI	421	1.439 (0.014)	0.204 (0.014)	0.108	(0.066, 0.151)	<0.001						
Placebo	280	1.331 (0.017)	0.096 (0.017)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 119 (Table 36); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 115 (Table 36)
Key: BL=baseline
Note: N=ITT Population

Table 28. Change in Peak FEV1 (L) at Day 168, Active-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
DB2113360												
UMEC 125/25	208	1.647 (0.019)	0.333 (0.019)	0.060	(0.006, 0.114)	0.028				0.076	(0.022, 0.131)	0.006

UMEC 62.5/25	207	1.659 (0.0190	0.345 (0.019)	0.072	(0.019, 0.125)	0.008				0.088	(0.035, 0.142)	0.001
VI 25	205	1.570 (0.0196)	0.257 (0.0196)									
TIO	203	1.586 (0.0194)	0.273 (0.0194)									
DB2113374												
UMEC 125/25	215	1.494 (0.018)	0.349 (0.018)	0.094	(0.044, 0.143)	<0.001	0.068	(0.018, 0.117)	0.007			
UMEC 62.5/25	217	1.494 (0.018)	0.349 (0.018)	0.093	(0.044, 0.142)	<0.001	0.067	(0.018, 0.117)	0.008			
UMEC 125	222	1.427 (0.0178)	0.282 (0.0178)									
TIO	215	1.401 (0.0176)	0.256 (0.0176)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 107 (Table 38); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 104 (Table 38)
Key: BL=baseline
Note: N=ITT population (excluding data from Investigator 040688 in Trial DB2113360)

Statistically significant results for the comparisons of both doses of the combination product to placebo, as well as for the comparisons of the monotherapies to placebo, were demonstrated. In addition, across the four primary efficacy trials, results for the comparisons of the combination products to their constituent monotherapies were all statistically significant. These results are supportive of the findings for the primary endpoint.

Rescue Medication Use

Change in rescue medication use, from Week 1 to Week 24, was evaluated in each of the four primary efficacy trials. Results for this endpoint from the placebo-controlled trials and active-controlled trials are provided in Table 29 and Table 30, respectively.

Table 29. Change in Mean Number of Puffs of Rescue Medication per Day at Week 24, Placebo-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2113361												
UMEC 125/25	403	2.2 (0.1)	-2.2 (0.1)	-1.5	(-1.9, -1.0)	<0.001	-0.7	(-1.0, -0.3)	0.001	-0.7	(-1.1, -0.3)	<0.001
UMEC 125	407	2.8 (0.1)	-1.5 (0.1)	-0.8	(-1.3, -0.4)	<0.001						
VI 25	404	2.9 (0.1)	-1.5 (0.1)	-0.8	(-1.2, -0.3)	<0.001						
Placebo	275	3.7 (0.2)	-0.7 (0.2)									
DB2113373												
UMEC 62.5/25	413	3.3 (0.2)	-2.3 (0.2)	-0.8	(-1.3, -0.3)	0.001	-0.6	(-1.0, -0.1)	0.014	0.1	(-0.3, 0.5)	0.675

UMEC 62.5	418	3.8 (0.2)	-1.7 (0.2)	-0.3	(-0.8, 0.2)	0.276						
VI	421	3.2 (0.2)	-2.4 (0.2)	-0.9	(-1.4, -0.4)	<0.001						
Placebo	280	4.1 (0.2)	-1.4 (0.2)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 132 (Table 42); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 127 (Table 42)
Key: BL=baseline
Note: N=ITT Population

Table 30. Change in Mean Number of Puffs of Rescue Medication per Day at Week 24, Active-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2113360												
UMEC 125/25	208	2.5 (0.2)	-2.0 (0.2)	-0.6	(-1.2, -0.1)	0.031				-0.2	(-0.8, 0.4)	0.450
UMEC 62.5/25	207	2.5 (0.2)	-2.0 (0.2)	-0.7	(-1.2, -0.1)	0.022				-0.3	(-0.8, 0.3)	0.385
VI 25	205	2.8 (0.2)	-1.8 (0.2)									
TIO	203	3.2 (0.2)	-1.4 (0.2)									
DB2113374												
UMEC 125/25	215	2.4 (0.2)	-3.2 (0.2)	-1.1	(-1.7, -0.5)	<0.001	-1.1	(-1.7, -0.5)	<0.001			
UMEC 62.5/25	217	2.9 (0.2)	-2.7 (0.2)	-0.6	(-1.2, 0.0)	0.069	-0.6	(-1.2, 0.0)	0.055			
UMEC 125	222	3.5 (0.2)	-2.1 (0.2)									
TIO	215	3.5 (0.2)	-2.1 (0.2)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 116 (Table 42); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 113 (Table 42)
Key: BL=baseline
Note: N=ITT population (excluding data from Investigator 040688 in Trial DB2113360)

Each of the UMEC/VI combination products demonstrated a statistically significant reduction in mean number of puffs of rescue medication compared to placebo in the single trial where this comparison was evaluated. With regard to the monotherapies, while the comparisons between VI and placebo, and for UMEC 125 mcg and placebo, were statistically significant, this was not the case for UMEC 62.5 mcg. Results for the comparisons between the combination products and their monocomponents were mixed with regard to statistical significance. These data, and particularly the lack of replicate, statistically significant results for the comparison between UMEC/VI 62.5 mcg/25 mcg and placebo, are not adequate to support a labeling claim.

SOBDA

The Applicant evaluated dyspnea with activity using the Shortness of Breath with Daily Activities (SOBDA) questionnaire. The SOBDA is a novel patient-reported outcome (PRO) developed by the Applicant for use in this development program, and has not been previously used in a regulatory context to support a product claim.

In its current form the SOBDA is a 13-item questionnaire administered via an electronic diary. Patients are instructed to complete the questionnaire each evening prior to bedtime, and to respond to the questions based on their experiences that day. The instrument queries the patient, "How short of breath were you when you [performed this activity] today?" The activities assessed are:

- putting on long pants or stockings
- putting on shoes (sandals)
- washing oneself
- reaching above one's head to put things away
- cleaning or fixing something at floor level
- putting things away in a cupboard or shelf at chest level
- putting things away at knee level
- preparing food or a meal
- picking up light objects off the floor
- carrying objects (e.g. bags, baskets) at one's side
- walking at a slow pace
- walking up 3 stairs
- walking up 8 stairs

The response options are:

- not at all
- slightly
- moderately
- severely
- so severe that I did not do the activity today
- I did not do the activity today

The instrument provides instruction to the patient that they should mark "I did not do the activity today" if they did not engage in the activity for reasons other than shortness of breath, and mark "so severe that I did not do the activity today" if they did not engage in the activity due to shortness of breath.

The values associated with each response varies depending on the particular item; together the data is used to generate a weekly mean SOBDA score ranging from 1 to 4, with greater scores indicating more shortness of breath with activity. The Applicant identifies a minimal clinically important difference of -0.1 to -0.2.

While the SOBDA assesses activities that are likely to be relevant to the patient, the instrument is problematic for a number of reasons. The Agency provided advice to the Applicant during the early development of the SOBDA (under IND 50,703), based largely on recommendations of the Study Endpoints and Labeling Development (SEALD) team. Issues identified with the SOBDA included concern that the response options, "I did not do the activity today" and "So severe that I did not do the activity today" were not mutually exclusive, and concern that one of the activities assessed ("How short of breath were you when you prepared food or a meal?") may not be a relevant daily activity for men (based on the results of qualitative interviews). A new SEALD consult for the evaluation of the SOBDA was obtained in response to this NDA submission (see review by Jessica Voqui, NDA 203-975, June 24, 2013); it concludes that while the Applicant reanalyzed qualitative data and provided additional information, they did not make major changes to the instrument. SEALD thus remains concerned about the content validity of the instrument and the ability of patients to discriminate between the response options described above.

This clinical review agrees with the concerns raised by SEALD. To that extent, the results of the SOBDA analyses presented below should be considered exploratory in nature.

Table 31. Change in Mean SOBDA Score at Week 24, Placebo-controlled Trials

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
DB2113361												
UMEC 125/25	403	1.74 (0.029)	-0.22 (0.029)	-0.15	(-0.24, -0.06)	0.002	-0.07	(-0.15, 0.01)	0.072	-0.12	(-0.20, -0.04)	0.004
UMEC 125	407	1.81 (0.029)	-0.15 (0.029)	-0.08	(-0.17, 0.02)	0.106						
VI 25	404	1.86 (0.029)	-0.10 (0.029)	-0.03	(-0.13, 0.06)	0.515						
Placebo	275	1.89 (0.038)	-0.07 (0.038)									
DB2113373												
UMEC 62.5/25	413	1.77 (0.029)	-0.23 (0.029)	-0.17	(-0.26, -0.08)	<0.001	-0.08	(-0.16, 0.01)	0.068	-0.03	(-0.11, 0.05)	0.498
UMEC 62.5	418	1.84 (0.029)	-0.16 (0.029)	-0.10	(-0.19, 0.00)	0.043						
VI	421	1.79 (0.030)	-0.21 (0.030)	-0.14	(-0.24, -0.05)	0.002						
Placebo	280	1.94 (0.037)	-0.06 (0.037)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 134 (Table 44), pg. 1333 (Table 6.73); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 129 (Table 44), pg. 1246 (Table 6.73)
Key: BL=baseline
Note: N=ITT Population

Table 32. Change in Mean SOBDA Score at Week 24, Active-controlled Trials

Treatment Arm	N	BL	Change from BL	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value	LS Mean	95% CI	p-value
DB2113360												
UMEC 125/25	208	1.82 (0.044)	-0.18 (0.044)	0.00	(-0.12, 0.12)	0.978				-0.02	(-0.14, 0.10)	0.786
UMEC 62.5/25	207	1.82 (0.042)	-0.18 (0.042)	0.00	(-0.12, 0.12)	0.986				-0.02	(-0.14, 0.10)	0.748
VI 25	205	1.83 (0.043)	-0.16 (0.043)									
TIO	203	1.82 (0.044)	-0.18 (0.044)									
DB2113374												
UMEC 125/25	215	1.68 (0.040)	-0.33 (0.040)	-0.13	(-0.24, -0.02)	0.023	-0.14	(-0.26, -0.03)	0.011			
UMEC 62.5/25	217	1.73 (0.040)	-0.29 (0.040)	-0.08	(-0.20, 0.03)	0.137	-0.10	(-0.21, 0.01)	0.079			
UMEC 125	222	1.83 (0.041)	-0.19 (0.041)									
TIO	215	1.81 (0.040)	-0.21 (0.040)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 118 (Table 44); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 115 (Table 44)
Key: BL=baseline
Note: N=ITT Population (excluding data from Investigator 040688 in Trial DB2113360)

Statistically significant results are observed for both of the UMEC/VI doses compared to placebo in the single trial where each was evaluated. The magnitude of the treatment ranges from -0.15 to -0.17; the clinical relevance of these findings is unknown.

SGRQ

Disease-specific health related quality of life was assessed in the UMEC/VI clinical development program using the St. George's Respiratory Questionnaire. Health-related quality-of-life instruments are described as one of the commonly used secondary efficacy endpoints in the Agency's Draft Guidance,[20] and there is regulatory precedent for labeling claims based on the SGRQ.[21]

[20] Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," November 2007. Available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf. Accessed August 5, 2013.
[21] Arcapta Neohaler (indacaterol inhalation powder) Prescribing Information, July 2011. Available at: http://www.pharma.us.novartis.com/product/pi/pdf/arcapta.pdf. Accessed August 5, 2013.

Change in SGRQ total score was evaluated in each of the four primary efficacy trials; a change in SGRQ total score of 4 units or greater was considered to represent a clinically meaningful improvement. Results of this analysis from the placebo-controlled and active-controlled trials are provided in Table 33 and Table 34, respectively. In addition, the Applicant conducted a responder analysis, the results of which are presented in Table 35 and Table 36 for the placebo-controlled and active-controlled trials, respectively.

Table 33. Change in SGRQ Total Score at Day 168, Placebo-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2113361												
UMEC 125/25	403	40.10 (0.67)	-7.43 (0.67)	-3.60	(-5.76, -1.44)	0.001	-3.29	(-5.13, -1.44)	<0.001	-2.72	(-4.59, -0.86)	0.004
UMEC 125	407	43.38 (0.66)	-4.14 (0.66)	-0.31	(-2.46, 1.85)	0.778						
VI 25	404	42.82 (0.68)	-4.71 (0.68)	-0.87	(-3.05, 1.30)	0.432						
Placebo	275	43.69 (0.88)	-3.83 (0.88)									
DB2113373												
UMEC 62.5/25	413	41.11 (0.75)	-8.07 (0.75)	-5.51	(-7.88, -3.13)	<0.001	-0.82	(-2.90, 1.27)	0.441	-0.32	(-2.41, 1.78)	0.767
UMEC 62.5	418	41.93 (0.75)	-7.25 (0.75)	-4.69	(-7.07, -2.31)	<0.001						
VI	421	41.43 (0.76)	-7.75 (0.76)	-5.19	(-7.58, -2.80)	<0.001						
Placebo	280	46.62 (0.95)	-2.56 (0.95)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 142 (Table 50); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 137 (Table 50)
Key: BL=baseline
Note: N=ITT Population

Table 34. Change in SGRQ Total Score at Day 168, Active-controlled Trials, ITT Population

Treatment Arm	N	BL	Change from BL	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2113360												
UMEC 125/25	208	40.74 (1.05)	-9.03 (1.05)	-1.41	(-4.34, 1.52)	0.346				-0.74	(-3.68, 2.20)	0.620
UMEC 62.5/25	207	42.90 (1.02)	-6.87 (1.02)	0.75	(-2.12, 3.63)	0.607				1.42	(-1.46, 4.30)	0.334
VI 25	205	41.48	-8.29									

		(1.06)	(1.06)									
TIO	203	42.15 (1.05)	-7.62 (1.05)									
DB2113374												
UMEC 125/25	215	38.60 (0.97)	-10.52 (0.97)	-0.74	(-3.41, 1.93)	0.588	-2.12	(-4.80, 0.57)	0.122			
UMEC 62.5/25	217	39.17 (0.98)	-9.95 (0.98)	-0.17	(-2.85, 2.52)	0.904	-1.55	(-4.25, 1.16)	0.262			
UMEC 125	222	40.72 (0.97)	-8.40 (0.97)									
TIO	215	39.34 (0.95)	-9.78 (0.95)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 126 (Table 51); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 123 (Table 50)
Key: BL=baseline
Note: N=ITT population (excluding data from Investigator 040688 in Trial DB2113360)

Table 35. SGRQ Responder Analysis at Day 168, Placebo-controlled Trials, ITT Population

Treatment Arm	N	Responder	Non-responder	Comparison to Placebo			Comparison to UMEC			Comparison to VI		
		n (%)	n (%)	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
DB2113361												
UMEC 125/25	403	173 (49)	183 (51)	1.7	(1.2, 2.4)	0.002	1.5	(1.1, 2.0)	0.013	1.4	(1.0, 1.9)	0.026
UMEC 125	407	144 (40)	217 (60)	1.2	(0.8, 1.7)	0.345						
VI 25	404	145 (41)	208 (59)	1.2	(0.9, 1.7)	0.254						
Placebo	275	80 (37)	139 (63)									
DB2113373												
UMEC 62.5/25	413	188 (49)	193 (51)	2.0	(1.4, 2.8)	<0.001	1.2	(0.9, 1.6)	0.178	1.1	(0.8, 1.4)	0.602
UMEC 62.5	418	172 (44)	216 (56)	1.6	(1.2, 2.3)	0.003						
VI	421	181 (48)	200 (52)	1.9	(1.3, 2.6)	<0.001						
Placebo	280	86 (34)	168 (66)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 144 (Table 51); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 139 (Table 51)
Key: OR=odds ratio
Note: N=ITT Population; Response defined as a SGRQ total score of 4 units below baseline or lower

Table 36. SGRQ Responder Analysis at Day 168, Active-controlled Trials, ITT Population

Treatment Arm	N	Responder	Non-responder	Comparison to TIO			Comparison to UMEC			Comparison to VI		
		n (%)	n (%)	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
DB2113360												
UMEC 125/25	208	99 (53)	87 (47)	1.0	(0.7, 1.6)	0.853				1.0	(0.7, 1.5)	0.998

UMEC 62.5/25	207	94 (49)	99 (51)	0.9	(0.6, 1.3)	0.537				0.8	(0.6, 1.3)	0.414
VI 25	205	97 (52)	89 (48)									
TIO	203	92 (52)	86 (48)									
DB2113374												
UMEC 125/25	215	100 (51)	97 (49)	0.9	(0.6, 1.3)	0.464	1.1	(0.8, 1.7)	0.518			
UMEC 62.5/25	217	103 (54)	87 (46)	1.0	(0.6, 1.5)	0.887	1.3	(0.9, 1.9)	0.219			
UMEC 125	222	97 (48)	104 (52)									
TIO	215	104 (55)	86 (45)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 128 (Table 52); Section 5.3.5.1 (DB2113374, Study Report Body), pg. 125 (Table 51)
Key: OR=odds ratio
Note: N=ITT population (excluding data from Investigator 040688 in Trial DB2113360); Response defined as a SGRQ total score of 4 units below baseline or lower

The results for comparison between UMEC/VI and placebo in change in total SGRQ were statistically significant for both doses of the combination, but the threshold for a clinically meaningful improvement was met only for the 62.5 mcg/25 mcg dose. There was no replication of this result, as the 62.5 mcg/25 mcg dose was compared to placebo in only a single trial. None of the analyses for change in total SGRQ score from the active-controlled trials were statistically significant. With regard to the responder analysis, the results for the comparison between UMEC/VI and placebo were statistically significant for both doses of the combination. None of the responder analyses from the active-controlled trials were statistically significant.

Overall, these data do not provide adequate support for a claim based on SGRQ. Replicate evidence of a statistically significant and clinically meaningful treatment effect for the comparison between combination product and placebo is required.

COPD Exacerbations

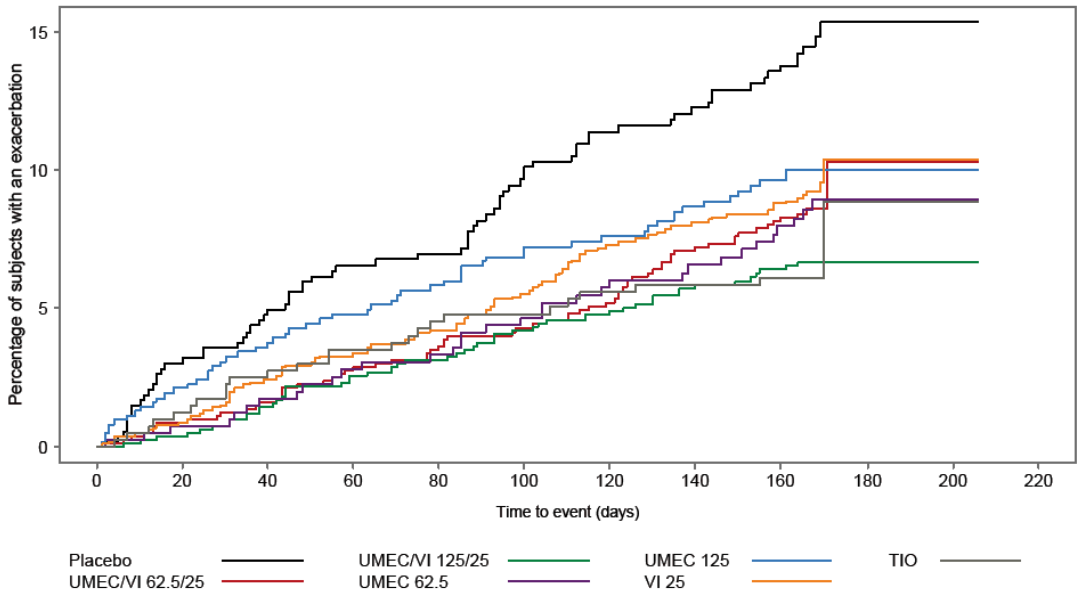
While the primary efficacy trials were not designed specifically for this purpose, the impact of UMEC/VI on COPD exacerbations was explored as an additional endpoint. As described in Section 5.3, the protocols for these trials defined a COPD exacerbation as an acute worsening of symptoms of COPD requiring treatment beyond trial medication or rescue albuterol/salbutamol, including the use of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization; this definition is similar to that used in the clinical development programs of products approved for the reduction of exacerbations in COPD. A COPD exacerbation resulted in a patient's withdrawal from the trial. Results of the analysis of time to first on-treatment COPD exacerbation for the integrated primary efficacy trial population are provided in Table 37 and Figure 22.

Table 37. Analysis of Time to First On-Treatment COPD Exacerbation, Integrated Primary Efficacy Trials, ITT Population

Arm	N	Pts Evnt n (%)	Pts Cens n (%)	Prob Evnt (%)	Comparison to P			Comparison to U*			Comparison to VI			Comparison to TIO		
					HZ	95% CI	p-value	HZ	95% CI	p-value	HZ	95% CI	p-value	HZ	95% CI	p-value
U/VI 125/25	826	50 (6)	776 (94)	6.7	0.4	0.2, 0.5	<0.001	0.7	0.5, 1.0	0.048	0.6	0.4, 0.9	0.007	1.1	0.7, 1.9	0.618
U/VI 62.5/25	837	67 (8)	770 (92)	10.3	0.5	0.3, 0.7	<0.001	0.9	0.5, 1.4	0.508	0.8	0.6, 1.1	0.207	1.5	0.9, 2.4	0.089
U 125	629	58 (9)	571 (91)	10.0	0.5	0.4, 0.8	0.002									
U 62.5	418	33 (8)	385 (92)	8.9	0.6	0.4, 0.9	0.011									
VI 25	1030	88 (9)	942 (91)	10.4	0.6	0.4, 0.8	0.002									
TIO	418	25 (6)	393 (94)	8.9												
P	555	73 (13)	482 (87)	15.3												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 203 (Table 84)
*The comparisons are for comparable UMEC doses; i.e. UMEC/VI 125 mcg/25mcg to UMEC 125 mcg, and UMEC/VI 62.5 mcg/25 mcg to UMEC 62.5 mcg
Key: P=placebo; Pts Evnt=patients with event; Pts Cens=patients censored; Prob Evnt=probability of having event; U=umeclidinium; V=vilanterol

Figure 22. Kaplan-Meier Plot of Time to First On-Treatment COPD Exacerbation, Integrated Primary Efficacy Trials, ITT Population



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 205 (Figure 18)

The percentage of patients with a COPD exacerbation was lower for the active treatment arms (6-9%) compared to placebo (13%). Hazard ratios for the comparison to placebo were statistically significant for both doses of UMEC/VI, as well as both doses of the UMEC monotherapy and VI. Hazard ratios for the comparison of the combination products to their monocomponents were statistically significant for the 125 mcg/25 mcg dose, but not the 62.5 mcg/25 mcg dose. Hazard ratios for the comparison of the combination products to TIO were not statistically significant. The Kaplan-Meier plot of time to first on-treatment COPD exacerbation demonstrates a separation between the active treatment arms and placebo.

While these results suggest a possible favorable impact of UMEC/VI on COPD exacerbations, the data must be interpreted with caution; given the design of the trials, these analyses are considered to be exploratory in nature. It should be noted that the Applicant is not seeking an indication pertinent to COPD exacerbation.

5.1.7 Subpopulations

The application includes an analysis of efficacy results for various subpopulations, including subgroups based on demographics (age, gender, race, geographic region), as well as subgroups based on disease and other characteristics (COPD severity, concomitant ICS use, bronchodilator reversibility, and smoking status). This review considers analyses of the primary endpoint trough FEV1 at Day 169 conducted for the pooled ITT population drawn from all four primary efficacy trials.

Demographics

This review presents subgroup analyses based on the demographic factors of age (Table 38) and gender (Table 39), race (Table 40), and geography (Table 41). Focusing on the results for the comparisons between UMEC/VI and placebo, for each of the subgroup analyses conducted, results across demographic categories are consistent with the analysis for the overall ITT population: both the 125 mcg/25 mcg and 62.5 mcg/25 doses are associated with a statistically significant treatment effect. While there was variability in the magnitude of effect size across demographic subgroups (184-235 mL for the 62.5 mcg/25 mcg dose, and 177-273 mL for the 125 mcg/25 mcg dose), these ranges are consistent with those observed for the overall ITT population across the primary efficacy trials and exercise endurance trials.

Age

Table 38. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Age

Arm	N	BL	Δ BL	Treatment Difference	Treatment Difference	Treatment Difference	Treatment Difference

				from Placebo			from U			from VI			from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
≤ 64 years															
U/VI 125/25	432	1.580 (0.014)	0.227 (0.014)	0.233	0.192, 0.274	<0.001	0.074	0.034, 0.113	<0.001	0.117	0.082, 0.152	<0.001	0.094	0.049, 0.140	<0.001
U/VI 62.5/25	443	1.531 (0.013)	0.0178 (0.013)	0.184	0.143, 0.224	<0.001	0.060	0.015, 0.106	0.01	0.068	0.033, 0.102	<0.001	0.045	0.000, 0.091	0.051
U 125	332	1.507 (0.016)	0.0153 (0.016)	0.159	0.116, 0.202	<0.001									
U 62.5	216	1.471 (0.020)	0.118 (0.020)	0.124	0.075, 0.172	<0.001									
VI 25	586	1.464 (0.012)	0.111 (0.012)	0.116	0.078, 0.154	<0.001									
TIO	205	1.486 (0.020)	0.133 (0.020)												
P	331	1.348 (0.016)	-0.006 (0.016)												
65-74 years															
U/VI 125/25	308	1.330 (0.013)	0.186 (0.013)	0.204	0.158, 0.250	<0.001	0.050	0.011, 0.090	0.013	0.111	0.075, 0.147	<0.001	0.066	0.022, 0.111	0.004
U/VI 62.5/25	299	1.350 (0.014)	0.207 (0.014)	0.224	0.178, 0.270	<0.001	0.091	0.044, 0.137	<0.001	0.131	0.095, 0.167	<0.001	0.086	0.041, 0.131	<0.001
U 125	229	1.280 (0.016)	0.136 (0.016)	0.153	0.104, 0.202	<0.001									
U 62.5	148	1.260 (0.020)	0.116 (0.020)	0.133	0.079, 0.187	<0.001									
VI 25	342	1.219 (0.013)	0.076 (0.013)	0.093	0.048, 0.137	<0.001									
TIO	159	1.264 (0.019)	0.120 (0.019)												
P	166	1.127 (0.020)	-0.017 (0.020)												
75-84 years															
U/VI 125/25	78	1.200 (0.026)	0.180 (0.026)	0.177	0.091, 0.262	<0.001	0.054	-0.022, 0.131	0.165	0.106	0.038, 0.174	0.002	0.052	-0.03, 0.133	0.213
U/VI 62.5/25	84	1.214 (0.025)	0.194 (0.025)	0.191	0.107, 0.274	<0.001	-0.006	-0.088, 0.077	0.894	0.120	0.052, 0.187	<0.001	0.066	-0.016, 0.147	0.115
U 125	61	1.145 (0.030)	0.126 (0.030)	0.123	0.032, 0.213	0.008									
U 62.5	49	1.219 (0.035)	0.200 (0.035)	0.196	0.103, 0.289	<0.001									
VI 25	93	1.094 (0.023)	0.074 (0.023)	0.071	-0.01, 0.152	0.084									
TIO	48	1.148 (0.034)	0.129 (0.034)												
P	49	1.023 (0.034)	0.003 (0.034)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 716-745 (Table 3.36)
Key: BL=baseline**; ΔBL=change from baseline; Diff=difference; U=umeclidinium**
Note: N= ITT Population, number of patients with analyzable data for one or more time points

Gender

Table 39. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Gender

Arm	N	BL	Δ BL	Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
Male															
U/VI 125/ 25	552	1.468 (0.011)	0.223 (0.011)	0.221	0.186, 0.256	<0.001	0.075	0.042, 0.107	<0.001	0.116	0.086, 0.145	<0.001	0.085	0.049, 0.121	<0.001
U/VI 62.5/ 25	584	1.448 (0.011)	0.203 (0.011)	0.201	0.167, 0.236	<0.001	0.053	0.017, 0.089	0.004	0.095	0.067, 0.124	<0.001	0.065	0.029, 0.101	<0.001
U 125	415	1.393 (0.013)	0.148 (0.013)	0.147	0.110, 0.184	<0.001									
U 62.5	296	1.395 (0.016)	0.150 (0.016)	0.148	0.108, 0.189	<0.001									
VI 25	686	1.352 (0.010)	0.107 (0.010)	0.106	0.073, 0.139	<0.001									
TIO	288	1.383 (0.015)	0.138 (0.015)												
P	367	1.246 (0.014)	0.002 (0.014)												
Female															
U/VI 125/ 25	266	1.421 (0.016)	0.176 (0.016)	0.204	0.154, 0.254	<0.001	0.041	- 0.006, 0.088	0.084	0.104	0.062, 0.145	<0.001	0.069	0.016, 0.123	0.011
U/VI 62.5/ 25	246	1.409 (0.016)	0.164 (0.016)	0.193	0.142, 0.243	<0.001	0.092	0.037, 0.148	0.001	0.092	0.050, 0.134	<0.001	0.058	0.004, 0.112	0.037
U 125	208	1.379 (0.018)	1.135 (0.018)	0.163	0.110, 0.216	<0.001									
U 62.5	120	1.316 (0.023)	0.072 (0.023)	0.100	0.040, 0.160	0.001									
VI 25	338	1.317 (0.014)	0.072 (0.014)	0.101	0.053, 0.148	<0.001									
TIO	126	1.351 (0.023)	0.106 (0.023)												
P	180	1.216 (0.020)	-0.029 (0.020)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 688-703 (Table 3.35)
Key: BL=baseline; ΔBL=change from baseline; Diff=difference; U=umeclidinium
Note: N= ITT Population, number of patients with analyzable data for one or more time points

Race

Table 40. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Race

Arm	N	BL	Δ BL	Treatment Difference from Placebo	Treatment Difference from U	Treatment Difference from VI	Treatment Difference from TIO

		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
White															
U/VI 125/25	688	1.453 (0.010)	0.208 (0.010)	0.217	0.186, 0.249	<0.001	0.064	0.035, 0.094	<0.001	0.115	0.089, 0.141	<0.001	0.105	0.072, 0.139	<0.001
U/VI 62.5/25	684	1.426 (0.010)	0.181 (0.010)	0.190	0.159, 0.221	<0.001	0.067	0.034, 0.101	<0.001	0.088	0.062, 0.114	<0.001	0.078	0.044, 0.111	<0.001
U 125	527	1.389 (0.012)	0.144 (0.012)	0.153	0.120, 0.186	<0.001									
U 62.5	352	1.358 (0.014)	0.114 (0.014)	0.123	0.086, 0.159	<0.001									
VI 25	893	1.338 (0.009)	0.093 (0.009)	0.102	0.073, 0.131	<0.001									
TIO	333	1.348 (0.014)	0.103 (0.014)												
P	467	1.236 (0.012)	-0.009 (0.012)												
non-White															
U/VI 125/25	130	1.452 (0.023)	0.207 (0.023)	0.208	0.133, 0.282	<0.001	0.064	-0.003, 0.131	0.060	0.096	0.034, 0.158	0.003	-0.018	-0.088, 0.051	0.604
U/VI 62.5/25	146	1.480 (0.021)	0.235 (0.021)	0.235	0.162, 0.308	<0.001	0.035	-0.041, 0.111	0.369	0.123	0.063, 0.183	<0.001	0.009	-0.059, 0.077	0.795
U 125	96	1.388 (0.026)	0.143 (0.026)	0.143	0.064, 0.222	<0.001									
U 62.5	64	1.445 (0.033)	0.200 (0.033)	0.200	0.113, 0.288	<0.001									
VI 25	131	1.356 (0.023)	0.112 (0.023)	0.112	0.038, 0.186	0.003									
TIO	81	1.471 (0.028)	0.226 (0.028)												
P	80	1.245 (0.031)	0.000 (0.031)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 1671-1686 (Table 3.144)
Key: BL=baseline; ΔBL=change from baseline; Diff=difference; U=umeclidinium
Note: N= ITT Population, number of patients with analyzable data for one or more time points

Geographic Region

Table 41. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Geographic Region

Arm	N	BL	Δ BL	Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
US															
U/VI 125/25	189	1.478 (0.019)	0.234 (0.019)	0.273	0.215, 0.332	<0.001	0.098	0.041, 0.154	<0.001	0.127	0.078, 0.177	<0.001	0.162	0.101, 0.224	<0.001
U/VI	225	1.420	0.175	0.215	0.158,	<0.001	0.062	0.004,	0.036	0.069	0.021,	0.005	0.104	0.043,	<0.001

62.5/25		(0.018)	(0.018)		0.272			0.119			0.116			0.164	
U 125	143	1.381 (0.022)	0.136 (0.022)	0.176	0.113, 0.238	<0.001									
U 62.5	118	1.358 (0.024)	0.113 (0.024)	0.153	0.088, 0.218	<0.001									
VI 25	253	1.351 (0.017)	0.106 (0.017)	0.146	0.090, 0.202	<0.001									
TIO	101	1.316 (0.026)	0.071 (0.026)												
P	134	1.205 (0.023)	-0.04 (0.023)												
ex-US															
U/VI 125/25	629	1.445 (0.010)	0.200 (0.010)	0.199	0.166, 0.232	<0.001	0.054	0.024, 0.085	<0.001	0.109	0.082, 0.136	<0.001	0.055	0.020, 0.089	0.002
U/VI 62.5/25	605	1.440 (0.010)	0.195 (0.010)	0.194	0.161, 0.227	<0.001	0.063	0.027, 0.098	<0.001	0.104	0.077, 0.131	<0.001	0.050	0.015, 0.084	0.005
U 125	480	1.391 (0.012)	0.146 (0.012)	0.145	0.110, 0.179	<0.001									
U 62.5	298	1.378 (0.015)	0.133 (0.015)	0.132	0.092, 0.171	<0.001									
VI 25	771	1.336 (0.009)	0.091 (0.009)	0.090	0.059, 0.121	<0.001									
TIO	313	1.390 (0.015)	0.145 (0.015)												
P	413	1.246 (0.013)	0.001 (0.013)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 1699-1714 (Table 3.145)
Key: BL=baseline; ΔBL=change from baseline; Diff=difference; U=umeclidinium
Note: N= ITT Population, number of patients with analyzable data for one or more time points

Disease and Other Characteristics

This review presents subgroup analyses based on the disease characteristics including COPD severity (Table 42), concomitant ICS use (Table 43), and bronchodilator reversibility (Table 44), as well as smoking status (Table 45). As is the case for the demographic subgroup analyses, results for the disease and other characteristics subgroup analyses are consistent with the analysis for the overall ITT population: both the 125 mcg/25 mcg and 62.5 mcg/25 doses are associated with a statistically significant treatment effect for the comparison to placebo. The ranges for the magnitude of effect size across subgroups were again generally consistent with those observed for the overall ITT population across the primary efficacy trials and exercise endurance trials.

COPD Severity

Table 42. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by COPD Severity

Arm	N	BL	Δ BL	Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
GOLD Stage II															
U/VI 125/ 25	358	1.478 (0.014)	0.233 (0.014)	0.237	0.195, 0.279	<0.001	0.060	0.021, 0.100	0.003	0.110	0.075, 0.144	<0.001	0.089	0.045, 0.132	<0.001
U/VI 62.5/ 25	407	1.445 (0.013)	0.200 (0.013)	0.204	0.163, 0.246	<0.001	0.029	-0.015, 0.072	0.193	0.077	0.044, 0.110	<0.001	0.056	0.013, 0.099	0.011
U 125	280	1.418 (0.016)	0.173 (0.016)	0.177	0.132, 0.222	<0.001									
U 62.5	190	1.416 (0.019)	0.171 (0.019)	0.175	0.127, 0.224	<0.001									
VI 25	496	1.368 (0.012)	0.124 (0.012)	0.127	0.088, 0.167	<0.001									
TIO	194	1.389 (0.018)	0.145 (0.018)												
P	236	1.241 (0.017)	-0.004 (0.017)												
GOLD Stages III and IV															
U/VI 125/ 25	457	1.432 (0.012)	0.188 (0.012)	0.199	0.160, 0.238	<0.001	0.065	0.029, 0.101	<0.001	0.120	0.087, 0.153	<0.001	0.073	0.031, 0.114	<0.001
U/VI 62.5/ 25	420	1.427 (0.013)	0.182 (0.013)	0.193	0.155, 0.232	<0.001	0.102	0.060, 0.144	<0.001	0.114	0.081, 0.147	<0.001	0.067	0.025, 0.109	0.002
U 125	341	1.367 (0.014)	0.122 (0.014)	0.134	0.093, 0.175	<0.001									
U 62.5	225	1.325 (0.018)	0.080 (0.018)	0.092	0.046, 0.137	<0.001									
VI 25	523	1.313 (0.012)	0.068 (0.012)	0.079	0.042, 0.117	<0.001									
TIO	217	1.360 (0.018)	0.115 (0.018)												
P	310	1.232 (0.016)	-0.011 (0.016)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 921-922, 935-936 (Table 3.41)
Key: BL=baseline; **ΔBL=change from baseline; Diff=difference; U=umeclidinium**
Note: N= ITT Population, number of patients with analyzable data for one or more time points

Concomitant ICS Use

Table 43. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Concomitant ICS Use

Arm	N	BL	Δ BL	Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
ICS user															
U/VI 125/ 25	387	1.447 (0.013)	0.203 (0.013)	0.205	0.164, 0.246	<0.001	0.045	0.006, 0.083	0.022	0.132	0.098, 0.167	<0.001	0.044	0.001, 0.087	0.045
U/VI 62.5/ 25	404	1.440 (0.013)	0.195 (0.013)	0.198	0.157, 0.238	<0.001	0.093	0.051, 0.136	<0.001	0.125	0.091, 0.159	<0.001	0.036	-0.006, 0.079	0.096
U 125	314	1.403 (0.015)	0.158 (0.015)	0.161	0.117, 0.204	<0.001									
U 62.5	218	1.347 (0.018)	0.102 (0.018)	0.104	0.057, 0.151	<0.001									
VI 25	484	1.315 (0.012)	0.070 (0.012)	0.073	0.034, 0.112	<0.001									
TIO	207	1.404 (0.018)	0.159 (0.018)												
P	271	1.242 (0.016)	-0.003 (0.016)												
ICS non-user															
U/VI 125/ 25	431	1.459 (0.013)	0.214 (0.013)	0.228	0.188, 0.267	<0.001	0.083	0.046, 0.120	<0.001	0.096	0.063, 0.129	<0.001	0.114	0.072, 0.157	<0.001
U/VI 62.5/ 25	426	1.431 (0.012)	0.186 (0.012)	0.200	0.161, 0.240	<0.001	0.034	-0.009, 0.078	0.124	0.069	0.036, 0.101	<0.001	0.087	0.045, 0.129	<0.001
U 125	309	1.375 (0.015)	0.131 (0.015)	0.144	0.102, 0.187	<0.001									
U 62.5	198	1.397 (0.019)	0.152 (0.019)	0.166	0.119, 0.214	<0.001									
VI 25	540	1.363 (0.011)	0.118 (0.011)	0.132	0.094, 0.170	<0.001									
TIO	207	1.344 (0.018)	0.099 (0.018)												
P	276	1.231 (0.016)	-0.014 (0.016)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 893-894, 907-908, (Table 3.40)
Key: BL=baseline; **ΔBL=change from baseline; Diff=difference; U=umeclidinium**
Note: N= ITT Population, number of patients with analyzable data for one or more time points

Bronchodilator Reversibility

Table 44. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Bronchodilator Reversibility

Arm	N	BL	Δ BL	Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
Not Reversible															
U/VI 125/ 25	547	1.412 (0.011)	0.167 (0.011)	0.181	0.147, 0.216	<0.001	0.046	0.014, 0.079	0.005	0.087	0.058, 0.116	<0.001	0.029	-0.006, 0.065	0.107
U/VI 62.5/ 25	582	1.419 (0.011)	0.173 (0.011)	0.188	0.154, 0.221	<0.001	0.059	0.023, 0.096	0.001	0.093	0.065, 0.121	<0.001	0.035	0.000, 0.071	0.048
U 125	414	1.366 (0.013)	0.121 (0.013)	0.135	0.098, 0.172	<0.001									
U 62.5	292	1.359 (0.016)	0.114 (0.016)	0.128	0.088, 0.168	<0.001									
VI 25	696	1.326 (0.010)	0.080 (0.010)	0.094	0.062, 0.127	<0.001									
TIO	303	1.383 (0.015)	0.138 (0.015)												
P	380	1.231 (0.014)	-0.014 (0.014)												
Reversible															
U/VI 125/ 25	268	1.536 (0.016)	0.290 (0.016)	0.282	0.231, 0.333	<0.001	0.097	0.051, 0.144	<0.001	0.165	0.123, 0.206	<0.001	0.188	0.131, 0.244	<0.001
U/VI 62.5/ 25	245	1.479 (0.016)	0.233 (0.016)	0.225	0.174, 0.276	<0.001	0.074	0.019, 0.129	0.008	0.108	0.066, 0.150	<0.001	0.131	0.073, 0.188	<0.001
U 125	206	1.438 (0.018)	0.193 (0.018)	0.185	0.131, 0.238	<0.001									
U 62.5	121	1.405 (0.023)	0.159 (0.023)	0.151	0.091, 0.211	<0.001									
VI 25	321	1.371 (0.014)	0.125 (0.014)	0.117	0.069, 0.166	<0.001									
TIO	105	1.348 (0.025)	0.103 (0.025)												
P	165	1.254 (0.021)	0.008 (0.021)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 977-978, 991-992, (Table 3.43)
Key: BL=baseline; **ΔBL=change from baseline; Diff=difference; U=umeclidinium**
Notes: N= ITT Population, number of patients with analyzable data for one or more time points; reversibility is to salbutamol

Smoking Status

Table 45. Trough FEV1 (L) at Day 169, Primary Efficacy Trials, ITT Population, by Smoking Status

Arm	N	BL	Δ BL	Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	LS Mean (SE)	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value	Diff.	95% CI	p-value
Former Smoker															
U/VI 125/ 25	410	1.437 (0.013)	0.193 (0.013)	0.193	0.151, 0.234	<0.001	0.064	0.026, 0.102	<0.001	0.098	0.064, 0.131	<0.001	0.045	0.004, 0.087	0.033
U/VI 62.5/ 25	446	1.431 (0.012)	0.186 (0.012)	0.186	0.145, 0.227	<0.001	0.059	0.016, 0.101	0.007	0.091	0.058, 0.124	<0.001	0.038	-0.003, 0.079	0.067
U 125	314	1.373 (0.015)	0.129 (0.015)	0.129	0.084, 0.173	<0.001									
U 62.5	209	1.372 (0.018)	0.127 (0.018)	0.127	0.079, 0.175	<0.001									
VI 25	517	1.340 (0.011)	0.095 (0.011)	0.095	0.056, 0.135	<0.001									
TIO	221	1.392 (0.017)	0.147 (0.017)												
P	259	1.245 (0.017)	0.000 (0.017)												
Current Smoker															
U/VI 125/ 25	408	1.468 (0.013)	0.224 (0.013)	0.237	0.197, 0.277	<0.001	0.065	0.027, 0.103	<0.001	0.128	0.094, 0.162	<0.001	0.118	0.075, 0.162	<0.001
U/VI 62.5/ 25	384	1.441 (0.013)	0.196 (0.013)	0.209	0.170, 0.249	<0.001	0.070	0.026, 0.113	0.002	0.100	0.066, 0.134	<0.001	0.091	0.047, 0.135	<0.001
U 125	309	1.403 (0.015)	0.159 (0.015)	0.172	0.130, 0.214	<0.001									
U 62.5	207	1.371 (0.018)	0.126 (0.018)	0.140	0.093, 0.186	<0.001									
VI 25	507	1.341 (0.012)	0.096 (0.012)	0.109	0.072, 0.147	<0.001									
TIO	193	1.350 (0.019)	0.105 (0.019)												
P	288	1.231 (0.016)	-0.013 (0.016)												

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 949-950, 963-964 (Table 3.42)
Key: BL=baseline; **ΔBL=change from baseline; Diff=difference; U=umeclidinium**
Note: N= ITT Population, number of patients with analyzable data for one or more time points

5.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Sections 3.1 and 3.2 for a discussion of the trials supporting dose selection for UMEC and VI. The totality of the phase 3 data do not suggest a clear efficacy

advantage for doses higher than UMEC/VI 62.5 mcg/25 mcg. The application puts forward only the 62.5 mcg/25 mcg dose for approval.

5.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary evidence for persistence of efficacy up to 6 months comes from the 24-week results from the primary efficacy trials, which are discussed in Sections 5.1.4 and 5.1.5.

5.1.10 Additional Efficacy Issues/Analyses

As described in Section 4.3, the clinical program included two replicate exercise endurance trials, which were randomized, double-blind, placebo-controlled, 2-period, incomplete block, and cross-over in design. Patients were randomized to one of twenty-six sequences which included of two of the following treatments: UMEC/VI 125 mcg/25 mcg once daily, UMEC/VI 62.5 mcg/25 mcg once daily, UMEC 125 mcg once daily, VI 25 mcg once daily, and placebo. Each treatment was delivered via DPI for a duration of 12 weeks. The trials prespecified two co-primary endpoints: exercise endurance time (ETT) post-dose at Week 12, and trough FEV1 at Week 12. Results for trough FEV1 are presented in Section 5.1.4 of this review, and results for ETT are provided in Table 46.

Table 46. 3-hour postdose ETT (s) at Week 12, Exercise Endurance Trials, ITT Population

Treatment Arm	N	Change	Treatment Difference from Placebo			Treatment Difference from UMEC*			Treatment Difference from VI		
		LS Mean (SE)	Difference	95% CI	p-value	Difference	95% CI	p-value	Difference	95% CI	p-value
DB2114417											
UMEC 125/25	144	69.1 (14.0)	32.4	-3.9, 68.8	0.080	19.3	-33.4, 71.9	0.472	42.4	-3.8, 88.7	0.072
UMEC 62.5/25	152	58.6 (13.8)	21.9	-14.2, 58.0	0.234	-4.6	-57.6, 48.4	0.865	31.9	-14.1, 77.9	0.174
UMEC 125	50	49.8 (23.8)	13.1	-38.9, 65.1	0.620						
UMEC 62.5	49	63.2 (23.9)	26.5	-25.9, 78.9	0.321						
VI 25	76	26.7 (19.7)	-10.0	-55.5, 35.4	0.665						
Placebo	170	36.7 (13.2)									
DB2114418											
UMEC 125/25	128	65.9 (17.5)	65.8	20.3, 111.3	0.005	-8.9	-77.8, 60.1	0.801	35.2	-22.7, 93.1	0.233
UMEC 62.5/25	130	69.5 (17.1)	69.4	24.5, 114.4	0.003	44.4	-21.8, 110.6	0.188	38.8	-18.9, 96.5	0.187

UMEC 125	41	74.8 (31.6)	74.7	6.0, 143.4	0.033						
UMEC 62.5	40	25.1 (30.2)	25.0	-41.0, 91.0	0.456						
VI 25	64	30.7 (24.8)	30.6	-26.8, 88.0	0.295						
Placebo	151	0.1 (16.7)									

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2114417, Study Report Body), pg. 594 (Table 6.06); Section 5.3.5.1 (DB2114418, Study Report Body), pg. 489 (Table 6.06)
*The comparisons are for comparable UMEC doses; i.e. UMEC/VI 125 mcg/25mcg to UMEC 125 mcg, and UMEC/VI 62.5 mcg/25 mcg to UMEC 62.5 mcg
Note: N= ITT population

Given that the Applicant is not seeking an exercise endurance claim for their proposed product, the ETT results are only briefly discussed here. Statistical significance for the co-primary endpoint of 3-hour postdose ETT at Week 12 was demonstrated only in a single trial (DB2114418). The magnitude of the effect size was consistent across the two UMEC/VI doses (65.8-69.4 s); however, the clinical relevance of these results is unclear. The Applicant notes that when these trials were planned a minimal clinically important difference (MCID) of 70 seconds and standard deviation of 114 seconds were used to calculate the required sample size, but that the expectation for MCID was revised based on a recent publication reporting a MCID of 45-85 seconds for the ESWT[22]. The 66-69 s EET observed in Trial DB2114418 does not meet the original MCID threshold identified by the Applicant, and the updated threshold of 45-85 requires further validation. Moreover, the Agency regards exercise endurance as an entity that is multi-factorial and influenced by many factors, including ones unrelated to COPD. To that extent, it is difficult to confirm that any change in exercise endurance time is solely attributable to a beneficial effect of the proposed product on the lungs.

6 Review of Safety

Safety Summary

The safety database for the proposed product consists of 17 completed trials in patients with COPD, and includes 2,454 patients treated with either UMEC/VI 62.5 mcg/25 mcg or 125 mcg/25 mcg, 1,851 patients treated with either UMEC 62.5 mcg or 125 mcg, and 2,501 patients treated with VI. Fourteen of these 17 trials had treatment periods of at least 4 weeks and a relevant UMEC/VI, UMEC, or VI arm; these 14 trials are collectively referred to as the "All COPD Clinical Studies" by the Applicant. Across the "All COPD Clinical Studies," 788 patients were treated with either UMEC/VI 62.5 mcg/25 mcg or 125 mcg/25 mcg for at least 24 weeks, and 146 treated with UMEC/VI 125 mcg/25 for at least 48 weeks. In addition, 524 patients were treated with either UMEC 62.5 mcg or

[22] Pepin V, Laviolett L, Brouillard C, et al. Significance of changes in endurance shuttle walking performance. *Thorax.* 2011;66:115-120.

125 mcg for at least 24 weeks, and 133 for at least 48 weeks. The extent of exposure was adequate for review.

Safety assessments conducted in the clinical development program include adverse event monitoring, clinical laboratory testing, vital signs, 12-lead electrocardiograms, Holter monitoring for a subset of patients, and thorough QT trials. This battery of assessments is considered appropriate for the evaluation of the proposed product.

A total of 48 deaths are reported for the seventeen COPD trials included in the UMEC/VI clinical development program. In the primary efficacy trials, the percentage of patients with fatal events is <1% across all treatment groups. In the long-term safety trial, 1, 0, and 4 deaths are reported for the placebo, UMEC/VI 125 mcg/25 mcg, and UMEC 125 mcg arms, respectively. A review of deaths by system organ class and preferred term reveals no discernible pattern in fatalities. Overall, the fatality data is notable only for the low number of events.

The overall percentage of patients with nonfatal SAEs is generally balanced across treatment arms. Nonfatal SAEs by system organ class and preferred term are also generally balanced across groups, with the exception of cardiac disorders in the primary efficacy trials, which are more common in the active treatment groups (0.5%-1.4%) compared to placebo (0.2%); however, the absolute number events is small and the pattern is not repeated in the long-term safety data.

The clinical development program prospectively identified adverse events of special interest, which included cardiovascular events, based largely on the known pharmacological effects of the two classes of drugs (LAMA and LABA) making up the combination. The Applicant's approach to evaluating cardiovascular adverse events was two-fold: an analysis of Major Adverse Cardiac Events (MACE) was conducted, along with an evaluation of cardiovascular adverse events of special interest (AESIs); these analyses represent different approaches to assessing the same safety data. In both the MACE and cardiovascular AESI analyses a numerical imbalance favoring placebo is demonstrated for events related to cardiovascular ischemia. In the MACE analysis, the imbalance is noted for narrow category of non-fatal myocardial infarction, but not the broader category of non-fatal cardiac ischemia; the imbalance in non-fatal myocardial infarction is seen across all UMEC/VI, UMEC, and VI treatment arms. In the cardiovascular AESI analysis, imbalances are noted in the primary efficacy trials, but not the long-term safety trial; these include an imbalance in the cardiac ischemia subgroup of the overall category of cardiovascular AESIs, and an imbalance in the overall category of serious cardiovascular AESIs, which appears be largely driven by events in cardiac ischemia subgroup. While these imbalances are noted, several features of the observed data decrease concern. The imbalances identified in the cardiovascular AESI analysis are for the primary efficacy trials; similar patterns are not demonstrated for the long-term safety trial. It is reasonable to expect that a signal for increased cardiac ischemia, if it represents a true risk, ought to be observed not just in

the primary efficacy trials, but also in the long-term safety trial which evaluated the higher UMEC/VI dose for a longer duration. This argument is tempered somewhat, however, by the fact that a greater percentage of patients in the UMEC/VI and UMEC treatment arms of the long-term safety trial withdrew due to abnormalities on ECGs and on 24-hour Holter monitoring compared to placebo; the safety profile of these patients after withdrawal cannot be known. Nevertheless, while small numerical imbalances were observed between the active treatment arms and placebo in the primary efficacy trials, the most notable feature of these analyses is the overall low number of events observed in the clinical development program, which is reassuring.

With regard to other supportive data, clinical laboratory analyses are notable for a small numerical increase in the percentage of patients with a creatine kinase shift to high, with the imbalance being more marked in the long-term safety trial. Creatine kinase (CK) is a nonspecific marker, and increases in CK occur with a variety of processes including muscle and cardiac diseases. The results of the analyses of vital signs, ECGs, 24-hour Holter monitoring, and thorough QT trials are unremarkable.

In conclusion, the size of the safety database and extent of exposure were adequate to permit review. While the data raise the possibility of an association between UMEC/VI and cardiovascular ischemia, concern is mitigated by both the reassuring safety profile observed in the long-term safety trial, as well by the low number of overall events.

6.1 Methods

6.1.1 Studies/Clinical Trials Used to Evaluate Safety

CLINICAL TRIALS USED TO EVALUATE SAFETY
The protocols for the primary efficacy and exercise endurance trials are discussed in detail in Section 4.3; a brief summary of the safety evaluations conducted in these trials is provided below. This is followed by a description of the protocol for the long-term safety trial.

Safety Evaluations, Primary Efficacy and Exercise Endurance Trials
Safety evaluations performed in the primary efficacy and exercise endurance trials included: vital signs, 12-lead ECGs, clinical laboratory assessments, and adverse event monitoring, which were conducting according to the schedules provided in Table 15, Table 16, and Table 17.

In addition, 24-hour Holter monitoring was conducted for a subset of approximately 13% in the placebo-controlled trials.

Long-Term Safety Trial

The administrative information and protocol for the long-term safety trial (DB2113359) is presented below.

The protocol for this trial was amended once; the summary below is based on the final version of the protocol. A description of the changes provided by the single protocol amendment follows the summary.

Administrative Information

DB2113359

- Study Title: "A 52-Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Tolerability of GSK573719 125 mcg once-daily alone and in combination with GW642444 25 mcg once-daily via novel Dry Powder Inhaler (NDPI) in Subjects with Chronic Obstructive Pulmonary Disease (COPD)."
- Study Dates: January 27, 2011 – July 23, 2012
- Study Sites: A total of 53 centers in the United States, Chile, Romania, Russian Federation, Slovakia, and South Africa
- Study Report Date: November 9, 2012

Objectives

Primary:

- To evaluate the safety and tolerability of UMEC/VI 125 mcg/25 mcg and UMEC 125 mcg compared with placebo over 52 weeks

Design

This was a randomized, double-blind, placebo-controlled, parallel-group, multicenter trial.

Treatments

Patients were randomized 2:2:1 to one of the following treatment arms:

- UMEC/VI 125 mcg/25 mcg once daily
- UMEC 125 mcg once daily
- Placebo DPI once daily

In addition, patients were provided albuterol/salbutamol for "as-needed" use.

Population

Key Inclusion Criteria:

- Outpatient
- 40 years of age or older
- Females:
    - Of non-child bearing potential – OR –

  - Of child bearing potential, with a negative pregnancy test at screening, and agreed to use contraception as per the protocol
- Diagnosis of COPD consistent ATS/ERS guidelines
- Current or former cigarette smokers with a history of ≥ 10 pack-years
- A post-albuterol/salbutamol FEV1/FVC ratio of < 0.70 and a post-albuterol/salbutamol FEV1 of ≥35% and ≤80% of predicted normal values using NHANES III reference equations at Visit 1

Key Exclusion Criteria:

- Pregnancy or lactation, either current or planned
- Current diagnosis of asthma
- Known respiratory disorders other than COPD including (but not limited to): α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or CT scan[23] with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta$_2$-agonist, lactose/milk protein or magnesium stearate
- History of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicated use of an inhaled anticholinergic
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- Lung volume reduction surgery within 12 months prior to Visit 1
- A significant abnormal ECG finding on the 12-lead ECG obtained at Visit 1
- A significant abnormal finding on 24-hour Holter monitoring at Visit 1
- Significantly abnormal screening laboratory test results at Visit 1
- Unable to withhold albuterol/salbutamol for the 4 hour period prior to spirometry testing at each trial visit
- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 47

Table 47. Prohibited medications and associated washout intervals, Long-term Safety Trial

Prohibited Medication	Washout Interval (prior to Visit 1)
Corticosteroids, depot	12 weeks
Corticosteroids, systemic oral or parenteral*	6 weeks
Antibiotics for lower respiratory tract infection#	6 weeks

[23] If no chest X-ray or CT scan was available from the 6 months prior to Visit 1, then a chest X-ray had to be obtained at Visit 1.

Cytochrome P450 3A4 strong inhibitors	6 weeks
LABA/ICS combination products, if to be discontinued completely	30 days
ICS at a dose > 1000 mcg of fluticasone propionate or equivalent@	30 days
Phosphodiesterase 4 Inhibitor	14 days
Tiotropium	14 days
Theophyllines	48 hours
Oral leukotriene inhibitors	48 hours
Oral $beta_2$-agonists, long-acting	48 hours
Inhaled LABA	48 hours
LABA/ICS combination products, if discontinuing LABA and switching to ICS only	48 hours for the LABA component
Inhaled sodium cromoglycate or nedrocromil sodium	24 hours
Oral $beta_2$-agonists, short-acting	12 hours
Inhaled short-acting $beta_2$-agonists%	4 hours
Inhaled short-acting anticholinergics^	4 hours
Inhaled short-acting anticholinergic/short-acting $beta_2$-agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359 Protocol Amendment 1), pg. 21-22 (unnumbered table)

*While exclusionary if used in the 6 weeks prior to screening (Visit 1), short-term (≤ 14 days) use of corticosteroids was permitted during the trial for the treatment of COPD exacerbations

While exclusionary if used in the 6 weeks prior to screening (Visit 1), short-term (≤ 14 days) use of antibiotics was permitted for the treatment of COPD exacerbations, lower respiratory tract infections, and non-respiratory tract infections

@Consistent use of an ICS at a dose ≤ 1000 mcg of fluticasone propionate was permitted; ICS use could not be initiated or discontinued within 30 days prior to Visit 1

%Use of trial provided albuterol/salbutamol was permitted during the trial, except in the 4 hours prior to spirometry testing

^Use of ipratropium bromide was permitted during the trial, except in the 4 hours prior to spirometry testing

- Use of oxygen therapy for greater than 12 hours a day
- Daily, prescribed use of short-acting bronchodilators via nebulizer
- Use of continuous positive pressure ventilation (CPAP), nocturnal positive pressure, or non-invasive positive pressure ventilation (NIPPV), including use for sleep apnea
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1
- A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1
- Previous use of UMEC, VI, UMEC/VI, fluticasone furoate/VI, or GSK233705/VI

Key Randomization Criteria:

- No evidence of a significantly abnormal 12-lead ECG pre-dose at Visit 2
- No COPD exacerbation or lower respiratory tract infection during run-in or at Visit 2

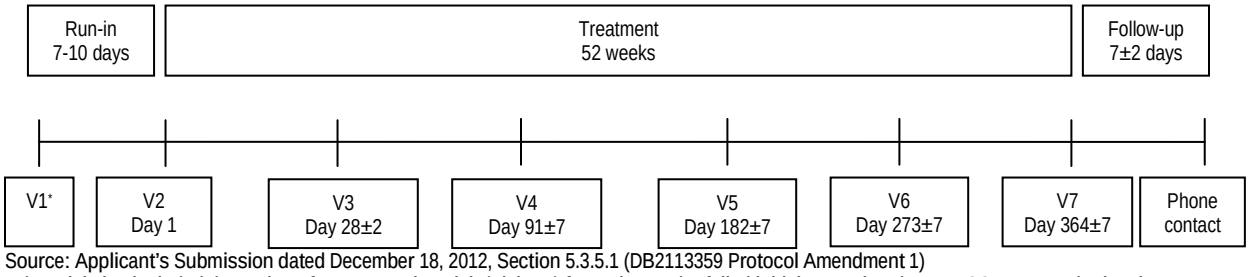
Withdrawal Criteria:

- Clinically important changes in laboratory assessments, per the Investigator's discretion
- Significant abnormal ECG finding
- Significant abnormal finding on 24-hour Holter monitoring
- Protocol-defined liver chemistry stopping criteria
- Positive urine pregnancy test

Trial Conduct

The trial consisted of a 7 to 10-day run-in period, a 52-week treatment period, and a follow-up period (approximately 7 days), with a total of 7 clinic visits and a follow-up contact by phone over the entire trial duration of approximately 54 weeks. A trial schematic is presented in Figure 23.

Figure 23. Schematic, Long-term Safety Trial



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359 Protocol Amendment 1)
* The Trial also included the option of a re-screening visit (Visit 1A) for patients who failed initial screening due to a COPD exacerbation, lower respiratory tract infection or another reason (per approval of the Applicant) during run-in or at Visit 2

Holter Monitoring:

Twenty-four hour Holter monitoring was conducted at screening (Visit 1) and during the treatment period at 3, 6, 9, and 12 months (Visits 4, 5, 6, and 7, respectively).

Spirometry:

Both pre- and post-bronchodilator spirometry was conducted at screening (Visit 1) for determination of eligibility and calculation of reversibility. Pre-dose (trough) spirometry was conducted at Visits 2-7.

Spirometry was to be conducted using equipment meeting or exceeding ATS minimal performance recommendations, with all sites using standardized equipment provided by an external vendor. For FEV1 and FVC, at least 3 (and no more than 8) acceptable

efforts were to be obtained; the largest FEV1 and FVC from the 3 acceptable efforts were to be recorded, regardless of whether they were obtained from the same effort. Spirometric assessments were to be initiated between 6:00 AM and 10:00 AM, and albuterol/salbutamol and/or ipratropium bromide was to be withheld for at least 4 hours. At Visit 1, COPD medications had to be withheld as specified in the exclusion criteria; at Visits 3 through 7, the morning dose of blinded trial drug was to be withheld. In addition, patients were to refrain from smoking and from drinking caffeinated beverages for 1 hour and 2 hours prior to testing, respectively.

COPD exacerbations:
The protocol defined COPD exacerbations as a worsening of symptoms requiring systemic corticosteroid, antibiotic, and/or hospitalization. Patients experiencing a COPD exacerbation during the treatment period were permitted to be treated with short courses (≤ 14 days) of systemic corticosteroids and/or antibiotics and to continue in the trial. COPD exacerbations were considered to be associated with the underlying disease and were not recorded as AEs unless the event met criteria necessary to be classified as a serious adverse reaction (see Section 6.1.2 of this review).

The full schedule of trial events is provided in Table 48.

Table 48. Schedule of Trial Events, Long-term Safety Trial

	Run-in		Treatment Period							Follow-up
	Visit 1 (Screening)	Visit 1A (Re-Screen)	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	EW	Phone Contact
	Day -7 to -10		Day 1	Day 28 (±2) Month 1	Day 91 (±7) Month 3	Day 182 (±7) Month 6	Day 273 (±7) Month 9	Day 364 (±7) Month 12		7±2 days after Visit 7 or EW
Informed Consent	X	X								
Demographics	X									
Medical and COPD history	X	X								
Verify Inclusion/Exclusion Criteria	X	X								
Concomitant Medication Assessment	X	X	X	X	X	X	X	X	X	
Smoking History/Status	X	X				X		X	X	
Smoking Cessation Counseling	X	X				X		X	X	
Physical Examination	X	X						X	X	
Reversibility Testing	X	X								
Chest X-ray[1]	X	X								
Verify Randomization Criteria			X							
Vital Signs	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X	X	X	X	X	X	X	X	
Holter monitor dispense	X	X			X	X	X	X		

COPD Exacerbation Assessment			X	X	X	X	X	X	X	
Spirometry	X	X	X	X	X	X	X	X		
AE Assessment			X	X	X	X	X	X	X	X
SAE Assessment	X	X	X	X	X	X	X	X	X	X
Hematology	X	X			X	X	X	X	X	
Chemistry	X	X			X	X	X	X	X	
Pharmacogenetics Sampling					X					
Pregnancy Test	X	X	X	X	X	X	X	X	X	
Collect Pregnancy Information										X
Dispense Rescue Medication as needed	X	X	X	X	X	X	X			
Collect Rescue Medication			X	X	X	X	X	X	X	
Dispense Diary Card	X	X	X	X	X	X	X			
Review/Collect Diary Card		X	X	X	X	X	X	X	X	
Dispense Investigational Product (IP)			X	X	X	X	X			
Collect IP				X	X	X	X	X	X	
Assess IP compliance[2]				X	X	X	X	X	X	
Demonstrate Proper Use of nDPI	X	X	X	X	X	X	X			

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359, Protocol Amendment 1), pg. 33-35 (Table 3)
[1] Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1; chest x-ray may be conducted after Visit 1 as long as results were reviewed prior to Visit 2
[2] Assessed by reviewing device dose counter

Endpoints

Endpoints included the following:

- Incidence of adverse events
- Incidence of COPD exacerbations
- Time to first COPD exacerbation
- Clinical laboratory tests
- Vital signs
- 12-lead ECG assessments
- Holter assessments
- Rescue mediation use
- Percentage of rescue-free days
- Trough FEV1 and FVC

Statistical Considerations

Sample Size:

The choice of sample size was chosen by the Applicant taking into account ICH guidelines and practical considerations. The Applicant set a goal of randomizing 200 patients in each of the UMEC/VI and UMEC arms, and 100 patients the placebo arm; with an anticipated maximum withdrawal rate of 40% at 52 weeks this was expected to

yield 120 patients in each active arm and 60 patients in the placebo who would have exposure data for the full year.

Analysis Population:
The primary population for all data analyses was specified to be the ITT Population, defined as all patients randomized to treatment who received at least one dose of randomized trial medication in the treatment period; patients were to be included in an analysis of a particular outcome if they provided at least one on-treatment assessment of that outcome.

Multiplicity:
No formal statistical hypothesis testing was planned for this safety trial, and so there was also no multiplicity adjustment.

Interim Analysis:
No interim analysis was planned.

Protocol Amendment
The original protocol was submitted on November 8, 2010. One protocol amendment was submitted on September 7, 2011, and is summarized below. The changes provided by this amendment are reflected in the protocol description above.

Protocol Amendment #1:
This protocol amendment clarified the protocol's time and events table, ECG withdrawal criteria, and permitted medications.

6.1.2 Categorization of Adverse Events

The following definitions were employed by the Applicant to describe adverse events reported for the UMEC/VI clinical development program:

Table 49. Applicant's Definitions of Adverse Events

Category	Abbreviation	Definition	Comments
Adverse Event	AE	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medical product.	
Serious Adverse Event	SAE	Any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, or was a congenital anomaly/birth defect.	Consistent 21 CFR § 312.32(a)

On-treatment	n/a	Events with onset on or after the date of first dose of study drug and up to 1 day after the last recorded dose of study drug	Applies to parallel-group trials
Post-treatment	n/a	Events with an onset 2 days or more after the date of the last recorded dose of study drug	Applies to parallel-group trials

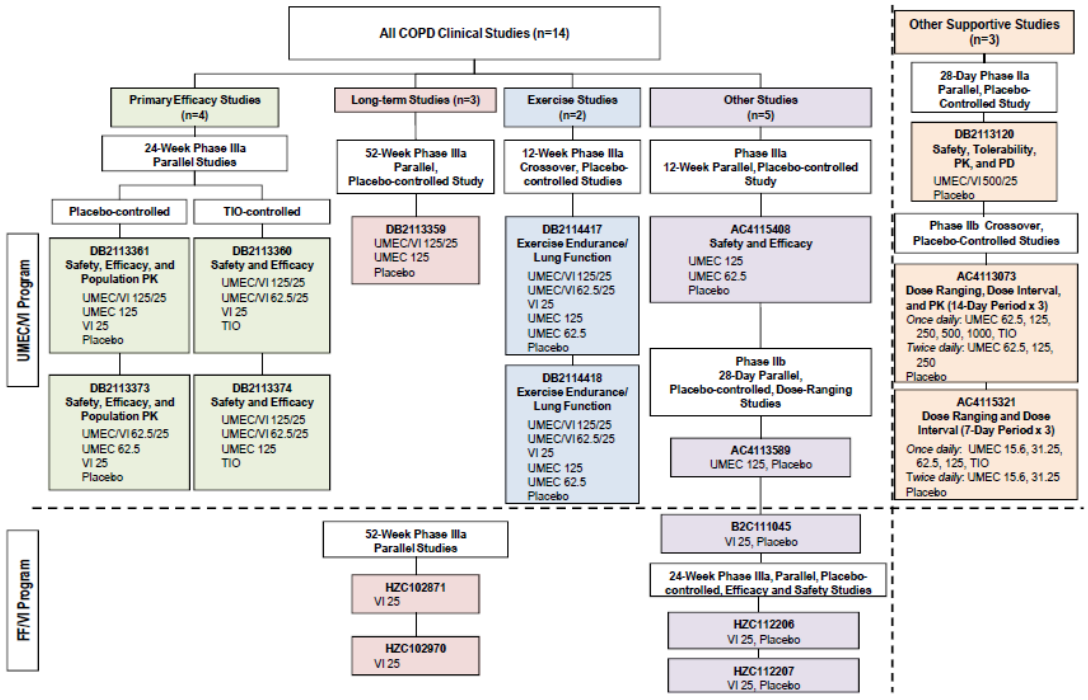
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 128-129

For all of the trials included in the core Phase 3 program, adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0. MedDRA version 15.0 was also used in the Applicant's ISS.

6.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Applicant's Integrated Summary of Safety (ISS) includes safety data from 17 completed clinical trials in patients with COPD. These trials are categorized by the Applicant into a number of groups, as depicted in Figure 24.

Figure 24. Applicant's Grouping of Trials



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 39 (Figure 1)
Note: The 14 trials included in the Applicant's "All COPD Clinical Studies" grouping had treatment periods of at least 4 weeks and a relevant UMEC/VI, UMEC, or VI arm. The 3 trials included in the Applicant's "Other Supportive Studies" grouping (DB2113120, AC4113073, and AC4115321) also evaluated COPD patients.

The focus of this clinical safety review is on the core UMEC/VI development program, which includes of the four primary efficacy trials (DB2113361, DB2113373, DB2113360, and DB2113374) and the one long-term safety trial (DB2113359). While the Applicant's approach to grouping the "primary efficacy" trials is the same as that taken by this review, their "long-term" grouping differs in that two additional trials (HZC102871 and HZC102970) are included. Trials HZC102871 and HZC102970 evaluated VI 25 mcg as part of the clinical development program for a related product, FF/VI. In this review top-line results (deaths, non-fatal SAEs) are presently separately for these trials under the moniker "FF/VI trials," along with results from trials HZC112206 and HZC112207. Top-line results from the additional trials listed in the Applicant's Figure 22 (DB2114417, DB2114418, AC4115408, AC4113589, B2C111045, DB2113120, AC4113073, and AC4115321) are presented in this review under the moniker "Other Trials." A summary of the groupings used in this review is provided in Table 50.

Table 50. Clinical Review's Grouping of Trials

Grouping	Trials
Primary Efficacy Trials	DB2113361, DB213373, DB2113360, DB2113374
Long-Term Safety Trial	DB21133459
Other Trials	DB2114417, DB2114418, AC4115408, AC4113589, B2C111045, DB2113120, AC4113073, AC4115321
FF/VI Trials	HZC102871, HZC102970, HZC112206, HZC112207

6.2 Adequacy of Safety Assessments

6.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

A summary of the extent of exposure across the clinical development program is provided in Table 51. These exposure data are organized by the trial subtypes defined for this clinical review in Table 50. The safety database for the proposed product consists of 17 completed trials in patients with COPD, and includes 2,454 patients treated with either UMEC/VI 62.5 mcg/25 mcg or 125 mcg/25 mcg, 1,851 patients treated with either UMEC 62.5 mcg or 125 mcg, and 2,501 patients treated with VI.

Table 51. Summary of Exposure, UMEC/VI Clinical Development Program

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
Primary Efficacy Trials	555	842	832	418	629	1034	423

Long-Term Safety Trial	109	N/A	226	N/A	227	N/A	N/A
Other Trials	788	282	272	252	325	241	91
FF/VI Trials	412	N/A	N/A	N/A	N/A	1226	N/A
Overall Total	1864	1124	1330	670	1181	2501	514

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 4 (Table 1)
Note: N=Number of patients in the ITT population for all trials except for AC4115408, AC4113073, and AC4115321, for which N represents the number of patients in the mITT population; patients in crossover trials are counted once under each treatment received; some trials included additional treatment arms to those shown here

The duration of exposure provided by the Applicant's "All COPD Clinical Studies" grouping of trials (i.e., the four primary efficacy trials, the long-term safety trial, and 9 additional trials as described in Figure 24) is summarized in Table 52.

Table 52. Summary of Exposure, Applicant's "All COPD Clinical Studies" Grouping of Trials

	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Exposure, days							
Mean (SD)	119 (78)	133 (49)	157 (88)	128 (51)	153 (97)	186 (113)	150 (46)
Median	110	166	167	165	166	168	167
Min, Max	1, 372	1, 177	1, 371	1, 179	1, 375	1, 384	1, 176
Range, n(%)							
> 4 weeks	1366 (83)	1066 (95)	1262 (95)	548 (95)	954 (88)	2296 (92)	395 (93)
> 8 weeks	1251 (76)	1034 (92)	1212 (91)	522 (91)	900 (83)	2153 (86)	382 (90)
> 12 weeks	1103 (67)	932 (83)	1129 (85)	450 (78)	827 (76)	2045 (82)	374 (88)
> 24 weeks	394 (24)	326 (29)	462 (35)	154 (27)	370 (34)	1147 (46)	116 (27)
> 36 weeks	73 (4)	0	160 (12)	0	154 (14)	622 (25)	0
> 48 weeks	66 (4)	0	146 (11)	0	133 (12)	590 (24)	0
> 52 weeks	19 (1)	0	37 (3)	0	35 (3)	209 (8)	0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 70 (Table 14)
Note: N=Number of patients in the ITT population

Across the "All COPD Clinical Studies," 788 patients were treated with either UMEC/VI 62.5 mcg/25 mcg or 125 mcg/25 mcg for at least 24 weeks, and 146 treated with UMEC/VI 125 mcg/25 for at least 48 weeks. In addition, 524 patients were treated with either UMEC 62.5 mcg or 125 mcg for at least 24 weeks, and 133 for at least 48 weeks. The extent of exposure was adequate for review.

The demographic, COPD disease characteristics of the ITT population from the primary efficacy trials are discussed in Section 5.1.2 (Table 18 and Table 19). These same characteristics for the ITT population from the long-term safety trial are provided in Table 53 and Table 54 below.

Table 53. Demographic and selected baseline characteristics for ITT population, long-term safety trial

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Age (years)			
Mean	60.1	61.4	61.7
SD	8.3	9.0	9.1
Min, Max	41, 82	40, 84	40, 85
Sex			
Male, n (%)	73 (67)	156 (69)	145 (64)
Race*			
White, n (%)	104 (95)	211 (93)	214 (94)
African America/ African heritage, n (%)	3 (3)	14 (6)	13 (6)
Asian, n (%)	2 (2)	1 (<1)	0
American Indian or Alaska native, n (%)	0	0	0
Native Hawaiian or other Pacific Islander, n (%)	0	0	0
Ethnicity			
Hispanic/Latino, n (%)	7 (6)	19 (8)	17 (7)
Not Hispanic/Latino, n (%)	102 (94)	207 (92)	210 (93)
Height (cm)			
Mean	169.8	168.3	168
SD	9.9	9.5	8.7
Min, Max	148, 196	143,190	143, 188
Weight (kg)			
Mean	79.7	79.0	79.0
SD	18.0	17.5	16.4
Min, Max	37, 137	36, 136	47,130
BMI (kg/m^2)			
Mean	27.7	27.9	28.1
SD	5.9	5.9	5.9
Min, Max	13.6, 43.3	16.4, 51.3	17.3, 54.6
Smoking status at Screening			
Current smoker, n (%)	71 (65)	135 (60)	148 (65)
Former smoker, n (%)	38 (35)	91 (40)	79 (35)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 48 (Table 10), pg. 49 (Table 11)
*Applicant's table includes additional subcategories for race

Table 54. COPD disease characteristics for ITT population, Long-Term Safety Trial

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
GOLD stage, n	109	224	225
I: FEV1 ≥80% predicted, n (%)	1 (<1)	0	0
II: 50%≤FEV1<80% predicted, n(%)	71 (65)	137 (61)	129 (57)
III: 30%≤FEV1<50% predicted, n (%)	37 (34)	87 (39)	96 (43)
IV: FEV1<30% predicted, n (%)	0	0	0
ICS use at Screening, n	109	226	227
ICS user, n (%)	40 (37)	80 (35)	73 (32)
ICS non-user, n (%)	69 (63)	146 (65)	154 (68)
Pre-bronchodilator	108	225	225

FEV1 (L), n			
Mean	1.579	1.498	1.432
SD	0.5714	0.5255	0.5120
Median	1.510	1.460	1.330
Min, Max	0.46, 3.28	0.44, 2.80	0.55, 3.12
Reversibility to Salbutamol, n	108	223	224
Not reversible, n (%)	72 (67)	145 (65)	152 (68)
Reversible, n (%)	36 (33)	78 (35)	72 (32)
COPD Type*, n	109	225	227
Chronic bronchitis, n (%)	74 (68)	159 (71)	162 (71)
Emphysema, n (%)	71 (65)	154 (68)	149 (66)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 52 (Table 14), pg. 51 (Table 13), pg. 50 (Table 12)
*Patients could select "chronic bronchitis," "emphysema," or both

Demographic and baseline characteristics were generally well balanced across treatment arms. As was the case with the primary efficacy trials, the majority of patients were of white race. In contrast to the primary efficacy trials, more patients in the long-term safety trial were classified as having Gold Stage II disease, fewer with Stage III, and none with Stage IV. Consistent with this, mean pre-bronchodilator FEV1 was higher in the long-term safety trial (1.4-1.6 L) compared to the primary efficacy trials (1.2-1.3). In addition, whereas the patient population in the primary efficacy trials was evenly split with regard to ICS use, in the long-term safety trial approximately two-thirds of patients were ICS non-users. Response to salbutamol was similar between the primary efficacy and long-term safety trials, with approximately one-third of each patient population demonstrating reversibility. As with the primary efficacy trials, both chronic bronchitis and emphysema were well-represented.

Past and current cormorbid conditions of the ITT population from the primary efficacy trials are discussed in Section 5.1.2 (Table 20). These same characteristics for the ITT population from the long-term safety trial are provided in (Table 55) below.

Table 55. Comorbid Conditions for ITT population, Long-Term Safety Trial

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Common Current Medical Conditions			
Any condition	88 (81)	190 (84)	196 (86)
Cardiovascular risk factors	70 (64)	151 (67)	155 (68)
Cardiac disorders	37 (34)	74 (33)	80 (35)
Musculoskeletal and connective tissue disorders	32 (29)	84 (37)	64 (28)
Metabolism and nutrition disorders	18 (17)	35 (15)	35 (15)
Psychiatric disorders	15 (14)	33 (15)	36 (16)
Vascular disorders	15 (14)	26 (12)	26 (11)
Endocrine disorders	13 (12)	26 (12)	15 (7)
Nervous system disorders	11 (10)	19 (8)	19 (8)
Common Past Medical Conditions			
Any condition	49 (45)	121 (54)	117 (52)

Cardiovascular risk factors	19 (17)	30 (13)	35 (15)
Respiratory, thoracic, and mediastinal disorders	10 (9)	33 (15)	37 (16)
Reproductive system and breast disorders	8 (7)	27 (12)	22 (10)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5 (5)	24 (11)	19 (8)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 53 (Table 15), pg. 54 (Table 16)
Note: "Common" conditions are defined as those reported in ≥ 10% of patients in any treatment group

Particular attention to the distribution of cardiovascular risk factors and cardiac disorders is warranted, as cardiovascular adverse events are discussed in detail in Section 6.3.5. Small imbalances between UMEC/VI 62.5 mcg/25 mcg and placebo and for UMEC 125 mcg and placebo are noted for current cardiovascular risk factors, but not for current cardiac disorders.

The disposition of patients participating in primary efficacy trials is discussed in Section 5.1.3 (Table 21); disposition of patients participating in the long-term safety trial is presented in Table 56 below.

Table 56. Subject Disposition, Long-Term Safety Trial

	Placebo	UMEC/VI 125/25	UMEC 125
Randomized	Number of Patients		
	109	227	227
Intent-To-Treat	Number of Patients (% of Randomized)		
	109 (100)	226 (>99)	227 (100)
Disposition	Number of Patients (% of ITT)		
Completion Status			
Completed*	66 (61)	143 (63)	133 (59)
Withdrawn	43 (39)	83 (37)	94 (41)
Primary Reason/Subreason for Withdrawal#			
Adverse event	13 (12)	17 (8)	21 (9)
Lack of Efficacy	9 (8)	1 (<1)	3 (1)
Exacerbation	4 (4)	1 (<1)	1 (<1)
Protocol deviation	2 (2)	6 (3)	6 (3)
Met protocol-defined stopping criteria	8 (7)	36 (16)	37 (16)
ECG abnormality	0	13 (6)	12 (5)
Holter abnormality	8 (7)	26 (12)	26 (11)
Lab abnormality	0	0	1 (<1)
Study closed/terminated	2 (2)	3 (1)	4 (2)
Lost to follow-up	1 (<1)	5 (2)	7 (3)
Withdrew consent	8 (7)	15 (7)	16 (7)
Patient relocated	1 (<1)	3 (1)	3 (1)
Frequency of visits	1 (<1)	0	2 (<1)
Burden of procedures	0	3 (1)	3 (1)
Other	6 (6)	9 (4)	9 (4)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 74 (Table 17); Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 195 (Table 5.01)
*A patient was considered to have completed the trial if they completed the last clinic visit excluding follow-up (Visit 7) and did not withdraw at the visit

#Patients recorded only a single primary reason for withdrawal; patients were not required to indicate a sub-reason, and were allowed to mark more than one sub-reason, if applicable

The overall percentage of patients who withdrew from the long-term safety trial was generally balanced across treatment groups (37-41%). More patients in the placebo arm withdrew due to adverse events and a lack of efficacy (including the occurrence of COPD exacerbations). In contrast, more patients in the UMEC/VI and UMEC arms withdrew as the result of meeting protocol-defined stopping criteria based on ECG and Holter monitoring results; the implications of these imbalances are discussed further in Section 6.3.5.

6.2.2 Explorations for Dose Response

The UMEC/VI clinical development program evaluated both the dose currently proposed for approval, 62.5 mcg/25 mcg, as well as a higher dose, 125 mcg/25 mcg, thereby allowing for an exploration of dose dependence for adverse events and other safety data. These analyses are embedded throughout this review of safety.

6.2.3 Special Animal and/or In Vitro Testing

The development program included an *in vitro* evaluation of hemoloytic potential in rat, dog, and human peripheral blood (WD2008/01499).

6.2.4 Routine Clinical Testing

The routine clinical testing in the primary efficacy and long-term safety trials included: serum chemistry, hematology, and 12-lead ECGs. In addition, 24-hour Holter monitoring was conducted in the placebo-controlled trials (for a subset of approximately 13% of patients), as well as in the long-term safety trial. The routine clinical testing was adequate.

6.2.5 Metabolic, Clearance, and Interaction Workup

The clinical development program contains a number of drug-drug interactions studies including DB21133950, which evaluated UMEC/VI and UMEC with verapamil; AC4110106, which evaluated UMEC in normal and poor CYP2D6 metabolizers; and HZA105548, which evaluated VI (as part of FF/VI) with ketoconazole. Clinical conclusions drawn from these studies are discussed in Section 6.5.5 of this review.

6.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The clinical development program prospectively identified adverse events of special interest (AESI), based largely on the known pharmacological effects of the two classes of drugs (LAMA and LABA) making up the combination. The AESI categories included: cardiovascular adverse events, anticholinergic events, metabolic events (i.e., effects on glucose and potassium), tremor, ocular effects, gallbladder disorders, intestinal obstruction, and lower respiratory tract infections/pneumonia. The results of these analyses are provided in Section 6.3.5.

6.3 Major Safety Results

6.3.1 Deaths

A total of 48 deaths are reported for the seventeen COPD trials included in the UMEC/VI clinical development program. A summary of deaths is provided in Table 57.

Table 57. Summary of Deaths, UMEC/VI Clinical Development Program

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials	555	842	832	418	629	1034	423
	2* (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Long-Term Safety Trial	109	--	226	--	227	--	--
	1 (<1)	--	0	--	4 (2)	--	--
Other Trials[#]	788	282	272	252	325	241	91
	0	1 (<1)	0	0	1 (<1)	0	0
FF/VI Trials	412	--	--	--	--	1226	--
	2 (<1)	--	--	--	--	16 (1)	--
Overall Total	1864	1124	1330	670	1181	2501	514
	5 (<1)	6 (<1)	1 (<1)	3 (<1)	7 (<1)	22 (<1)	2 (<1)

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 4 (Table 1), pg. 5 (Table 2); Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 150 (Table 86)
Note: N=Number of patients in the ITT population for all trials except for AC4115408, AC4113073, and AC4115321, for which N represents the number of patients in the mITT population; patients in crossover trials are counted once under each treatment received; some trials included additional treatment arms to those shown here
Note: n(%) = number (percentage) of deaths for each trial grouping
Note: This table includes both on-treatment and post-treatment deaths
*A post-treatment death reported after trial closure for a patient in the placebo group of Trial DB2113373 is not included in this count
[#]A death reported for the VI 6.25 mcg treatment group of Trial B2C111045 is not included in this table

Most notable in these data are the low overall number of events, which limits their interpretability. In the primary efficacy trials, the percentage of patients with fatal events is <1% across all treatment groups. While the percentage of deaths reported for the UMEC/VI 62.5 mcg/25 mcg treatment arm was slightly higher than that reported for placebo (0.6% vs. 0.4%), no dose-related pattern is observed, with zero deaths reported for the UMEC/VI 125 mcg/25 mcg treatment arm. In the long-term safety trial, 1, 0, and 4 deaths are reported for the placebo, UMEC/VI 125 mcg/25 mcg, and UMEC 125 mcg arms, respectively. Various numerical imbalances are noted between the monotherapy arms and placebo in both the primary efficacy and long-term safety trial; however, the absence of dose dependence (where applicable), and the lack of corresponding imbalances for the related combination products, is reassuring.

A summary of deaths, by SOC and PT, for the primary efficacy and long-term safety trials, is provided in Table 58 and Table 59, respectively.

Table 58. Summary of Deaths, by SOC and PT, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any fatal AE	2* (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Respiratory, thoracic, and mediastinal disorders							
Any event	0	2 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
COPD	0	2 (<1)	0	1 (<1)	0	2 (<1)	0
Acute respiratory failure	0	0	0	1 (<1)	0	0	0
Respiratory arrest	0	0	0	0	0	0	1 (<1)
Respiratory failure	0	1 (<1)	0	0	0	0	0
Cardiac disorders							
Any event	0	2 (<1)	0	0	0	2 (<1)	0
Acute myocardial infarction	0	0	0	0	0	1 (<1)	0
Cardiac arrest	0	1 (<1)	0	0	0	0	0
Cardiac failure acute	0	0	0	0	0	1 (<1)	0
Myocardial infarction	0	1 (<1)	0	0	0	0	0
General disorders and administration site conditions							
Any event	0	1 (<1)	0	1 (<1)	0	1 (<1)	0

Sudden death	0	0	0	1 (<1)	0	1 (<1)	0
Death	0	1 (<1)	0	0	0	0	0
Neoplasms benign, malignant and unspecified							
Any event	0	0	0	0	2 (<1)	1 (<1)	0
Metastases to bone	0	0	0	0	1 (<1)	1 (<1)	0
Lung neoplasm malignant	0	0	0	0	0	1 (<1)	0
Metastases to CNS	0	0	0	0	1 (<1)	0	0
Non-small cell lung cancer	0	0	0	0	1 (<1)	0	0
Pancreatic carcinoma metastatic	0	0	0	0	1 (<1)	0	0
Gastrointestinal disorders							
Any event	0	0	1 (<1)	0	0	0	1 (<1)
Upper GI hemorrhage	0	0	1 (<1)	0	0	0	1 (<1)
Infections and infestations							
Any event	1 (<1)	0	0	1 (<1)	0	0	0
Peritonitis	0	0	0	1 (<1)	0	0	0
Pneumonia	1 (<1)	0	0	0	0	0	0
Hepatobiliary disorders							
Any event	0	0	0	1 (<1)	0	0	0
Cholecystitis	0	0	0	1 (<1)	0	0	0
Nervous system disorders							
Any event	0	1 (<1)	0	0	0	0	0
Hemorrhagic stroke	0	1 (<1)	0	0	0	0	0
Renal and urinary disorders							
Any event	0	0	0	0	0	1 (<1)	0
Renal failure acute	0	0	0	0	0	1 (<1)	0
Vascular disorders							
Any event	1 (<1)	0	0	0	0	0	0
Arteriosclerosis	1 (<1)	0	0	0	0	0	0

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 1-2 (Table 88A)
Abbreviations: AE(s)=adverse event(s); CNS=central nervous system; COPD=chronic obstructive pulmonary disease; GI=gastrointestinal
Note: This table includes both on-treatment and post-treatment deaths
* A post-treatment death reported after trial closure for a patient in the placebo group of Trial DB2113373 is not included in this count

Table 59. Summary of Deaths, by SOC and PT, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Any fatal AE	1 (<1)	0	4 (2)
Cardiac disorders			
Any event	1 (<1)	0	1 (<1)
Cardiac failure acute	0	0	1 (<1)
Coronary artery insufficiency	1 (<1)	0	0
Neoplasms benign, malignant and unspecified			
Any event	0	0	2 <1)
Metastases to spine	0	0	1 (<1)
Metastases to liver	0	0	1 (<1)
Infections and infestations			
Any event	0	0	1 (<1)
Pneumonia	0	0	1 (<1)

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 3 (Table 90A)
Abbreviations: AE(s)=adverse event(s)
Note: This table includes both on-treatment and post-treatment deaths

Across the primary efficacy and long-term safety trials, the only PT reported more than once per treatment arm as a fatal AE was "COPD" (n=2 for each of the UMEC/VI 62.5 mcg/25 mcg and VI groups). No patterns in fatalities are discernible from these data.

Adjudication of Deaths

The Applicant enlisted an external, independent, blinded committee to conduct an adjudication of fatal cases. The adjudication committee was charged with designating the primary cause of death, selecting a subcategory corresponding to the primary cause, and assessing whether the death was associated with the patient's known COPD. The primary and subcategories used in the adjudication are provided in Table 60; the results of the adjudication for the primary efficacy trials and the long-term safety trial follow in Table 61 and Table 62.

Table 60. Categories for Assignment of Cause of Death for Adjudicated Fatal AEs

Primary Cause of Death	Subcategory
Cardiovascular	Sudden death Myocardial infarction/ischemic heart disease Congestive heart failure Stroke

	Hemorrhagic Thromboembolic Indeterminate Other cardiovascular cause
Respiratory	COPD exacerbation With evidence of pneumonia Without evidence of pneumonia Pneumonia/respiratory tract infection without COPD exacerbation Asthma associated Pulmonary embolism Other respiratory cause
Cancer	Lung Breast Colorectal Unknown primary Other cancer cause
Other	N/A
Unknown	Inadequate information Indeterminate

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 176 (Table 98)

Table 61. Adjudicated Fatal Serious Adverse Reports, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any fatal AE	3* (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Cardiovascular Total	1 (<1)	2 (<1)	0	0	0	2 (<1)	0
Sudden death	1 (<1)	1 (<1)	0	0	0	0	0
Myocardial infarction/ ischemic heart disease	0	0	0	0	0	1 (<1)	0
Congestive heart failure	0	0	0	0	0	1 (<1)	0
Stroke - hemorrhagic	0	1 (<1)	0	0	0	0	0
Respiratory Total	1 (<1)	2 (<1)	0	1(<1)	0	1 (<1)	0
COPD exacerbation without pneumonia	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
Cancer Total	0	0	0	0	2 (<1)	1 (<1)	0
Lung cancer	0	0	0	0	1 (<1)	0	0
Unknown primary	0	0	0	0	0	1 (<1)	0
Other cancer	0	0	0	0	1 (<1)	0	0

Other Total	0	0	1 (<1)	1 (<1)	0	0	1 (<1)
Unknown Total	1 (<1)	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
Inadequate information	1 (<1)	1 (<1)	0	1 (<1)	0	0	0
Indeterminate	0	0	0	0	0	2 (<1)	1 (<1)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 177 (Table 99)
* One post-treatment death (Trial DB2113373, Patient 2441) was reported after trial closure; this patient was not included in the clinical database, but the case was adjudicated. For this reason, the totals for fatal AEs in the placebo group in this table and in Tables 57 and 58 do not match.
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease
Note: This table includes both on-treatment and post-treatment deaths

Table 62. Adjudicated Fatal Serious Adverse Reports, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Any fatal AE	1 (<1)	0	4 (2)
Cardiovascular Total	1 (<1)	0	1 (<1)
Myocardial infarction/ ischemic heart disease	1 (<1)	0	0
Congestive heart failure	0	0	1 (<1)
Respiratory Total	0	0	1 (<1)
COPD exacerbation with pneumonia	0	0	1 (<1)
Cancer Total	0	0	3 (1)
Unknown primary	0	0	3 (1)
Other Total	0	0	0
Unknown Total	0	0	0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 178 (Table 100)
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease

As was described for the analysis of fatal events by preferred terms, the adjudicated analysis of fatal events for both the primary efficacy and the long-term safety trials is notable only for the low overall number of events.

6.3.2 Nonfatal Serious Adverse Events

A summary of nonfatal serious adverse events (SAEs) is provided in Table 63.

Table 63. Summary of Nonfatal Serious Adverse Events, UMEC/VI Clinical Development Program

	Placebo	UMEC/VI	UMEC/VI	UMEC	UMEC	VI	TIO

		62.5/25	125/25	62.5	125	25	
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials	555	842	832	418	629	1034	423
	24 (4)	47 (6)	43 (5)	27 (6)	35 (6)	54 (5)	20 (5)
Long-Term Safety Trial	109	--	226	--	227	--	--
	7 (6)	--	14 (6)	--	15 (7)	--	--
Other Trials	788	282	272	252	325	241	91
	11 (1)	6 (2)	9 (3)	2 (<1)	6 (2)	9 (4)	0
FF/VI Trials	412	--	--	--	--	1226	--
	20 (5)	--	--	--	--	147 (12)	--
Overall Total	1864	1124	1330	670	1181	2501	514
	62 (3)	53 (5)	66 (5)	29 (4)	56 (5)	210 (8)	20 (4)

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 4 (Table 1), pg. 5 (Table 3)
Note: N=Number of patients in the ITT population for all trials except for AC4115408, AC4113073, and AC4115321, for which N represents the number of patients in the mITT population; patients in crossover trials are counted once under each treatment received; some trials included additional treatment arms to those shown here
Note: n(%) = number (percentage) of deaths for each trial grouping
Note: This table includes on-treatment events

The percentage of patients with nonfatal SAEs was generally balanced across treatment arms, with the exception of a higher rate for the VI monotherapy in the "Other" and "FF/VI" trial groupings.

A summary of nonfatal SAEs reported for 2 or more patients in any treatment arm in the primary efficacy and long-term safety trials, by SOC and PT, is provided in Table 64 and Table 65, respectively.

Table 64. Nonfatal SAE PTs Reported for ≥ 2 Patients in any Treatment Arm, by SOC and PT, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any non-fatal SAE	24 (4)	47 (6)	43 (5)	27 (6)	35 (6)	54 (5)	20 (5)
Respiratory, thoracic, and mediastinal disorders							
Any event	13 (2)	18 (2)	16 (2)	12 (3)	8 (1)	15 (1)	4 (<1)
COPD	11 (2)	18 (2)	14 (2)	11 (3)	6 (<1)	11 (1)	4 (<1)
Respiratory failure	0	2 (<1)	0	1 (<1)	0	0	0
Pleurisy	0	0	0	0	0	2 (<1)	0
Infections and							

infestations							
Any event	3 (<1)	13 (2)	10 (1)	4 (<1)	6 (<1)	10 (<1)	7 (2)
Pneumonia	3 (<1)	4 (<1)	6 (<1)	0	4 (<1)	2 (<1)	4 (<1)
Infective exacerbation of chronic airways disease	0	2 (<1)	0	2 (<1)	0	1 (<1)	0
Bronchitis	0	3 (<1)	0	0	0	1 (<1)	0
Cardiac disorders							
Any event	1 (<1)	5 (<1)	4 (<1)	6 (1)	7 (1)	8 (<1)	0
Atrial fibrillation	0	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)	0
Coronary artery disease	0	0	2 (<1)	2 (<1)	0	1 (<1)	0
Myocardial infarction	0	2 (<1)	1 (<1)	0	1 (<1)	0	0
Acute myocardial infarction	0	0	0	0	1 (<1)	2 (<1)	0
Ventricular extrasystoles	0	0	0	0	2 (<1)	0	0
Gastrointestinal disorders							
Any event	5 (<1)	2 (<1)	2 (<1)	3 (<1)	1 (<1)	10 (<1)	1 (<1)
Lower gastrointestinal hemorrhage	0	0	0	0	0	2 (<1)	0
Injury, poisoning and procedural complications							
Any event	0	4 (<1)	6 (<1)	1 (<1)	4 (<1)	4 (<1)	2 (<1)
Meniscus lesion	0	2 (<1)	0	0	0	0	0
Neoplasms benign, malignant and unspecified							
Any event	3 (<1)	4 (<1)	5 (<1)	0	3 (<1)	1 (<1)	3 (<1)
Lung neoplasm malignant	0	1 (<1)	2 (<1)	0	0	0	0
Prostate cancer	0	0	2 (<1)	0	0	0	0
Nervous system disorders							
Any event	2 (<1)	0	3 (<1)	2 (<1)	1 (<1)	6 (<1)	2 (<1)
Syncope	0	0	1 (<1)	1 (<1)	0	2 (<1)	1 (<1)
Cerebrovascular accident	1 (<1)	0	0	0	1 (<1)	2 (<1)	0
General disorders and							

administration site conditions							
Any event	0	1 (<1)	0	0	3 (<1)	1 (<1)	2 (<1)
Chest pain	0	1 (<1)	0	0	2 (<1)	0	0
Non-cardiac chest pain	0	0	0	0	0	0	2 (<1)
Hepatobiliary disorders							
Any event	0	2 (<1)	0	2 (<1)	0	2 (<1)	0
Cholecystitis chronic	0	0	0	2 (<1)	0	0	0

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 6-10 (Table 4)
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease
Note: This table includes on-treatment events

Table 65. Nonfatal SAE PTs Reported for ≥ 2 Patients in any Treatment Arm, by SOC and PT, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Any nonfatal SAE	7 (6)	14 (6)	15 (7)
Respiratory, thoracic and mediastinal disorders			
Any event	4 (4)	3 (1)	5 (2)
COPD	3 (3)	2 (<1)	4 (2)
Cardiac disorders			
Any event	2 (2)	3 (1)	4 (2)
Coronary artery disease	1 (<1)	2 (<1)	1 (<1)
Infections and infestations			
Any event	0	1 (<1)	6 (3)
Pneumonia	0	0	2 (<1)
Urinary tract infection	0	0	2 (<1)

Source: Applicant's Submission dated April 26, 2013, Section 1.11.3 (Efficacy Information Amendment), pg. 11-12 (Table 5)
Abbreviations: AE(s)=adverse event(s)
Note: This table includes on-treatment events

In the primary efficacy and long-term safety trials, PTs reported as nonfatal SAEs were generally balanced across treatment groups. In the primary efficacy trial, the PT most commonly reported as a nonfatal SAE was COPD; these events were evenly distributed between the placebo and UMEC/VI groups. Most other PTs in either the primary efficacy or long-term safety trials were reported for only 2 patients or fewer. Imbalances

in cardiac disorders between the active treatment groups (0.5-1.4%) and placebo (0.2%) are noted for the primary efficacy trials, but the absolute number of events is small and this pattern is not repeated in the long-term safety data. A detailed analysis of cardiovascular adverse events of special interest is provided in Section 6.3.5 of this review.

Adjudication of Nonfatal SAEs

An adjudication of nonfatal SAEs was conducted in addition to the adjudication of deaths. A primary and subcategory was designated for each event; the categories used were the same as those described for the fatal events in Table 60, with the exception of cancer and sudden death, which were both omitted from the nonfatal SAE analysis. Results of the adjudicated analysis of nonfatal SAEs for the primary efficacy trials and the long-term safety trial are provided in Table 66 and Table 67, respectively.

Table 66. Adjudicated Nonfatal SAEs, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any nonfatal SAE	25 (5)	49 (6)	45 (5)	27 (6)	37 (6)	57 (6)	20 (5)
Cardiovascular Total	2 (<1)	7 (<1)	8 (<1)	4 (<1)	11 (2)	13 (1)	2 (<1)
Myocardial infarction/ ischemic heart disease	0	5 (<1)	3 (<1)	3 (<1)	4 (<1)	5 (<1)	0
Congestive heart failure	0	0	0	0	1 (<1)	1 (<1)	0
Stroke – any type	1 (<1)	0	0	0	1 (<1)	2 (<1)	0
Thromboembolic	1 (<1)	0	0	0	0	1 (<1)	0
Indeterminate	0	0	0	0	1 (<1)	1 (<1)	0
Other cardiovascular	1 (<1)	2 (<1)	5 (<1)	1 (<1)	5 (<1)	5 (<1)	2 (<1)
Respiratory Total	13 (2)	27 (3)	20 (2)	13 (3)	10 (2)	22 (2)	9 (2)
COPD exacerbation with pneumonia	3 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)	1 (<1)	2 (<1)
COPD exacerbation without pneumonia	9 (2)	21 (2)	13 (2)	12 (3)	4 (<1)	15 (1)	3 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	4 (<1)	2 (<1)	0	1 (<1)	4 (<1)	3 (<1)
Pulmonary embolism	0	0	0	0	1 (<1)	1 (<1)	0
Other respiratory	2 (<1)	1 (<1)	3 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Other Total	10 (2)	16 (2)	20 (2)	12 (3)	16 (3)	22 (2)	9 (2)
Unknown Total	1 (<1)	0	1 (<1)	0	0	1 (<1)	0
Inadequate information	0	0	1 (<1)	0	0	0	0

Indeterminate	1 (<1)	0	0	0	0	1 (<1)	0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 185 (Table 104)
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease
Note: This table includes both on-treatment and post-treatment events

Table 67. Adjudicated Non-Fatal SAEs, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Any non-fatal SAE	7 (6)	14 (6)	15 (7)
Cardiovascular Total	2 (2)	3 (1)	3 (1)
Myocardial infarction/ ischemic heart disease	1 (<1)	2 (<1)	2 (<1)
Congestive heart failure	1 (<1)	0	0
Other cardiovascular	1 (<1)	1 (<1)	1 (<1)
Respiratory Total	3 (3)	4 (2)	5 (2)
COPD exacerbation with pneumonia	0	0	1 (<1)
COPD exacerbation without pneumonia	3 (3)	2(<1)	2 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	1 (<1)	1 (<1)
Other respiratory	0	1 (<1)	1 (<1)
Other Total	2 (2)	7 (3)	7 (3)
Unknown Total	1 (<1)	0	0
Indeterminate	1 (<1)	0	0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 186 (Table 105)
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease
Note: This table includes both on-treatment and post-treatment events

In general, adjudicated nonfatal SAEs were balanced across treatment arms in the primary efficacy trials, with the exception of the imbalances in the overall count of cardiovascular events, most notably for UMEC 125 mcg compared to placebo. Imbalances in myocardial infarction/ischemic heart disease between the active treatment groups (0.4-0.7%) and placebo (0 events) are also noted. These patterns are not repeated in the long-term safety data. A detailed analysis of cardiovascular adverse events of special interest is provided in Section 6.3.5 of this review.

6.3.3 Dropouts and/or Discontinuations

A summary of adverse events leading to dropout (defined as the discontinuation of study treatment or withdrawal from the study) is provided in Table 68. Adverse events leading to dropout reported for three or more patients (in any treatment arm) are presented in Table 69 and Table 70 for the primary efficacy and long-term safety trials, respectively.

Table 68. Summary of Adverse Events Leading to Dropout, UMEC/VI Clinical Development Program

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Primary Efficacy Trials	555	842	832	418	629	1034	423
	26 (5)	50 (6)	47 (6)	31 (7)	41 (7)	59 (6)	20 (5)
Long-Term Safety Trial	109	--	226	--	227	--	--
	12 (11)	--	17 (8)	--	20 (9)	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 1658 (Table 2.36); Section 5.3.5.1 (DB2113359), pg. 582 (Table 7.13)
Note: Dropout is defined as discontinuation of study treatment or withdrawal from the study
Note: N=Number of patients in the ITT population
Note: n(%) = number (percentage) of AEs leading to Dropout for each trial grouping

Table 69. Adverse Events Leading to Dropout Reported for ≥ 3 Patients in any Treatment Arm, by SOC and PT, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE leading to dropout	26 (5)	50 (6)	47 (6)	31 (7)	41 (7)	59 (6)	20 (5)
Respiratory, thoracic, and mediastinal disorders							
Any event	16 (3)	20 (2)	16 (2)	14 (3)	10 (2)	17 (2)	5 (1)
COPD	14 (3)	19 (2)	14 (2)	11 (3)	8 (1)	13 (1)	4 (<1)
Dyspnea	1 (<1)	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)	0
Respiratory failure	0	3 (<1)	0	1 (<1)	0	0	0
Infections and infestations							
Any event	5 (<1)	17 (2)	14 (2)	7 (2)	10 (2)	10 (<1)	10 (2)
Pneumonia	4 (<1)	5 (<1)	7 (<1)	1 (<1)	6 (<1)	4 (<1)	5 (1)

Upper respiratory tract infection	0	1 (<1)	3 (<1)	2 (<1)	0	3 (<1)	1 (<1)
Lower respiratory tract infection	0	3 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)
Bronchitis	0	4 (<1)	0	0	0	1 (<1)	0
Cardiac disorders							
Any event	2 (<1)	5 (<1)	4 (<1)	8 (2)	6 (<1)	13 (1)	1 (<1)
Tachycardia	1 (<1)	0	0	3 (<1)	1 (<1)	1 (<1)	0
Ventricular tachycardia	0	1 (<1)	0	1 (<1)	0	3 (<1)	0
General disorders and administration site conditions							
Any event	0	3 (<1)	0	2 (<1)	8 (1)	3 (<1)	2 (<1)
Chest pain	0	1 (<1)	0	0	3 (<1)	1 (<1)	1 (<1)
Chest discomfort	0	0	0	0	3 (<1)	0	0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 1658-1666 (Table 2.36)
Note: Dropout is defined as discontinuation of study treatment or withdrawal from the study
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease

Table 70. Adverse Events Leading to Dropout Reported for ≥ 3 Patients in any Treatment Arm, by SOC and PT, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Any AE leading to dropout	12 (11)	17 (8)	20 (9)
Cardiac disorders			
Any event	8 (7)	9 (4)	12 (5)
Ventricular extrasystoles	1 (<1)	1 (<1)	4 (2)
Supraventricular tachycardia	1 (<1)	1 (<1)	3 (1)
Sinus tachycardia	1 (<1)	0	3 (1)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 582-583 (Table 7.13)
Note: Dropout is defined as discontinuation of study treatment or withdrawal from the study
Abbreviations: AE(s)=adverse event(s)

The overall percentage of patients with any AE leading to dropout is generally balanced across treatment groups in both the primary efficacy and long-term safety trials. In the primary efficacy trials, COPD and pneumonia are the most commonly reported AEs leading to dropout; similar percentages of patients in the placebo and UMEC/VI treatment arms withdrew as a result of these events. A numerical imbalance favoring

placebo compared to UMEC/VI is observed for the infections and infestations SOC, and appears to be driven by upper and lower respiratory tract infections as well as bronchitis, but not pneumonia. Pneumonia is reviewed as an adverse event of special interest (AESI) in Section 6.3.5 of this review. Imbalances in the overall category of cardiac disorders between the monotherapy arms (1.0-1.9%) and placebo (0.4%) are noted for the primary efficacy trials; the percentage of patients was similar between the combination arms (0.5-0.6%) and placebo. A detailed analysis of cardiovascular adverse events of special interest is provided in Section 6.3.5 of this review. Overall, most PTs in either the primary efficacy or long-term safety trials were reported for only 3 patients or fewer.

6.3.4 Significant Adverse Events

Adverse events leading to dropout are discussed in Section 6.3.3. There were no events leading to dose reduction, as dose reduction was not performed in the primary efficacy and long-term safety trials. The overall incidence of adverse events by severity, for the primary efficacy and long-term safety trials, is not provided in the submission. Adverse events of special interest are discussed in Section 6.3.5.

6.3.5 Submission Specific Primary Safety Concerns

The clinical development program prospectively identified adverse events of special interest (AESI), based in part on the known pharmacological effects of the two classes of drugs (LAMA and LABA) making up the combination. The AESI categories included: cardiovascular adverse events, anticholinergic events, metabolic events (i.e., effects on glucose and potassium), tremor, ocular effects, gallbladder disorders, intestinal obstruction, and lower respiratory tract infections/pneumonia. Each of these categories is discussed in turn below.

Cardiovascular Adverse Events

The Applicant's approach to evaluating cardiovascular adverse events was two-fold: an analysis of Major Adverse Cardiac Events (MACE) was conducted, along with an evaluation of cardiovascular AESIs.

MACE Analysis

The Applicant conducted two MACE analyses, one using a "broad" definition for MACE, and one based on a more restricted "narrow" set of criteria; the latter used the preferred terms of "myocardial ischemia" and "acute myocardial infarction" in place of the larger cardiac ischemic special interest AE subgroup. These two sets of criteria are described in Table 71.

Table 71. Applicant's MACE criteria

	Broad Criteria	Narrow Criteria
Ischemia/Infarction	Cardiac Ischemia Special Interest AE Subgroup • Myocardial Infarction SMQ (excluding fatalities) • Other Ischemic Heart Disease SMQ (excluding fatalities)	Myocardial ischemia PT Acute myocardial infarction PT
Stroke	Stroke Special Interest AE Subgroup • CNS Hemorrhages and Cerebrovascular Conditions SMQ (excluding fatalities)	Stroke Special Interest AE Subgroup • CNS Hemorrhages and Cerebrovascular Conditions SMQ (excluding fatalities)
Cardiovascular Death	Adjudicated Cardiovascular Deaths	Adjudicated Cardiovascular Deaths

The Applicant's MACE analyses were conducted using a pooled ITT population from trials evaluating UMEC/VI or UMEC with a treatment duration of at least 12 weeks: the four primary efficacy trials, the long-term safety trial, the two exercise endurance trials, and Trial AC4115408. Results from these analyses are presented in Table 72.

Table 72. MACE Analyses, Trials DB2113361, DB2113373, DB2113360, DB2113374, DB2114417, DB2114418, DB2113359, AC4115408, ITT Population

	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
Incidence	Number (%) of Subjects						
Broad-definition MACE	20 (2)	15 (1)	22 (2)	9 (2)	14 (1)	17 (1)	6 (1)
Narrow-definition MACE	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 AESI	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 AESI	4 (<1)	0	3 (<1)	1 (<1)	2 (<1)	4 (<1)	1 (<1)
Incidence Rate	Number of Subjects with Events per 1000 Subject-Years						
Broad-definition MACE	54.3	36.8	38.4	44.5	31.2	38.5	34.7
Narrow-definition MACE	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Adjudicated CV death	5.4	4.9	0	0	2.2	4.5	0
Non-fatal cardiac ischemia AESI	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 AESI	10.9	0	5.2	4.9	4.5	9.1	5.8
Total Number of MACE	Number of Events						

Events							
Total broad-definition MACE Events	22	16	22	11	15	18	6
Total narrow-definition MACE Events	8	5	6	2	7	8	1

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 241 (Table 138)
Key: CV=cardiovascular; MACE=Major Adverse Cardiac Events; MI=myocardial infarction; SY=subject-years
Note: Incidence rate calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Given that the duration of treatment varied across the trials included in the above MACE analyses, this review focuses on results for incidence rate, which takes into account duration of exposure. The overall incidence rate for MACE, using both the broad and narrow definitions, is higher for the placebo arm compared to both doses of UMEC/VI; it is also higher for placebo compared to both doses of UMEC, VI (the incidence rate for the narrow definition is only slightly higher for placebo vs. VI), and TIO. The incidence rate for adjudicated cardiovascular death is similar across the placebo, UMEC/VI 62.5 mcg/25 mcg, and VI arms and higher for placebo compared to UMEC 125 mcg; there were no adjudicated cardiovascular deaths in the UMEC/VI 125 mcg/25 mcg, UMEC 62.5 mcg, and TIO arms. The incidence rate for non-fatal stroke AESI was higher for placebo compared to both doses of UMEC/VI (with no events for UMEC/VI 62.5 mcg/25 mcg), both doses of UMEC, and TIO; the incidence rate for non-fatal stroke AESI was comparable between placebo and VI.

With regard to cardiac ischemia, while the overall incidence rate for broad category of non-fatal cardiac ischemia was either higher for placebo compared to the other arms (both doses of UMEC/VI, UMEC 125 mcg, VI and TIO) or comparable (UMEC 62.5 mcg), an imbalance favoring placebo is observed for the narrow category of non-fatal myocardial infarction. This imbalance is true for each treatment arm compared to placebo, with incidence rates of 8.9, 7.4, 6.2, 4.9, 4.5, and 2.7 for the UMEC 125 mcg, UMEC/VI 62.5 mcg/25 mcg, UMEC 125 mcg/25 mcg, UMEC 62.5 mcg, VI, and placebo arms, respectively. There were no non-fatal myocardial infarction events for the TIO treatment arm. Most notable, however, is the low absolute number of non-fatal MI events across all treatment arms.

Cardiovascular AESIs

In addition to the MACE analyses, the Applicant's evaluation of cardiovascular adverse events included an assessment of prespecified cardiovascular adverse events of special interest (AESI). The subgroups and terms included in the Applicant's cardiovascular AESI are described in Table 73.

Table 73. Cardiovascular AESI: Subgroups and Terms

Subgroup	Terms
Acquired Long QT	PTs: conduction disorder

	electrocardiogram QT prolonged long QT syndrome
Cardiac Arrhythmia	Cardiac Arrhythmias SMQ
Cardiac Failure	Cardiac Failure SMQ
Cardiac Ischemia	Myocardial Infarction SMQ Other Ischemic Heart Disease SMQ
Hypertension	Hypertension SMQ
Sudden Death	PTs: Sudden cardiac death Sudden death Cardiac arrest Cardio-respiratory arrest Cardiac death
Stroke	CNS hemorrhages and cerebrovascular SMQ

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 194 (Table 110)

The Applicant's cardiovascular AESI analysis was conducted for the ITT populations from the primary efficacy trials, long-term safety trial, exercise endurance trials, and the Applicants "All COPD" grouping of trials (see Figure 24). The overall incidence and exposure-adjusted frequency for on-treatment cardiovascular AESIs, by trial grouping, are presented in Table 74.

Table 74. Cardiovascular AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	40 (7)	70 (8)	55 (7)	41 (10)	52 (8)	95 (9)	27 (6)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	25 (23)	--	34 (15)	--	49 (22)	--	--
Exercise	N=321	N=282	N=272	N=89	N=91	N=140	--
	8 (2)	7 (2)	10 (4)	2 (2)	1 (1)	6 (4)	--
All COPD	N=1637	N=1124	N=1330	N=576	N=1087	N=2501	N=423
	129 (8)	77 (7)	99 (7)	45 (8)	107 (10)	243 (10)	27 (6)
Exposure-adjusted frequency	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
	192.7	202.4	163.6	244.2	208.9	231.0	156.0
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	311.0	--	192.6	--	293.1	--	--
Exercise	SY=68	SY=62	SY=60	SY=20	SY=19	SY=30	--
	117.0	112.7	166.9	100.8	51.7	199.5	--
All COPD	SY=535	SY=408	SY=573	SY=202	SY=454	SY=1271	SY=173
	241.2	188.7	172.9	222.4	235.5	191.2	156.0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 196 (Table 111); Section 5.3.5.1 (DB2113359), pg. 584 (Table 7.14)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Focusing on exposure-adjusted frequency, the results for the primary efficacy trials are mixed: the frequency is generally comparable between the combinations and placebo, but higher for the VI and the UMEC 62.5 monotherapy compared to placebo. In the long-term safety trial the exposure-adjusted frequency is lower for the UMEV/VI arm and UMEC arms compared to placebo. In the exercise trials an imbalance favoring placebo is seen for the higher dose of the combination, but not the lower; there is also an imbalance for VI compared to placebo, but not for either of the UMEC monotherapy arms. For the Applicant's broad grouping of "all COPD" trials, the exposure-adjusted frequency for the placebo arm exceeds that for either of the UMEC/VI arms, and is higher or comparable to the UMEC and VI monotherapy arms.

Given the broad nature of the various types of events included in the overall cardiovascular AESI, it is useful to examine these data by AESI subgroup. Results for the primary efficacy and long-term safety trials are presented in Table 75 and Table 76, respectively.

Table 75. Cardiovascular AESIs (On-treatment) by Subgroup, Primary Efficacy Trials, ITT Population

	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
Incidence	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)
Exposure-adjusted frequency	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: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 197 (Table 113)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Table 76. Cardiovascular AESIs (On-treatment) by Subgroup, Long-term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227

	SY=80	SY=177	SY=167
Incidence	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)
Exposure-adjusted frequency	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: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 217 (Table 123)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Focusing on exposure-adjusted frequency, in the primary efficacy trials the results for the comparison between the combination products and placebo demonstrate imbalances favoring placebo for acquired long QT, cardiac ischemia, and hypertension. With regard to the acquired long QT imbalance, the low number of observed events and the results of the dedicated QT trials (see Section 6.4.4), is reassuring. The imbalance (compared to placebo) in cardiac ischemia events is similar for the two UMEC/VI doses; serious ischemic events are discussed further below. Regarding the hypertension subgroup of cardiovascular AESIs, there is no dose response observed for the combination arms, but a consistent imbalance favoring placebo is noted for the monotherapies; mean change in blood pressure is discussed in Section 6.4.3. In the long-term safety trial, no imbalances favoring placebo are observed for the UMEC/VI 125 mcg/25 mcg arm; imbalances in several subgroups (cardiac arrhythmias, cardiac failure, and stroke) are observed for the UMEC 125 mcg monotherapy.

Serious Cardiovascular AESIs

The overall incidence and exposure-adjusted frequency of serious on-treatment cardiovascular AESIs observed in the primary efficacy and long-term safety trial is provided in Table 77.

Table 77. Serious Cardiovascular AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	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)	--	--

Exposure-adjusted frequency	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: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 210 (Table 119); pg. 212 (Table 120); pg. 221 (Table 126); pg. 222 (Table 127)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Focusing on exposure-adjusted frequency, in the primary efficacy trials an imbalance favoring placebo is seen for both doses of UMEC/VI as well as for the monotherapies; as imbalance is also seen for the comparison between placebo and tiotropium. In the long-term safety trial, the exposure-adjusted frequency for serious cardiovascular AESIs is higher for placebo as compared to UMEC/VI 125 mcg/25 mcg; the exposure-adjusted frequency is slightly higher for the UMEC 125 mcg monotherapy.

Serious on-treatment cardiovascular AESIs by subgroup, for the primary efficacy and long term safety trials, are presented in Table 78 and Table 79, respectively.

Table 78. Serious Cardiovascular AESIs, by Subgroup, Primary Efficacy Trials, ITT Population

	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
Incidence	Number (%) of Subjects						
Acquired long QT	0	0	0	1 (<1)	0	0	0
Cardiac arrhythmias	0	1 (<1)	2 (<1)	4 (<1)	4 (<1)	6 (<1)	1 (<1)
Cardiac failure	0	0	1 (<1)	0	0	3 (<1)	0
Cardiac ischemia	1 (<1)	6 (<1)	3 (<1)	4 (<1)	3 (<1)	6 (<1)	1 (<1)
Hypertension	0	0	0	0	1 (<1)	1 (<1)	0
Sudden death	0	0	0	0	0	1 (<1)	0
Stroke	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	3 (<1)	1 (<1)
Exposure-adjusted frequency	Number of Subjects with Events per 1000 Subject-Years						
Acquired long QT	0	0	0	6.0	0	0	0
Cardiac arrhythmias	0	2.9	5.9	23.8	16.1	14.6	5.8
Cardiac failure	0	0	3.0	0	0	7.3	0
Cardiac ischemia	4.8	17.3	8.9	23.8	12.1	14.6	5.8
Hypertension	0	0	0	0	4.0	2.4	0
Sudden death	0	0	0	0	0	2.4	0
Stroke	4.8	2.9	3.0	0	4.0	7.3	5.8

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 210-211 (Table 119); pg. 212-213 (Table 120)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Table 79. Serious Cardiovascular AESIs by Subgroup, Long-term Safety Trial, ITT Population

	Placebo N=109 SY=80	UMEC/VI 125/25 N=226 SY=177	UMEC 125 N=227 SY=167
Incidence	Number (%) of Subjects		
Acquired long QT	0	0	0
Cardiac arrhythmias	0	0	1 (<1)
Cardiac failure	1 (<1)	1 (<1)	2 (<1)
Cardiac ischemia	2 (2)	3 (1)	2 (<1)
Hypertension	0	1 (<1)	1 (<1)
Sudden death	0	0	0
Stroke	0	0	1 (<1)
Exposure-adjusted frequency	Number of Subjects with Events per 1000 Subject-Years		
Acquired long QT	0	0	0
Cardiac arrhythmias	0	0	6.0
Cardiac failure	12.4	5.7	12.0
Cardiac ischemia	24.9	17.0	12.0
Hypertension	0	5.7	6.0
Sudden death	0	0	0
Stroke	0	0	6.0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 221 (Table 126); pg. 222 (Table 127)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

An examination of serious cardiovascular AESI by subgroup reveals that the imbalance favoring placebo compared to UMEC/VI observed in the primary efficacy trials is largely driven by an imbalance in the cardiac ischemia subgroup, particularly for the comparison between placebo and UMEC/VI 62.5 mcg/25 mcg. No such pattern was observed for the long-term safety trial. Serious cardiovascular AESIs categorized in the cardiac ischemia subgroup, by preferred term, are presented for the primary efficacy trials in Table 80.

Table 80. Serious Cardiovascular AESIs, Cardiac Ischemia Subgroup, by Preferred Term, Primary Efficacy Trials, ITT Population

	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
Incidence	Number (%) of Subjects						
Any term	1 (<1)	6 (<1)	3 (<1)	4 (<1)	3 (<1)	6 (<1)	1 (<1)
Acute myocardial infarction	0	0	0	0	1 (<1)	3 (<1)	0
Angina pectoris	1 (<1)	0	0	0	0	1 (<1)	0
Angina unstable	0	1 (<1)	0	1 (<1)	1 (<1)	0	0
Cardiac enzymes increased	0	0	0	0	0	1 (<1)	0
Coronary artery disease	0	0	2 (<1)	2 (<1)	0	1 (<1)	0
ECG T wave inversion	0	1 (<1)	0	0	0	0	0
Myocardial infarction	0	3 (<1)	1 (<1)	0	1 (<1)	0	0
Myocardial ischemia	0	1 (<1)	0	0	0	0	0
Troponin increased	0	0	0	1 (<1)	0	0	0
Vascular graft occlusion	0	0	0	0	0	0	1 (<1)
Exposure-adjusted	Number of Subjects with Events per 1000 Subject-Years						

frequency							
Any term	4.8	17.3	8.9	23.8	12.1	14.6	5.8
Acute myocardial infarction	0	0	0	0	4.0	7.3	0
Angina pectoris	4.8	0	0	0	0	2.4	0
Angina unstable	0	2.9	0	6.0	4.0	0	0
Cardiac enzymes increased	0	0	0	0	0	2.4	0
Coronary artery disease	0	0	5.9	11.9	0	2.4	0
ECG T wave inversion	0	2.9	0	0	0	0	0
Myocardial infarction	0	8.7	3.0	0	4.0	0	0
Myocardial ischemia	0	2.9	0	0	0	0	0
Troponin increased	0	0	0	6.0	0	0	0
Vascular graft occlusion	0	0	0	0	0	0	5.8

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 211 (Table 119), pg. 212-213 (Table 120)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

On review of the preferred terms reported for the cardiac ischemia subgroup, it is noted that "myocardial infarction" and "myocardial ischemia" events were reported for 4 patients in the UMEC/VI 62.5 mcg/25 mcg treatment group, and for no subjects in the placebo arm. There was only one event of "myocardial infarction" and no events of "myocardial ischemia" reported for the UMEC/VI 125 mcg/25 mcg treatment group.

Summary of Cardiovascular Adverse Events

The Applicant's analysis of cardiovascular adverse events included both a MACE analysis, as well as an evaluation of cardiovascular AESIs. These analyses represent different approaches to assessing the same safety data.

In both the MACE and cardiovascular AESI analyses a numerical imbalance favoring placebo is demonstrated for events related to cardiovascular ischemia. In the MACE analysis, the imbalance is noted for narrow category of non-fatal myocardial infarction, but not the broader category of non-fatal cardiac ischemia; the imbalance in non-fatal myocardial infarction is seen across all UMEC/VI, UMEC, and VI treatment arms. In the cardiovascular AESI analysis, imbalances are noted in the primary efficacy trials, but not the long-term safety trial; these include an imbalance in the cardiac ischemia subgroup of cardiovascular AESIs, and an imbalance in the overall category of serious cardiovascular AESIs, which appears to be largely driven by events in cardiac ischemia subgroup.

Several features of the observed data decrease concern regarding the numerical imbalances described above. The imbalances identified in the cardiovascular AESI analysis are for the primary efficacy trials; similar patterns are not demonstrated for the long-term safety trial. It is reasonable to expect that a signal for increased cardiac ischemia, if it represents a true risk, ought to be observed not just in the primary efficacy trials, but also in the long-term safety trial which evaluated the higher UMEC/VI dose for a longer duration. This argument is tempered somewhat, however, by the fact that a greater percentage of patients in the UMEC/VI and UMEC treatment arms of the long-term safety trial withdrew due to abnormalities on ECGs and on 24-hour Holter

monitoring compared to placebo (see Table 56); the safety profile of these patients after withdrawal cannot be known. Nevertheless, while small numerical imbalances were observed between the active treatment arms and placebo in the primary efficacy trials, the most notable feature of these analyses is the overall low number of events observed in the clinical development program, which is reassuring.

Anticholinergic Adverse Events

The Applicant utilized the anticholinergic syndrome SMQ to evaluate anticholinergic adverse effects, which included the PT "urinary retention." In addition, urinary retention adverse events were also analyzed as a separate group including the following preferred terms: urinary retention, urinary hesitation, micturition frequency decreased, urine flow decreased, and Fowler's syndrome. The results of the analyses of anticholinergic effects AESIs and urinary retention adverse events are provided in Table 81 and Table 82, respectively. The incidence of anticholinergic effects AESIs was balanced across treatment arms. The incidence of urinary retention AESIs was low across the clinical development program.

Table 81. Anticholinergic Effects AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	22 (4)	25 (3)	43 (5)	18 (4)	29 (5)	40 (4)	15 (4)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	2 (2)	--	5 (2)	--	5 (2)	--	--
Exposure-adjusted frequency	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
	106.0	72.3	127.9	107.2	116.5	97.3	86.7
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	24.9	--	28.3	--	29.9	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 278 (Table 185)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Table 82. Urinary Retention AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	0	1 (<1)	0	0	2 (<1)	1 (<1)	2 (<1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	0	--	0	--	--
Exposure-adjusted frequency	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
	0	2.9	0	0	8.0	2.4	11.6

Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	0	--	0	--	0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 254 (Table 154)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Metabolic Adverse Events (Effects of Glucose and Potassium)

Adverse events related to changes in glucose and potassium were analyzed using relevant PTs. The results for glucose are provided in Table 83 and for potassium in Table 84.

Table 83. Effects on Glucose AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	2 (<1)	11 (1)	4 (<1)	7 (2)	11 (2)	17 (2)	6 (1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	8 (4)	--	1 (<1)	--	--
Exposure-adjusted frequency	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	31.8	11.9	41.7	44.2	41.3	34.7
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	0	--	45.3	--	6.0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 244 (Table 141)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

An imbalance favoring placebo is observed across all treatment groups in both the primary efficacy and long-term safety trials; this is not unexpected given the association between the LABA class and hyperglycemia. Only one event was classified as a SAE in the primary efficacy trials, and this was for the TIO treatment arm; there were no events classified as SAEs in the long-term safety trial. The absence of SAEs related to changes in glucose is reassuring.

Table 84. Effects on Potassium AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	1 (<1)	0	2 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	0	--	1 (<1)	--	--
Exposure-adjusted frequency	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
	4.8	0	5.9	0	4.0	2.4	5.8
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--

	0	--	0	--	6.0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 242 (Table 139)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

The incidence of effects on potassium AESIs was low across the clinical development program.

Tremor

Adverse events pertaining to tremor were analyzed using the higher level term (HLT) of tremor (excluding congenital) (Table 85). The overall incidence of tremor AESIs was low across the clinical program.

Table 85. Tremor AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	2 (<1)	1 (<1)	0	3 (<1)	1 (<1)	1 (<1)	1 (<1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	0	--	0	--	--
Exposure-adjusted frequency	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	2.9	0	17.9	4.0	2.4	5.8
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	0	--	0	--	0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 252 (Table 153)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Ocular Effects

Adverse events pertaining to ocular effects were analyzed using the glaucoma SMQ and visual disorders NEC HLT (Table 86). A small numerical imbalance favoring placebo was observed for the UMEC 125 mcg monotherapy in the primary efficacy trials, but not in the long-term safety trial.

Table 86. Ocular AESIs, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	5 (<1)	7 (<1)	7 (<1)	3 (<1)	8 (1)	6 (<1)	1 (<1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	1 (<1)	--	1 (<1)	--	1 (<1)	--	--
Exposure-adjusted	Number of Subjects with Events per 1000 Subject-Years						

frequency							
Primary Efficacy	SY=208	SY=346	SY=336	SY=168	SY=249	SY=411	SY=173
	24.1	20.2	20.8	17.9	32.1	14.6	5.8
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	12.4	--	5.7	--	6.0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 256 (Table 155)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Gallbladder Disorders

Adverse events pertaining to gallbladders disorders were analyzed using the Gallbladder-related Disorders SMQ (Table 87). The overall incidence of gallbladder disorders AESIs was low across the clinical program.

Table 87. Gallbladder Disorders AESI, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	1 (<1)	2 (<1)	0	3 (<1)	0	2 (<1)	0
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	0	--	2 (<1)	--	--
Exposure-adjusted frequency	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
	4.8	5.8	0	17.9	0	4.9	0
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	0	--	0	--	12.0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 263 (Table 165)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Intestinal Obstruction

Adverse events pertaining to intestinal obstruction were analyzed using the Gastrointestinal Obstruction SMQ (Table 88). The overall incidence of intestinal obstruction AESIs was low across the clinical program.

Table 88. Intestinal Obstruction AESI, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	2 (<1)	1 (<1)	0	0	0	0	0
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	0	--	0	--	--

Exposure-adjusted frequency	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	2.9	0	0	0	0	0
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	0	--	0	--	0	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 273 (Table 179)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Lower Respiratory Tract Infection/Pneumonia

Adverse events related to lower respiratory tract infections (LRTI) and pneumonia were analyzed using relevant PTs. It should be noted that the clinical development program did not require that diagnoses of pneumonia be confirmed by chest radiograph, and that the overall category of LRTI and pneumonia AESIs includes both pneumonia events as well as other types of pulmonary infections such as bronchitis. The results for the overall category of LRTI/Pneumonia AESIs and subcategory of serious LRTI/Pneumonia AESIs are provided in Table 89 and Table 90, respectively.

Table 89. LRTI and Pneumonia AESI, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	8 (1)	26 (3)	23 (3)	6 (1)	22 (3)	14 (1)	17 (4)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	2 (2)	--	5 (2)	--	11 (5)	--	--
Exposure-adjusted frequency	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
	38.5	75.2	68.4	35.7	88.4	34.0	98.2
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	24.9	--	28.3	--	68.5	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 289 (Table 199)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Table 90. Serious LRTI and Pneumonia AESI, by Trial Grouping, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Incidence	Number (%) of Subjects						
Primary Efficacy	N=555	N=842	N=832	N=418	N=629	N=1034	N=423
	4 (<1)	10 (1)	6 (<1)	3 (<1)	5 (<1)	6 (<1)	4 (<1)
Long-term Safety	N=109	--	N=226	--	N=227	--	--
	0	--	1 (<1)	--	3 (1)	--	--
Exposure-adjusted frequency	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
	19.3	28.9	17.8	17.9	20.1	14.6	23.1
Long-term Safety	SY=80	--	SY=177	--	SY=167	--	--
	0	--	5.7	--	17.9	--	--

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 292 (Table 203), pg. 293 (Table 204), pg. 295 (Table 207), pg. 295 (Table 208)
Key: SY=subject-years
Note: Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

Examining the overall category first, in the primary efficacy trials a numerical imbalance favoring placebo is observed for both UMEC/VI arms, as well as for the higher-dose UMEC monotherapy and tiotropium. In the long-term safety trial, a numerical imbalance favoring placebo is observed for the UMEC 125 mcg treatment arm. For the subcategory of serious events, in the primary efficacy trials an imbalance favoring placebo is observed for only the UMEC/VI 62.5 mcg/25 mcg treatment arm. The number of serious events observed in the long-term safety trial was low across the treatment groups.

Given the known association between ICS/LABA combination products and pneumonia in COPD, it is useful to examine the incidence of pneumonia/LRTI events by ICS use. This analysis is provided for the primary efficacy trials in Table 91.

Table 91. Incidence of LRTI and Pneumonia AESI, by ICS Use, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
Number (%) of Subjects							
ICS User							
Any Term	6 (2)	13 (3)	13 (3)	2 (<1)	10 (3)	8 (2)	10 (5)
ICS Non-User							
Any Term	2 (<1)	13 (3)	10 (2)	4 (2)	12 (4)	6 (1)	7 (3)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 2909-2910 (Table 2.171)

For the overall category of LRTI and Pneumonia AESIs, the patterns observed are generally irrespective of ICS use, with small numerical imbalances favoring placebo noted for several treatment groups.

In summary, while an imbalance in LRTI and Pneumonia AESIs favoring placebo is noted for the primary efficacy trials, the low incidence of both overall and serious LRTI and pneumonia AESIs observed for UMEC/VI in the long-term safety trial is reassuring.

6.4 Supportive Safety Results

6.4.1 Common Adverse Events

Common adverse events reported for 3% or more of patients (in any treatment group) in the primary efficacy and long-term safety trials are presented in Table 92 and Table 93.

Table 92. Common Adverse Events Reported for ≥ 3% Patients in any Treatment Arm, by PT, Primary Efficacy Trials, ITT Population

	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=1034	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)
Dyspnea	14 (3)	10 (1)	4 (<1)	4 (<1)	11 (2)	20 (2)	3 (<1)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 134 (Table 74)
Note: This table includes on-treatment AEs
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease; URTI=upper respiratory tract infection

Table 93. Common Adverse Events Reported for ≥ 3% Patients in any Treatment Arm, by PT, Long-Term Safety Trial, ITT Population

	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)
Nasopharyngitis	5 (5)	11 (5)	20 (9)
Ventricular Extrasystoles	5 (5)	11 (5)	12 (5)
Extrasystoles	4 (4)	10 (4)	10 (4)
Back pain	3 (3)	10 (4)	9 (4)
Hypertension	5 (5)	8 (4)	4 (2)
Sinusitis	3 (3)	8 (4)	6 (3)
Influenza	5 (5)	6 (3)	5 (2)

Cough	1 (<1)	6 (3)	6 (3)
URTI	3 (3)	2 (<1)	8 (4)
COPD	3 (3)	3 (1)	6 (3)
Ventricular tachycardia	4 (4)	4 (2)	3 (1)
Supraventricular tachycardia	1 (<1)	2 (<1)	6 (3)
Supraventricular extrasystoles	1 (<1)	1 (<1)	6 (3)
Sinus tachycardia	1 (<1)	0	6 (3)
Dyspnea	3 (3)	3 (1)	0
Pneumonia	0	0	6 (3)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 138 (Table 76)
Note: This table includes on-treatment AEs
Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease; URTI=upper respiratory tract infection

In the primary efficacy trials, a small imbalance in the overall percentage of patients reporting AEs is noted between the UMEC/VI treatment arms and placebo (53% of patients for either of the UMEC/VI groups versus 48% for the placebo group). An imbalance of at least 1% favoring placebo over either UMEC/VI group is observed for only the events of cough and arthralgia. In the long-term safety trial, the overall percentage of patients reporting AEs is similar between the placebo and UMEC/VI treatment arms (52% and 53%, respectively), and somewhat higher for the UMEC 125 mcg monotherapy arm (58%). An imbalance of at least 1% favoring placebo over UMEC/VI is observed for the events of headache, back pain, sinusitis, and cough.

6.4.2 Laboratory Findings

Chemistry

The percentages of patients with shifts to low or high values in chemistry parameters are presented in Table 94 for the primary efficacy trials and in Table 95 for the long-term safety trial.

Table 94. Shift Table of Chemistry Parameters, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
Alanine aminotransferase							
N	522	803	776	389	603	983	405
To High, n (%)	16 (3)	24 (3)	27 (3)	10 (3)	21 (3)	28 (3)	14 (3)
Albumin							
N	522	804	777	389	604	982	405

To Low, n (%)	1 (<1)	3 (<1)	0	1 (<1)	1 (<1)	3 (<1)	0
To High, n (%)	7 (1)	6 (<1)	17 (2)	2 (<1)	9 (1)	15 (2)	4 (<1)
Alkaline phosphatase							
N	522	804	776	389	603	983	405
To Low, n (%)	0	0	0	0	0	0	0
To High, n (%)	17 (3)	34 (4)	27 (3)	14 (4)	16 (3)	20 (2)	10 (2)
Aspartate aminotransferase							
N	521	803	776	389	604	983	405
To High, n (%)	13 (2)	21 (3)	26 (3)	7 (2)	18 (3)	20 (2)	14 (3)
Bicarbonate							
N	521	803	776	389	604	982	405
To Low, n (%)	39 (7)	87 (11)	68 (9)	42 (11)	54 (9)	77 (8)	33 (8)
To High, n (%)	0	0	0	2 (<1)	1 (<1)	2 (<1)	0
Bilirubin, Total							
N	522	804	777	389	604	983	405
To High, n (%)	3 (<1)	14 (2)	15 (2)	2 (<1)	8 (1)	18 (2)	5 (1)
Bilirubin, Direct							
N	522	802	776	389	604	982	405
To High, n (%)	2 (<1)	5 (<1)	3 (<1)	2 (<1)	3 (<1)	5 (<1)	1 (<1)
Bilirubin, Indirect							
N	522	802	776	389	604	982	405
To High, n (%)	0	8 (<1)	4 (<1)	1 (<1)	3 (<1)	9 (<1)	3 (<1)
Calcium							
N	521	803	776	389	604	982	405
To Low, n (%)	11 (2)	23 (3)	7 (<1)	13 (3)	13 (2)	15 (2)	5 (1)
To High, n (%)	14 (3)	19 (2)	22 (3)	5 (1)	22 (4)	28 (3)	8 (2)
Chloride							
N	522	804	777	389	603	982	405
To Low, n (%)	12 (2)	5 (<1)	10 (1)	2 (<1)	5 (<1)	14 (1)	4 (<1)
To High, n (%)	23 (4)	46 (6)	37 (5)	18 (5)	29 (5)	50 (5)	17 (4)
Creatine kinase							
N	521	804	777	389	604	980	405
To High, n (%)	19 (4)	46 (6)	52 (7)	10 (3)	27 (4)	70 (7)	20 (5)
Creatinine							
N	522	804	777	389	604	982	405
To Low, n (%)	39 (7)	53 (7)	53 (7)	36 (9)	47 (8)	75 (8)	34 (8)
To High, n (%)	7 (1)	14 (2)	9 (1)	8 (2)	1 (<1)	18 (2)	7 (2)
GGT							
N	522	804	777	389	604	982	405
To High, n (%)	33 (6)	46 (6)	47 (6)	15 (4)	38 (6)	43 (4)	29 (7)
Glucose							
N	522	804	777	389	604	982	404
To Low, n (%)	14 (3)	27 (3)	24 (3)	11 (3)	24 (4)	28 (3)	15 (4)
To High, n (%)	72 (14)	97 (12)	105 (14)	57 (15)	82 (14)	127 (13)	54 (13)

Phosphorus							
N	522	804	777	389	603	982	405
To Low, n (%)	27 (5)	22 (3)	23 (3)	15 (4)	17 (3)	42 (4)	20 (5)
To High, n (%)	22 (4)	30 (4)	32 (4)	18 (5)	32 (5)	33 (3)	15 (4)
Potassium							
N	521	803	775	389	604	982	405
To Low, n (%)	8 (2)	5 (<1)	6 (<1)	5 (1)	5 (<1)	12 (1)	3 (<1)
To High, n (%)	21 (4)	28 (3)	23 (3)	13 (3)	20 (3)	33 (3)	14 (3)
Sodium							
N	522	804	777	389	603	981	405
To Low, n (%)	17 (3)	9 (1)	23 (3)	11 (3)	14 (2)	21 (2)	13 (3)
To High, n (%)	11 (2)	13 (2)	8 (1)	5 (1)	9 (1)	12 (1)	5 (1)
Total Protein							
N	522	804	777	389	604	982	405
To Low, n (%)	5 (<1)	11 (1)	5 (<1)	1 (<1)	2 (<1)	10 (1)	1 (<1)
To High, n (%)	3 (<1)	6 (<1)	6 (<1)	0	2 (<1)	3 (<1)	3 (<1)
Urea (BUN)							
N	522	804	777	389	604	982	405
To Low, n (%)	6 (1)	12 (1)	11 (1)	3 (<1)	10 (2)	6 (<1)	2 (<1)
To High, n (%)	21 (4)	29 (4)	17 (2)	16 (4)	18 (3)	32 (3)	10 (2)
Uric acid							
N	520	804	776	387	604	981	405
To Low, n (%)	20 (4)	25 (3)	18 (2)	14 (4)	18 (3)	30 (3)	16 (4)
To High, n (%)	30 (6)	40 (5)	39 (5)	13 (3)	21 (3)	51 (5)	19 (5)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 2964-2983 (Table 3.01)
Note: This includes labs performed at any time post-baseline, including at scheduled, unscheduled, and early withdrawal visits

Table 95. Shift Table of Chemistry Parameters, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Alanine aminotransferase			
N	99	218	217
To High, n (%)	6 (6)	12 (6)	15 (7)
Albumin			
N	99	218	217
To Low, n (%)	0	1 (<1)	1 (<1)
To High, n (%)	3 (3)	9 (4)	5 (2)
Alkaline phosphatase			
N	99	218	217
To Low, n (%)	0	0	0
To High, n (%)	7 (7)	11 (5)	7 (3)

Aspartate aminotransferase			
N	99	218	217
To High, n (%)	6 (6)	10 (5)	12 (6)
Bicarbonate			
N	99	218	217
To Low, n (%)	14 (14)	38 (17)	19 (9)
To High, n (%)	0	3 (1)	0
Bilirubin, Total			
N	99	218	217
To High, n (%)	1 (1)	12 (6)	7 (3)
Bilirubin, Direct			
N	99	218	217
To High, n (%)	0	2 (<1)	3 (1)
Bilirubin, Indirect			
N	99	218	217
To High, n (%)	0	1 (<1)	2 (<1)
Calcium			
N	99	218	216
To Low, n (%)	1 (1)	2 (<1)	4 (2)
To High, n (%)	11 (11)	14 (6)	11 (5)
Chloride			
N	99	218	217
To Low, n (%)	1 (1)	4 (2)	3 (1)
To High, n (%)	12 (12)	22 (10)	20 (9)
Creatine kinase			
N	99	218	217
To High, n (%)	6 (6)	27 (12)	23 (11)
Creatinine			
N	99	218	217
To Low, n (%)	12 (12)	30 (14)	33 (15)
To High, n (%)	1 (1)	2 (<1)	7 (3)
GGT			
N	99	218	217
To High, n (%)	8 (8)	23 (11)	20 (9)
Glucose			
N	99	218	217
To Low, n (%)	6 (6)	16 (7)	3 (1)
To High, n (%)	13 (13)	38 (17)	37 (17)
Phosphorus			
N	98	218	216
To Low, n (%)	6 (6)	12 (6)	8 (4)
To High, n (%)	9 (9)	16 (7)	17 (8)
Potassium			
N	99	218	217

To Low, n (%)	1 (1)	2 (<1)	5 (2)
To High, n (%)	9 (9)	16 (7)	22 (10)
Sodium			
N	99	218	217
To Low, n (%)	4 (4)	10 (5)	5 (2)
To High, n (%)	5 (5)	2 (<1)	4 (2)
Total Protein			
N	99	218	217
To Low, n (%)	1 (1)	2 (<1)	2 (<1)
To High, n (%)	0	3 (1)	3 (1)
Urea (BUN)			
N	99	218	217
To Low, n (%)	3 (3)	6 (3)	8 (4)
To High, n (%)	6 (6)	13 (6)	9 (4)
Uric acid			
N	99	218	216
To Low, n (%)	1 (1)	10 (5)	6 (3)
To High, n (%)	14 (14)	17 (8)	19 (9)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 654-673 (Table 7.19)
Note: This includes labs performed at any time post-baseline, including at scheduled, unscheduled, and early withdrawal visits

In general, the percentages of patients with shifts in chemistry laboratory values are balanced across treatments arms in both the primary efficacy and long-term safety trials, with some exceptions, which are noted below.

Bilirubin

In both the primary efficacy and long-term safety trials there is a small numerical increase in the percentage of patients with a total bilirubin shift to high; in the primary efficacy trials an increase is also seen for indirect bilirubin. There is no accompanying imbalance in the percentage of patients with a change in alkaline phosphatase in either the primary efficacy or long-term safety trials. A small imbalance in the percentage of patients with a GGT shift to high is seen in the long-term safety trial, but not the primary efficacy trials. Gallbladder disorders adverse events of special interest (AESI) are discussed in Section 6.3.5; the overall incidence of these events was low across the clinical program.

Creatine kinase

In both the primary efficacy and long-term safety trials there is a small numerical increase in the percentage of patients with a creatine kinase shift to high, with the imbalance being more notable in the long-term safety trial. Creatine kinase (CK) is a nonspecific marker, and increases in CK occur with a variety of processes including muscle and cardiac diseases. An increase in events related to cardiovascular ischemia is described in Section 6.3.5 of this review.

Other
In the long-term safety trial alone an increase in the percentage of patients with a glucose shift to high is noted. An increase in glucose AESIs in both the primary efficacy and long-term safety trials is described in Section 6.3.5 of this review; only one of these events was classified as a SAE, and that was for a patient treated with tiotropium.

In the long-term safety trial alone a numerical increase is seen in the percentage of patients with a uric acid shift to low. The clinical relevance of this finding is unclear.

In the long-term safety trial alone a numerical increase is seen in the percentage of patients with a creatinine shift to high, but only for the UMEC 125 mg monotherapy arm.

Hematology
The percentages of patients with shifts to low or high values in chemistry parameters are presented in Table 96 for the primary efficacy trials and in Table 97 for the long-term safety trial.

Table 96. Shift Table of Hematology Parameters, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
WBC Count							
N	519	792	771	384	604	973	405
To Low, n (%)	6 (1)	15 (2)	10 (1)	5 (1)	5 (<1)	13 (1)	6 (1)
To High, n (%)	43 (8)	55 (7)	54 (7)	23 (6)	47 (8)	67 (7)	36 (9)
Lymphocytes (percentage)							
N	516	792	769	382	602	970	404
To Low, n (%)	52 (10)	67 (8)	69 (9)	45 (12)	67 (11)	102 (11)	34 (8)
To High, n (%)	7 (1)	29 (4)	31 (4)	6 (2)	12 (2)	38 (4)	19 (5)
Neutrophils (percentage)							
N	516	792	769	382	602	970	404
To Low, n (%)	6 (1)	35 (4)	29 (4)	11 (3)	15 (2)	35 (4)	17 (4)
To High, n (%)	56 (11)	73 (9)	83 (11)	49 (13)	72 (12)	114 (12)	49 (12)
Neutrophils (ANC)							
N	516	792	769	382	602	970	404
To Low, n (%)	3 (<1)	22 (3)	21 (3)	7 (2)	16 (3)	23 (2)	7 (2)
To High, n (%)	36 (7)	52 (7)	52 (7)	29 (8)	42 (7)	67 (7)	34 (8)
Eosinophils (percentage)							
N	516	792	769	382	602	970	404
To High, n (%)	38 (7)	53 (7)	56 (7)	24 (6)	36 (6)	54 (6)	30 (7)
Monocytes (percentage)							
N	516	792	769	382	602	970	404

To High, n (%)	23 (4)	50 (6)	35 (5)	19 (5)	27 (4)	60 (6)	21 (5)
Basophils (percentage)							
N	516	792	769	382	602	970	404
To High, n (%)	0	1 (<1)	0	0	2 (<1)	2 (<1)	1 (<1)
Hemoglobin							
N	520	802	775	385	606	979	407
To Low, n (%)	30 (6)	39 (5)	29 (4)	23 (6)	16 (3)	57 (6)	19 (5)
To High, n (%)	14 (3)	29 (4)	18 (2)	11 (3)	9 (1)	31 (3)	14 (3)
Platelet Count							
N	510	785	765	375	596	962	394
To Low, n (%)	7 (1)	15 (2)	14 (2)	6 (2)	11 (2)	16 (2)	8 (2)
To High, n (%)	12 (2)	10 (1)	16 (2)	5 (1)	6 (1)	19 (2)	5 (1)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 3004-3014 (Table 3.03)
Note: This includes labs performed at any time post-baseline, including at scheduled, unscheduled, and early withdrawal visits

Table 97. Shift Table of Hematology Parameters, Primary Efficacy Trials, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
WBC Count			
N	99	218	217
To Low, n (%)	1 (1)	2 (<1)	5 (2)
To High, n (%)	9 (9)	23 (11)	20 (9)
Lymphocytes (percentage)			
N	99	218	217
To Low, n (%)	11 (11)	22 (10)	21 (10)
To High, n (%)	5 (5)	11 (5)	12 (6)
Neutrophils (percentage)			
N	99	218	217
To Low, n (%)	3 (3)	7 (3)	12 (6)
To High, n (%)	11 (11)	27 (12)	30 (14)
Eosinophils (percentage)			
N	99	218	217
To High, n (%)	9 (9)	11 (5)	14 (6)
Monocytes (percentage)			
N	99	218	217
To High, n (%)	5 (5)	13 (6)	18 (8)
Basophils (percentage)			
N	99	218	217
To High, n (%)	0	0	0

Hemoglobin			
N	99	218	217
To Low, n (%)	8 (8)	24 (11)	27 (12)
To High, n (%)	2 (2)	8 (4)	11 (5)
Platelet Count			
N	99	216	217
To Low, n (%)	4 (4)	6 (3)	6 (3)
To High, n (%)	1 (1)	5 (2)	3 (1)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 706-715 (Table 7.23)
Note: This includes labs performed at any time post-baseline, including at scheduled, unscheduled, and early withdrawal visits

In general, the percentages of patients with shifts in hematology laboratory values are balanced across treatments arms in both the primary efficacy and long-term safety trials. Several small numerical imbalances are noted in the either the primary efficacy trials (lymphocytes shift to high, neutrophils shift to low) or long-term safety trials (hemoglobin to either low or high) trials, but not in both.

6.4.3 Vital Signs

Mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate observed in the primary efficacy and long-term safety trials are provided in Table 98 and Table 99, respectively.

Table 98. Least Squares Mean Changes from Baseline in Vital Signs, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
Systolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline							
Day 1							
10 min	-0.3 (0.4)	-0.8 (0.3)	-0.5 (0.3)	0.2 (0.5)	0.6 (0.4)	-0.4 (0.3)	-0.4 (0.5)
45 min	-0.9 (0.4)	-0.3 (0.3)	-0.5 (0.4)	-0.4 (0.5)	-0.3 (0.4)	-0.7 (0.3)	-0.8 (0.5)
Day 168							
Predose	0.4 (0.7)	0.7 (0.5)	-0.7 (0.5)	0.9 (0.8)	0.2 (0.6)	1.0 (0.5)	0.6 (0.8)
10 min	-0.3 (0.6)	-0.7 (0.5)	0.1 (0.5)	-0.5 (0.8)	0.3 (0.6)	-0.3 (0.4)	0.1 (0.7)
45 min	-0.2 (0.6)	-0.3 (0.5)	-0.4 (0.5)	0.5 (0.8)	-0.5 (0.6)	-0.6 (0.5)	0.2 (0.7)
Diastolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline							
Day 1							
10 min	0.0 (0.3)	-0.7 (0.2)	-0.2 (0.2)	0.5 (0.4)	0.2 (0.3)	-0.1 (0.2)	0.2 (0.3)
45 min	0.0 (0.3)	-0.4 (0.2)	-0.6 (0.2)	0.0 (0.4)	-0.1 (0.3)	-0.1 (0.2)	-0.3 (0.4)
Day 168							

Predose	0.1 (0.4)	0.0 (0.3)	0.1 (0.3)	0.2 (0.5)	-0.2 (0.4)	0.2 (0.3)	0.5 (0.5)
10 min	-0.4 (0.4)	-0.9 (0.3)	-0.1 (0.3)	-0.8 (0.5)	0.0 (0.4)	-0.6 (0.3)	0.3 (0.5)
45 min	-0.9 (0.4)	-0.8 (0.3)	-0.5 (0.3)	-0.2 (0.5)	-1.0 (0.4)	-0.4 (0.3)	0.6 (0.5)
Heart Rate (bpm), LS Mean Change (SE) from Baseline							
Day 1							
10 min	-2.2 (0.3)	-1.9 (0.2)	-2.3 (0.2)	-2.6 (0.3)	-2.5 (0.3)	-2.0 (0.2)	-2.6 (0.3)
45 min	-3.1 (0.3)	-2.6 (0.2)	-3.2 (0.3)	-3.5 (0.4)	-3.7 (0.3)	-2.9 (0.2)	-3.4 (0.4)
Day 168							
Predose	1.1 (0.5)	-0.1 (0.4)	0.4 (0.4)	0.2 (0.6)	-0.6 (0.5)	0.6 (0.3)	1.5 (0.5)
10 min	-1.3 (0.5)	-2.3 (0.4)	-1.2 (0.4)	-2.6 (0.6)	-2.5 (0.4)	-1.5 (0.3)	-0.7 (0.5)
45 min	-2.3 (0.5)	-3.1 (0.4)	-2.1 (0.4)	-3.0 (0.6)	-3.7 (0.5)	-1.9 (0.3)	-1.5 (0.5)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 334 (Table 238)

Table 99. Least Squares Mean Change from Baseline in Vital Signs, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Systolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline			
Day 1			
10 min	-0.9 (0.8)	-1.4 (0.6)	-0.2 (0.6)
45 min	-0.5 (0.9)	-1.4 (0.6)	-1.1 (0.6)
Month 12			
Predose	0.4 (1.6)	0.8 (1.1)	-0.4 (1.2)
10 min	-0.3 (1.4)	-1.7 (1.0)	0.1 (1.0)
45 min	-1.0 (1.6)	-1.8 (1.1)	-1.2 (1.2)
Diastolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline			
Day 1			
10 min	0.4 (0.6)	-1.3 (0.4)	-0.2 (0.4)
45 min	-0.2 (0.6)	-1.6 (0.4)	-1.0 (0.4)
Month 12			
Predose	0.7 (1.1)	-0.5 (0.7)	-0.2 (0.8)
10 min	-1.4 (1.0)	-2.0 (0.7)	-0.4 (0.7)
45 min	-1.4 (1.0)	-3.5 (0.7)	-0.7 (0.7)
Heart Rate (bpm), LS Mean Change (SE) from Baseline			
Day 1			
10 min	-2.8 (0.6)	-2.5 (0.4)	-2.5 (0.4)
45 min	-4.1 (0.6)	-2.9 (0.4)	-4.1 (0.4)
Month 12			
Predose	-0.5 (1.2)	-0.8 (0.8)	-0.2 (0.8)

10 min	-1.3 (1.1)	-1.0 (0.8)	-1.4 (0.8)
45 min	-2.0 (1.1)	-3.3 (0.8)	-3.2 (0.8)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 336-337 (Table 240)

For both the primary efficacy and long-term safety trials mean changes from baseline in vital signs were either balanced across treatment groups or not likely to be of clinical relevance. Cardiovascular adverse events of special interest, including events of arrhythmia and hypertension, are discussed in Section 6.3.5 of this review.

6.4.4 Electrocardiograms (ECGs)

The Applicant's evaluation of cardiovascular safety included 12-lead electrocardiograms (ECGs), 24-hour Holter monitoring in a subset of patients, and dedicated studies evaluating potential effects on cardiac conduction (i.e. "Thorough QT" studies); these are each described in turn below. Cardiovascular adverse events of special interest, including events of arrhythmia, are discussed earlier in this review (see Section 6.3.5).

12-Lead Electrocardiograms (ECGs)

Mean changes from baseline in electrocardiographic parameters observed in the primary efficacy and long-term safety trials are provided in Table 100 and Table 101, respectively.

Table 100. Least Squares Mean Changes from Baseline in ECG Parameters, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
Heart Rate (bpm), LS Mean Change (SE) from Baseline							
Day 1							
10 min	-3.2 (0.3)	-2.7 (0.2)	-2.2 (0.2)	-2.9 (0.3)	-3.7 (0.3)	-2.6 (0.2)	-3.5 (0.3)
45 min	-4.1 (0.3)	-4.1 (0.2)	-3.9 (0.2)	-4.7 (0.4)	-5.4 (0.3)	-3.9 (0.2)	-4.7(0.3)
Day 168							
Predose	0.9 (0.5)	0.0 (0.4)	0.8 (0.4)	0.2 (0.6)	-0.2 (0.5)	0.6 (0.3)	2.9 (0.6)
10 min	-2.5 (0.5)	-2.3 (0.4)	-0.8 (0.4)	-3.3 (0.6)	-3.4 (0.5)	-2.2 (0.4)	-0.3 (0.6)
45 min	-3.1 (0.5)	-3.7 (0.4)	-2.3 (0.4)	-3.8 (0.6)	-4.9 (0.5)	-3.0 (0.3)	-2.0 (0.6)
PR (msec), LS Mean Change (SE) from Baseline							
Day 1							
10 min	0.3 (0.4)	0.1 (0.4)	-0.6 (0.4)	0.9 (0.5)	0.5 (0.4)	-0.2 (0.3)	0.5 (0.5)
45 min	-0.3 (0.5)	0.1 (0.4)	0.6 (0.4)	0.4 (0.6)	0.9 (0.4)	0.4 (0.3)	1.9 (0.6)
Day 168							
Predose	-1.0 (0.7)	0.6 (0.5)	0.3 (0.5)	-0.6 (0.8)	0.8 (0.7)	0.1 (0.5)	0.8 (0.8)
10 min	-1.2 (0.7)	0.1 (0.6)	-0.3 (0.6)	0.9 (0.9)	1.0 (0.7)	0.6 (0.5)	0.7 (0.8)

45 min	-0.5 (0.7)	1.2(0.6)	0.5 (0.6)	0.6 (0.9)	1.2 (0.7)	1.0 (0.5)	1.7 (0.8)
QTcF (msec), LS Mean Change (SE) from Baseline							
Day 1							
10 min	-0.5 (0.5)	0.9 (0.4)	0.5 (0.4)	0.4 (0.6)	-0.4 (0.5)	0.8 (0.4)	-1.3 (0.6)
45 min	-0.5 (0.5)	1.4 (0.4)	1.3 (0.4)	0.6 (0.7)	0.4 (0.5)	1.1 (0.4)	0.3 (0.6)
Day 168							
Predose	-0.3 (0.8)	0.5 (0.6)	0.3 (0.6)	-1.1 (1.0)	0.5 (0.7)	0.0 (0.6)	-1.3 (0.9)
10 min	-0.8 (0.8)	1.0 (0.6)	1.6 (0.7)	-1.3 (1.0)	-0.3 (0.8)	0.1 (0.6)	-1.0 (0.9)
45 min	-0.8 (0.8)	0.6 (0.6)	0.9 (0.7)	-1.7 (1.0)	0.3 (0.8)	-0.2 (0.6)	-1.8 (0.9)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 350 (Table 248), pg. 352 (Table 250), pg. 353 (Table 251)

Table 101. Least Squares Mean Changes from Baseline in ECG Parameters, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Heart Rate (bpm), LS Mean Change (SE) from Baseline			
Day 1			
10 min	-2.4 (0.5)	-1.7 (0.3)	-2.8 (0.3)
45 min	-4.0 (0.6)	-2.8 (0.4)	-4.5 (0.4)
Month 12			
Predose	0.9 (1.1)	-0.6 (0.8)	0.4 (0.8)
10 min	-0.2 (1.1)	-0.8 (0.8)	-1.1 (0.8)
45 min	-1.5 (1.2)	-2.1 (0.8)	-2.6 (0.9)
PR (msec), LS Mean Change (SE) from Baseline			
Day 1			
10 min	0.4 (0.9)	-0.9 (0.6)	1.5 (0.6)
45 min	1.0 (1.0)	0.4 (0.7)	1.4 (0.7)
Month 12			
Predose	-3.9 (1.6)	-0.8 (1.1)	-3.8 (1.1)
10 min	-5.1 (1.6)	-1.6 (1.1)	-2.6 (1.1)
45 min	-3.8 (1.7)	-1.6 (1.1)	-2.6 (1.1)
QTcF (msec), LS Mean Change (SE) from Baseline			
Day 1			
10 min	-0.6 (1.0)	0.9 (0.7)	-1.0 (0.7)
45 min	-0.3 (1.1)	0.5 (0.8)	-0.2 (0.8)
Month 12			
Predose	-2.8 (2.1)	2.0 (1.4)	-0.1 (1.5)
10 min	-3.3 (2.0)	1.3 (1.4)	0.5 (1.5)
45 min	-2.6 (2.0)	-0.5 (1.3)	-0.5 (1.4)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 360 (Table 255), pg. 362 (Table 257), pg. 363 (Table 258)

For both the primary efficacy and long-term safety trials mean changes from baseline in ECG parameters were either balanced across treatment groups or not likely to be of clinical relevance.

The overall percentage of patients with clinically significant abnormalities on ECG post-baseline, and clinically significant abnormalities reported in 3% or more of patients, are presented in Table 102 for the primary efficacy trials and Table 103 for the long-term safety trial.

Table 102. Clinically Significant Abnormalities on ECG at Any Time Post-Baseline, Overall and Reported for ≥ 3% of Patients, Primary Efficacy Trials, ITT Population

	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=1034	TIO N=423
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any clinically significant abnormality	123 (22)	161 (19)	178 (21)	76 (18)	112 (18)	222 (21)	83 (20)
ST depression	32 (6)	50 (6)	49 (6)	27 (6)	27 (4)	50 (5)	22 (5)
Frequent VPD≥3	25 (5)	40 (5)	35 (4)	16 (4)	23 (4)	39 (4)	16 (4)
Ectopic supraventricular beats	16 (3)	30 (4)	35 (4)	14 (3)	21 (3)	34 (3)	15 (4)
RBBB with QTcF <530 msec	23 (4)	22 (3)	28 (3)	9 (2)	19 (3)	32 (3)	12 (3)
T waves flat	14 (3)	22 (3)	16 (2)	9 (2)	16 (3)	28 (3)	14 (3)
Short PR interval	15 (3)	18 (2)	18 (2)	12 (3)	9 (1)	27 (3)	8 (2)
T wave inversion	14 (3)	21 (2)	24 (3)	11 (3)	5 (<1)	22 (2)	10 (2)
Occasional VPD<3	11 (2)	21 (2)	20 (2)	11 (3)	12 (2)	19 (2)	7 (2)
Ectopic supraventricular rhythm	10 (2)	12 (1)	25 (3)	8 (2)	15 (2)	21 (2)	7 (2)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 354 (Table 252), pg. 355-358 (Table 253)
Note: This includes the worst interpretation recorded post-baseline, including at scheduled, unscheduled, and early withdrawal visits
Key: RBBB= right bundle branch block; VPD=ventricular premature depolarization

Table 103. Clinically Significant Abnormalities on ECG at Any Time Post-Baseline, Overall and Reported for ≥ 3% of Patients, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Any clinically	25 (23)	54 (24)	58 (26)

significant abnormality			
ST depression	13 (12)	21 (9)	16 (7)
Frequent VPD≥3	1 (<1)	12 (5)	13 (6)
T waves flat	5 (5)	9 (4)	11 (5)
T wave inversion	3 (3)	7 (3)	10 (4)
RBBB with QTcF <530 msec	2 (2)	9 (4)	7 (3)
Ectopic supraventricular beats	1 (<1)	6 (3)	9 (4)
First degree AV block	1 (<1)	5 (2)	6 (3)
Short PR interval	3 (3)	2 (<1)	6 (3)
Occasional VPD<3	2 (2)	7 (3)	2 (<1)
Ectopic supraventricular rhythm	3 (3)	0	7 (3)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 364 (Table 259), pg. 365 (Table 260)
Note: This includes the worst interpretation recorded post-baseline, including at scheduled, unscheduled, and early withdrawal visits

Key: RBBB= right bundle branch block; VPD=ventricular premature depolarization

The overall percentage of patients with clinically significant abnormalities on ECG post-baseline was balanced across treatment groups in both the primary efficacy and long-term safety trials. The percentages of patients with the most common (occurring in 3% or more of patients) clinically significant ECG abnormalities was consistently balanced across treatment groups in the primary efficacy trials; several small numerical imbalances favoring placebo are noted for the long-term safety trial (frequent ventricular premature depolarizations, ectopic supraventricular betas, first degree AV block).

24-hour Holter Monitoring

Twenty-hour Holter monitoring was conducted in the placebo-controlled trials (for a subset of approximately 13% of patients) as well as in the long-term safety trial. In the placebo-controlled trials Holter monitoring was conducted at screening and on Days 1, 84, and 168. In the long-term safety trial it was conducted at screening and at months 3, 6, 9, and 12. A summary of 24-hour Holter interpretations is provided in Table 104 and Table 105 for the placebo-controlled and long-term safety trials, respectively.

Table 104. Summary of 24-Hour Holter Interpretations, Placebo-Controlled Trials, Subset Population

	Placebo N=73	UMEC/VI 62.5/25 N=53	UMEC/VI 125/25 N=55	UMEC 62.5 N=54	UMEC 125 N=53	VI 25 N=108

	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Screening						
n	73	52*	55	54	53	107
Any clinically significant abnormality	26 (36)	15 (29)	19 (35)	18 (33)	15 (28)	26 (24)
Post-baseline#						
n	72	53*	55	54	53	107
Any clinically significant abnormality	43 (60)	28 (53)	25 (45)	30 (56)	29 (55)	52 (49)
Change from Screening to Post-baseline#						
n	72	53*	55	54	53	107
Unfavorable clinically significant change	28 (39)	19 (36)	14 (25)	20 (37)	22 (42)	33 (31)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 389 (Table 282)
*One patient had an unscheduled Screening assessment that is not captured in the Screening section of this table; the patient is captured in the post-baseline and change from screening to post-baseline sections of the table
#This includes Holters conducted at any time after screening, both scheduled and unscheduled

Table 105. Summary of 24-Hour Holter Interpretations, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Screening			
n	109	226	227
Any clinically significant abnormality	26 (24)	63 (28)	62 (27)
Post-baseline*			
n	90	207	198
Any clinically significant abnormality	47 (52)	114 (55)	109 (55)
Change from Screening to Post-baseline*			
n	90	207	198
Unfavorable clinically significant change	39 (43)	87 (42)	86 (43)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 394 (Table 286)
#Includes both scheduled and unscheduled Holters

In the placebo-controlled trials, no imbalances favoring placebo are noted for the combination products in either clinically significant abnormalities at any time post-baseline, or in unfavorable clinically significant change from screening to post-baseline. In addition, there are no notable imbalances between treatment arms in the long-term safety trial.

The overall percentage of patients with clinically significant abnormalities on 24-hour Holter monitoring post-randomization, and clinically significant abnormalities reported in 3% or more of patients, are presented in Table 106 for the primary efficacy trials and Table 107 for the long-term safety trial.

Table 106. Clinically Significant Abnormalities on 24-Hour Holter Monitoring at Any Time Post-Randomization Reported for ≥ 3% of Patients, Placebo-Controlled Trials, Subset Population

	Placebo N=73	UMEC/VI 62.5/25 N=53	UMEC/VI 125/25 N=55	UMEC 62.5 N=54	UMEC 125 N=53	VI 25 N=108
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients post-randomization[#], n	72	53	55	54	53	107
Any clinically significant abnormality	43 (60)	28 (53)	25 (45)	30 (56)	28 (53)	52 (49)
Ventricular couplets	27 (38)	17 (32)	15 (27)	16 (30)	17 (32)	29 (27)
Bigeminy	29 (40)	15 (28)	15 (27)	18 (33)	11 (21)	30 (28)
NSVT (>100 bpm, 3-30 beats)	11 (15)	5 (9)	2 (4)	4 (7)	7 (13)	12 (11)
PVC > 1000/24 hr	9 (13)	4 (8)	3 (5)	4 (7)	6 (11)	4 (4)
Ectopic supraventricular beats	1 (1)	1 (2)	3 (5)	4 (7)	3 (6)	6 (6)
Trigeminy	4 (6)	1 (2)	1 (2)	3 (6)	1 (2)	1 (<1)
RBBB	1 (1)	1 (2)	1 (2)	2 (4)	2 (4)	2 (2)
Idioventricular rhythm (≤100 bpm, wide QRS)	1 (1)	1 (2)	0	3 (6)	0	3 (3)
Sustained supraventricular tachycardia (>100 bpm, >30 beats)	1 (1)	1(2)	0	2 (4)	0	3 (3)
Sinus pause ≥ 2	2 (3)	2 (4)	1 (2)	0	1 (2)	0

seconds						
PVC >4000 in 24 hr	2 (3)	1 (2)	0	2 (4)	0	1 (<1)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 390-391 (Table 283)
Key: NSVT=non-sustained ventricular tachycardia; PVC=premature ventricular complex; RBBB=right bundle branch block
#Includes both scheduled and unscheduled Holters

Table 107. Clinically Significant Abnormalities on 24-Hour Holter Monitoring at Any Time Post-Randomization Reported for ≥ 3% of Patients, Long-Term Safety Trial, ITT Population

	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
	n (%)	n (%)	n (%)
Patients post-randomization#, n	90	206	198
Any clinically significant abnormality	47 (52)	114 (55)	109 (55)
Bigeminy	25 (28)	74 (36)	60 (30)
Ventricular couplets	32 (36)	62 (30)	54 (27)
NSVT (<100 bpm, 3-30 beats)	11 (12)	22 (11)	16 (8)
PVC >1000/24 hr	5 (6)	17 (8)	16 (8)
Ectopic supraventricular beats	4 (4)	7 (3)	17 (9)
Trigeminy	5 (6)	12 (6)	10 (5)
Sustained supraventricular tachycardia (>100 bpm, >30 beats)	2 (2)	5 (2)	9 (5)
RBBB	0	7 (3)	7 (4)
PVC >4000/24 hr	2 (2)	8 (4)	4 (2)
Idioventricular rhythm (≤100 bpm, wide QRS)	2 (2)	2 (<1)	8 (4)
Ectopic supraventricular rhythm	2 (2)	2 (<1)	7 (4)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 395-396 (Table 287)
Key: NSVT=non-sustained ventricular tachycardia; PVC=premature ventricular complex; RBBB=right bundle branch block
#Includes both scheduled and unscheduled Holters

Among the most common (occurring in 3% or more of patients) clinically significant Holter abnormalities observed in the placebo-controlled trials, numerical imbalances favoring placebo are noted for ectopic supraventricular beats, RBBB, idioventricular rhythm, sustained supraventricular tachycardia, and sinus pause. Both the absolute number of patients with these findings and the magnitude of the imbalances are generally small. In the long-term safety trial, numerical imbalances favoring placebo compared to UMEC/VI and/or UMEC are noted for a number of the common (occurring in 3% or more of patients) clinically significant Holter abnormalities. The magnitude of these imbalances is generally small.

Studies of Cardiac Conduction (i.e. "Thorough QT" studies)

A dedicated study (DB2114635) evaluating the potential effects of UMEC/VI (125 mcg/25 mcg and 500 mcg/100 mcg) and UMEC (500 mcg) on cardiac conduction ("Thorough QT" study) was conducted. Study DB2114635 was a randomized, placebo-controlled, incomplete block, 4-period crossover study in healthy subjects. Subjects were randomized to 4 of 5 treatments, each 10 days in duration. Moxifloxacin 400 mg was included as a positive control. The Agency's Interdisciplinary Review Team (IRT) for QT Studies reviewed the results from this study and concluded that no significant QTc prolongation effects were detected for either UMEC/VI 125 mcg/25 mcg or UMEC 500 mcg. For both UMEC/VI 125 mcg/25 mcg and UMEC 500 mcg the largest upper bounds of the 2-sided 90% CI for the mean differences between active and placebo was below 10 ms, the threshold for regulatory concern. An effect was demonstrated for moxifloxacin, thus establishing assay sensitivity. The IRT review does note that the largest upper bounds of the 2-sided 90% CI for the mean difference between UMEC/VI 500 mcg/100 mcg and placebo was 10.7, exceeding the 10 ms threshold for regulatory concern; however, it is noted that this dose is associated with concentrations that are likely to be above those for the predicted worst case scenario for either VI (drug interaction with ketoconazole) or UMEC (accumulation due to repeated dose). An increase in heart rate was also observed, with largest upper bounds of the 2-sided 90% CI for the mean differences between UMEC/VI 125 mcg/25 mcg and placebo and UEMC/VI 500 mcg/100 mcg and placebo of 10.5 and 22.3 bpd, respectively.

A "Thorough QT" study evaluating FF/VI was also conducted (HZA102936), and is discussed in the clinical review of the NDA for that product (see clinical review by Dr. Sofia Chaudhry, NDA 204-275, March 18, 2013). The largest upper bounds of the 2-sided 90% CI for the mean difference between FF/VI 200 mcg/25 mcg and placebo was below the 10 ms threshold of regulatory concern, but the largest upper bound of the 2-side 90% CI for the mean difference between FF/VI 800 mcg/ 100 mcg and placebo was above 12.2 ms, exceeding the threshold. It was noted that the FF/VI 800 mcg/100 mcg dose is associated with concentrations above those for the predicted worst case scenario for VI (hepatic impairment).

6.4.5 Special Safety Studies/Clinical Trials

See 6.4.4 for a description of DB2114635 and HZA102936 ("Thorough QT" studies).

6.4.6 Immunogenicity

As a combination of two small molecules, UMEC/VI is not anticipated to induce an immune response, and immunogenicity was not assessed.

6.5 Other Safety Explorations

6.5.1 Dose Dependency for Adverse Events

As noted in Section 6.2.2, the dose dependency for adverse events is discussed throughout this safety review.

6.5.2 Time Dependency for Adverse Events

No specific analysis of time dependency was conducted for adverse events.

6.5.3 Drug-Demographic Interactions

A summary of adverse events by gender is provided in Table 108 and by age in Table 109. While the Applicant's submission includes an analysis of adverse events by race, this analysis is limited by the small sample size for non-Whites, and so is not discussed in this review.

Table 108. Summary of Adverse Events, by Gender, Primary Efficacy Trials, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE							
Female	185	249	269	120	211	341	130
	104 (56)	166 (67)	144 (54)	68 (57)	132 (63)	191 (56)	71 (55)
Male	370	593	563	298	418	693	293

	160 (43)	281 (47)	294 (52)	148 (50)	216 (52)	327 (47)	137 (47)
Any SAE							
Female	185	249	269	120	211	341	130
	9 (5)	17 (7)	9 (3)	8 (7)	14 (7)	18 (5)	10 (8)
Male	370	593	563	298	418	693	293
	17 (5)	33 (6)	34 (6)	19 (6)	23 (6)	41 (6)	12 (4)
Any AE Leading to Dropout*							
Female	185	249	269	120	211	341	130
	9 (5)	18 (7)	12 (4)	10 (8)	15 (7)	16 (5)	8 (6)
Male	370	593	563	298	418	693	293
	17 (5)	32 (5)	35 (6)	21 (7)	26 (6)	43 (6)	12 (4)

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 409 (Table 299), pg. 555-556 (Table 1.21)
*Defined as the discontinuation of study treatment or withdrawal from the study
Note: This table includes on-treatment AEs
Abbreviations: AE=adverse event; SAE=serious adverse event

The percentage of patients with any AE is higher for females than males across most treatment arms; however, the percentage of any SAE and any AE leading to dropout was similar across the two genders.

An imbalance between UMEC/VI 62.5 mcg/25 mcg and placebo in any AE is noted for females. A similar imbalance (though of lesser magnitude) was observed for the overall population (see Section 6.4.1).

Table 109. Summary of Adverse Events, by Age, Primary Efficacy Trials, ITT Population

	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N	N	N	N	N	N	N
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Any AE							
<64 years	335	453	445	217	335	592	213
	158 (47)	224 (49)	222 (50)	110 (51)	185 (55)	299 (51)	103 (48)
65-74 years	170	300	309	148	232	346	160
	81 (48)	167 (56)	175 (57)	78 (53)	128 (55)	173 (50)	76 (48)
75-84 years	49	85	78	50	61	93	48
	25 (51)	52 (61)	41 (53)	27 (54)	34 (56)	43 (46)	28 (58)
≥85 years	1	4	0	3	1	3	2
	0	4 (100)	0	1 (33)	1 (100)	3 (100)	1 (50)
Any SAE							
<64 years	335	453	445	217	335	592	213
	10 (3)	23 (5)	16 (4)	15 (7)	12 (4)	37 (6)	13 (6)
65-74 years	170	300	309	148	232	346	160

	12 (7)	19 (6)	22 (7)	11 (7)	21 (9)	16 (5)	7 (4)
75-84 years	49	85	78	50	61	93	48
	4 (8)	7 (8)	5 (6)	1 (2)	4 (7)	6 (6)	2 (4)
≥85 years	1	4	0	3	1	3	2
	0	1 (25)	0	0	0	0	0
Any AE Leading to Dropout*							
<64 years	335	453	445	217	335	592	213
	9 (3)	23 (5)	24 (5)	17 (8)	21 (6)	40 (7)	11 (5)
65-74 years	170	300	309	148	232	346	160
	14 (8)	18 (6)	19 (6)	8 (5)	14 (6)	15 (4)	5 (3)
75-84 years	49	85	78	50	61	93	48
	3 (6)	9 (11)	4 (5)	6 (12)	6 (10)	4 (4)	4 (8)
≥85 years	1	4	0	3	1	3	2
	0	0	0	0	0	0	0

Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 410 (Table 300), pg. 555-556 (Table 1.21)
*Defined as the discontinuation of study treatment or withdrawal from the study
Note: This table includes on-treatment AEs
Abbreviations: AE=adverse event; SAE=serious adverse event

The submission included an analysis of adverse events by age; as the number of patients in the ≥ 85 years of age category is small, this review focuses on the data for the <64 years of age, 65-74 years of age, and 75-84 years of age categories.

The percentage of patients with any AE, any SAE, and any AE leading to dropout in both the UMEC/VI 62.5 mcg/25 mcg and placebo treatment arms increases with age, with the magnitude of increase being larger for UMEC/VI 62.5 mcg/25 mcg. While increases with age are observed in some of the adverse event subgroups for some of the other treatment arms, these patterns are not as consistent as those noted for the UMEC/VI 62.5 mcg and placebo arms.

An imbalance between placebo and either one or both of the UMEC/VI treatment arms in any AE is noted across most of the age subcategories. A similar imbalance (though of lesser magnitude) was observed for the overall population (see Section 6.4.1).

6.5.4 Drug-Disease Interactions

The submission does not include an analysis of AEs by COPD severity.

The effect of renal function on the pharmacokinetics of UMEC/VI, UMEC, and VI were evaluated in trials DB2114636 (UMEC/VI and UMEC) and HZA113970 (VI as part of FF/VI). The effect of hepatic function on the pharmacokinetics of UMEC/VI, UMEC, and VI were evaluated in trials DB2114637 (UMEC/VI and UMEC) and HZA111789 (VI). These results were reviewed by the Clinical Pharmacology team. In patients with severe renal impairment, an increase in systemic VI exposure was noted, and in

patients with mild, moderate, or severe hepatic impairment, a decrease in systemic VI exposure was noted; however, the Clinical Pharmacology team recommends no dosage adjustments for use in either renal or hepatic impairment.

6.5.5 Drug-Drug Interactions

The clinical development program contains a number of drug-drug interactions studies including DB21133950, which evaluated UMEC/VI and UMEC with verapamil; AC4110106, which evaluated UMEC in normal and poor CYP2D6 metabolizers; and HZA105548, which evaluated VI (as part of FF/VI) with ketoconazole. These results were reviewed by the Clinical Pharmacology team, which does not recommend any dose adjustments in the context of co-administration with verapamil, in patients using concomitant CYP2D6 inhibitors or with genetic polymorphisms of CYP2D6 metabolism, or during co-administration with ketoconazole.

6.6 Additional Safety Evaluations

6.6.1 Human Carcinogenicity

No specific trials were conducted to assess for carcinogenicity in humans. The nonclinical review notes that two-year carcinogenicity studies were conducted in rats and mice, and both bioassays were negative for test-article related tumors.

6.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred in the UMEC/VI COPD clinical development program.

6.6.3 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Given the nature of the drug substances, drug abuse, withdrawal, and rebound are not anticipated for this combination product. Additionally, the mode of administration and low systemic bioavailability make abuse less likely.

6.7 Additional Submissions / Safety Issues

The Applicant provided a 120-Day Safety Update on April 12, 2013. This submission includes safety data from five ongoing trials evaluating UMEC/VI in patients with COPD,

which are summarized in Table 110. All treatments in these trials are administered once-daily. The original Application also noted an additional four ongoing trials (ALA116402, HZC113782, HZC113108, HZA113714); these trials are not included in the 120-Day Safety Update as they were either evaluating other indications (i.e., asthma) and/or part of the FF/VI development program.

Table 110. Ongoing Trials Included in 120-Day Safety Update

Trial	Objective	Design	N planned/ N randomized	Treatments	Duration	Primary Endpoint
DB2116133	Lung function	R, DB, CO	172/182	UMEC/VI 62.5/25 UMEC 62.5 VI 25	14 days	Weighted mean FEV1 0-6 hours post-dose
DB2114634	Efficacy, safety in Asia	R, DB, PG, PC	191 191 191 /263	UMEC/VI 125/25 UMEC/VI 62.5/25 P	24 weeks	Trough FEV1
CRT116277	Exercise endurance	R, DB, CO	24/5	UMEC/VI 125/25 UMEC 125	4 weeks	Change in dyspnea intensity (modified 10-point Borg scale)
DB2115362	Long-term safety in Japanese patients	OL	120/131	UMEC/VI 125/25	52 weeks	Incidence and severity of adverse events
AC4115361	Long-term safety in Japanese patients	OL	120/131	UMEC 125	52 weeks	Incidence and severity of adverse events

Source: Applicant's Submission dated April 12, 2013
Note: N planned=estimated number of planned randomized patients; N randomized=actual number of patients randomized by cut-off date

The 120-Day Safety Update includes data for the reporting period from August 23, 2012, through December 18, 2012. Data from trials DB2116133, DB2114634, and CRT116277 are blinded; data from trials DB2115362 and AC4115361 are unblinded as they are open-label in design. The number of planned and actual randomized patients (by the cut-off date) is provided in Table 110; the duration of exposure accumulated by the cut-off date is not included in the submission.

A total of three deaths are reported in this 120-Day Safety Update; all of the deaths are from Trial DB2115362, which is an open-label trial evaluating the long-term safety of

UMEC/VI 125 mcg/25 mcg. One of the deaths occurred in a 70 year-old male patient with a past medical history of colon cancer. The patient developed carcinomatous peritonitis 242 days after the start of UMEC/VI 125 mcg/25 mcg. This death was associated with three SAEs: malignant ascites, metastases to spine, and metastases to pelvis. Given the history of prior malignancy, this fatality is unlikely to be related to UMEC/VI.

A second fatality, associated with the SAE "COPD," is reported for a 71 year-old male treated with UMEC/VI 125 mcg/25 mcg for 181 days. A third fatality, associated with the SAE "sudden death" is reported for an 83-year old male treated with UMEC/VI 125 mcg/25 mcg for an unknown duration. It is not possible to draw definitive conclusions about causality based on the limited information available for these two fatal events.

A total of 30 non-fatal SAEs in 23 patients are reported in this 120-Day Safety Update, and are summarized in Table 111.

Table 111. Non-fatal SAEs, 120-Day Safety Update

Trial	Patients with non-fatal SAEs, n	Non-fatal SAEs, n	PTs (n)
DB2116133	1	1	Myocardial infarction (1)
DB2114634	10	13	COPD (7) Pneumonia (3) Road traffic accident (1) Hip fracture (1) Transient ischemic attack (1)
CRT116277	0	0	--
DB2115362	7	11	Pneumonia/pneumonia bacterial (3) COPD (4) Multiple injuries (1) Dysphagia (1) Shock hemorrhagic (1) Cor pulmonale (1)
AC4115361	5	5	COPD (2) Cerebral infarction (1) Gastric cancer (1) Colon adenoma (1)

Source: Applicant's Submission dated April 12, 2013, Section 5.3.5.3 (120-Day Safety Update Report Body), pg. 10-12

The SAE PTs reported for the five ongoing trials are similar to those reported in the original application.

Overall, no new or unexpected events are identified from the 120-Day Safety Update.

7 Postmarket Experience

UMEC/VI is not available for marketing in any country.

8 Literature Review/References

A PubMed search performed by this Reviewer [search term: umeclidinium AND vilanterol; no limits] was conducted on June 14, 2013, and yielded 4 references.[24,25,26,27] A brief review of these publications was performed. No new safety signals were identified.

[24] Mehta R, Kelleher D, Preece A, et al. Effect of verapamil on systemic exposure and safety of umeclidinium and vilanterol: a randomized and open-label study. *Int J Chron Obstruc Pulmon Dis.* 2013;8:159-67.
[25] Kelleher DL, Mehta RS, Jean-Francois BM, et al. Safety, tolerability, pharmacodynamics and pharmacokinetics of umeclidinium and vilanterol alone and in combination: a randomized crossover trial. *PLoS One.* 2012;7:e50716.
[26] Feldman G, Walker RR, Brooks J, et al. 28-Day safety and tolerability of umeclidinium in combination with vilanterol in COPD: a randomized placebo-controlled trial. *Pulm Pharmacol Ther.* 2012;25:465-71.
[27] Cazzola M, Page CP, Calzetta L, Matera MG. Pharmacology and therapeutics of bronchodilators. *Pharmacol Rev.* 2012;64:450-504.

Statistical Review for the Pulmonary-Allergy Drugs Advisory Committee Meeting

September 10, 2013

Umeclidinium/Vilanterol Inhalation Powder
NDA 203,975

Dose: Umeclidinium/Vilanterol 62.5 mcg/25 mcg once daily

Proposed indication: Maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease

Reviewer: Gregory Levin, PhD
Team Leader: Joan Buenconsejo, PhD
Division Director: Thomas Permutt, PhD

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

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1 EXECUTIVE SUMMARY

The contents of this document reflect preliminary findings and opinions based on reviews of the information submitted by the applicant in the new drug application (NDA) 203,975. These materials do not represent the final position of the Agency.

This document considers the inhaled umeclidinium and vilanterol combination product for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Umeclidinium (UMEC), a long-acting muscarinic antagonist, and vilanterol (VI), a long-acting β_2 agonist, are not currently marketed as single-ingredient products. Umeclidinium is a new molecular entity, and is currently under review as a monotherapy. Breo Ellipta, a related GlaxoSmithKline combination product containing vilanterol and the inhaled corticosteroid fluticasone furoate, was recently approved by the Agency.

We focus on the primary efficacy Studies 361, 373, 360, and 374, which were phase 3, multicenter, randomized, double-blind, parallel-group clinical trials designed to evaluate the 24-week efficacy of UMEC/VI for treatment of airflow obstruction in COPD. Patients in these studies had moderate-to-severe airflow obstruction, an extensive smoking history, and dyspnea. Concomitant use of systemic corticosteroids or additional long-acting bronchodilators was prohibited, but patients were permitted to use a stable dose of inhaled corticosteroids and study-provided salbutamol for as-needed relief medication.

In the only one of the four primary efficacy studies (Study 373) that included both placebo and UMEC/VI 62.5/25 mcg treatment arms, the combination product provided a statistically significant 0.167 L (95% confidence interval: 0.128, 0.207) improvement over placebo in the primary endpoint, 24-week mean change from baseline in trough FEV_1. There was also independent, supportive evidence of a treatment effect on FEV_1 from a 12-week phase 3 cross-over study, from comparisons against the active comparator tiotropium, and from results for the higher 125/25 mcg dose. The effectiveness of UMEC/VI was also supported by trends toward benefit with respect to several additional endpoints, including trough FEV_1 at earlier time points, weighted mean FEV_1, St. George's Respiratory Questionnaire (SGRQ) score, Shortness of Breath with Daily Activities (SOBDA) score, daily rescue medication use, and rate of COPD exacerbation. Estimated treatment effects for UMEC/VI 62.5/25 mcg were largely consistent across subgroups of interest, including sex, age, race, and geographic region.

There was evidence of the contribution of UMEC 62.5 mcg to the efficacy of the UMEC/VI 62.5/25 mcg combination product in Studies 360 and 373. There was evidence of the contribution of VI 25 mcg to the efficacy of the combination in only a single study (Study 373), but there was supportive evidence from independent, related study data. Supportive data included results from Study 361 for the higher 125/25 mcg dose, exploratory analyses from two phase 3 cross-over studies, and findings of efficacy relative to placebo for the VI monotherapy. There was also replicate evidence of efficacy, relative to placebo, for the UMEC monotherapy at the proposed 62.5 mcg dose.

There were substantial missing data in the primary efficacy studies, with dropout rates ranging from 15% to 33%. Dropouts on active treatment showed improvement in FEV_1 before withdrawal. Because the primary mixed effects model assumes that patient outcomes after withdrawal are missing at random, model estimates rely on the assumption that the treatment effect observed before dropout persisted after patients stopped taking the therapy. This assumption is implausible because bronchodilators are generally considered symptomatic and not disease-modifying therapies, and any FEV_1 improvement attributable to

a bronchodilator will likely go away within a few days of treatment discontinuation. Therefore, if the estimand of interest is the effectiveness of the assigned treatment in all randomized participants, at real world achievable adherence and tolerability, the mixed effects model used in the primary analysis likely does not provide a reliable estimate of the truth. As a result, we gave importance to a sensitivity analysis that multiply imputed missing data under the assumption that dropouts on all treatment arms would have had outcomes similar to those that were observed among completers in the control group. Statistical significance was maintained for all relevant treatment comparisons using this sensitivity analysis, but estimated magnitudes of treatment effect were approximately 20-30% smaller than those based on the primary analysis. For example, in Study 373, the estimated mean improvement in FEV_1 on UMEC/VI 62.5/25, relative to placebo, was 0.132 L (95% CI: 0.092, 0.173), as compared to 0.167 L (95% CI: 0.128, 0.207) in the primary analysis.

The complete safety evaluation was conducted by Dr. Jennifer Pippins, the Medical Reviewer, but we performed additional analyses to explore potential cardiovascular safety signals. Rates of major adverse cardiac events (MACE) were similar across the treatment arms, but an analysis of cardiovascular-related serious adverse events in the primary efficacy studies suggested a possible trend toward greater risk on the UMEC, VI, and UMEC/VI treatment arms, as compared to placebo and tiotropium. This imbalance in the rates of cardiovascular-related serious adverse events was not evident in analyses that included data from all of the phase 3 studies.

2 INTRODUCTION

2.1 Overview

2.1.1 Background

Chronic obstructive pulmonary disease (COPD) is a common, progressive disease that causes symptoms such as coughing and shortness of breath, and increases risks of disability and death. Patients with COPD may have chronic bronchitis and/or emphysema. Chronic bronchitis is characterized by inflammation of the lining of bronchial tubes that leads to increased mucus formation and airflow obstruction. In emphysema, the air sacs (alveoli) at the end of the smallest airways (bronchioles) in the lung are damaged and the amount of gas exchange is reduced.

Medications used to treat patients with COPD include bronchodilators and/or steroids. Bronchodilators, usually administered through an inhaler, relax muscles around the airways to improve airflow and relieve symptoms. There are two major types of bronchodilators: β_2 agonists, which act on β_2 receptors, and muscarinic antagonists, which inhibit the action of cholinergic nerves. Bronchodilators may be short-acting or long-acting, and many have been approved by FDA for treatment of airflow obstruction in COPD. Approved bronchodilators include but are not limited to the short-acting β_2 agonist salbutamol, short-acting muscarinic antagonist ipratropium, long-acting β_2 agonists (LABAs) salmeterol and formoterol, and long-acting muscarinic antagonists (LAMAs) tiotropium and aclidinium bromide. FDA has also improved inhalers that combine a LABA and inhaled corticosteroid (ICS), such as Advair (salmeterol and fluticasone propionate) and Symbicort (formoterol and budesonide). No LAMA/LABA combination products have been approved by FDA.

This review considers the inhaled umeclidinium plus vilanterol combination product for long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including chronic bronchitis and emphysema. Umeclidinium (UMEC), a long-acting muscarinic antagonist, and

vilanterol, a long-acting β_2 agonist, are not currently marketed as single-ingredient products (monotherapies). Two doses, UMEC/VI 62.5/25 mcg once daily and 125/25 mcg once daily, were evaluated in the phase 3 clinical development program, but only the lower 62.5/25 mcg dose is proposed for approval. We often omit the mcg unit when referring to doses of UMEC and VI in this document.

2.1.2 History of Drug Development

The applicant submitted the results of seven phase 3 clinical trials to support the regulatory approval of UMEC/VI for treatment of airflow obstruction in patients with COPD. The clinical development program for UMEC/VI was introduced to the Division of Pulmonary, Allergy, and Rheumatology Products under IND 106,616. UMEC and VI were developed under INDs 104,479 and 74,696, respectively, and dose-ranging studies were conducted separately for the UMEC and VI monotherapies.

Neither component is currently marketed as a single-ingredient inhalation product. Umeclidinium is a new molecular entity, and is currently under review as a monotherapy (NDA 205,382). A related GlaxoSmithKline combination product, Breo Ellipta (vilanterol/fluticasone furoate), was recently approved by the Agency (under NDA 204,275). This combination LABA/ICS inhalation powder is indicated for treatment of airway obstruction and reduction of exacerbations in patients with COPD, and the proposed dose of vilanterol (25 mcg) is the same as that in the UMEC/VI combination product. The dose selection, safety, and effectiveness of VI were reviewed as part of the Breo Ellipta program.

We next summarize important meetings and correspondence with the applicant. An end-of-phase 2 meeting was held on October 29, 2010. FDA generally agreed with the two proposed phase 3 placebo-controlled clinical trial designs, but recommended further exploration of UMEC doses lower than 125 mcg. FDA also requested justification of trough forced expiratory volume in 1 second (FEV_1) as the primary endpoint in the NDA submission, and noted that additional spirometric and non-spirometric outcomes would be evaluated during NDA review. It was also noted that only about 20-25% of the phase 3 study populations would come from North America, so generalizability of results to the United States would be a review issue.

FDA also sent comments to the applicant on December 17, 2010 regarding the proposed phase 3 study designs. The Division noted that replicate evidence of safety and efficacy was needed for each dose of the UMEC monotherapy, but that the proposed designs allowed comparisons of each dose against placebo only once. A preNDA meeting occurred on January 18, 2012. FDA expressed concern about dose selection because the results of the phase 3 trials would be needed to help determine the appropriate dose. The Division also stated that the clinical development program must provide replicate evidence of efficacy for both monotherapies, as well as substantial evidence of the efficacy and safety of UMEC /VI as compared to each monotherapy (and that this typically means replicate positive trials). FDA recommended that the applicant first submit an NDA for the UMEC monotherapy. Finally, it was noted that information regarding an active comparator is typically not included in a product label unless doing so is necessary to support the proposed use in the intended population.

Several meetings occurred between 2006 and 2010 to discuss the applicant's development of the Shortness of Breath with Daily Activities Questionnaire (SOBDA) as a patient-reported outcome measure of dyspnea. FDA indicated several concerns, including a determination that the content validity of the instrument had not been established. FDA submitted an information request to the applicant on February 24, 2013 regarding the potential effect of missing data on the reliability of efficacy results. FDA requested additional sensitivity analyses that did not rely on the assumption that observed treatment

effects before withdrawal would be preserved after patients stopped taking the therapy. The applicant responded with results based on two additional sensitivity analyses (see 3.2.2 for more details).

2.1.3 Specific Studies Reviewed

This review focuses on four phase 3 randomized clinical trials designed to evaluate the 24-week efficacy of UMEC/VI for treatment of airflow obstruction in COPD. Studies DB2113361 (361) and DB2113373 (373) were 24-week, randomized, double-blind, parallel-group, placebo-controlled clinical trials. Studies DB2113360 (360) and DB2113374 (374) were 24-week, randomized, double-blind, parallel-group, active-controlled clinical trials in which the LAMA tiotropium was the active treatment for comparison. Studies 361, 373, 360, and 374 will be referred to as the *primary efficacy studies*.

We also discuss results from three additional phase 3 studies of the combination product. Studies DB2114417 (417) and DB2114418 (418) were 12-week, randomized, double-blind, placebo-controlled, incomplete block, cross-over clinical trials to evaluate the efficacy of UMEC/VI with respect to both exercise endurance and lung function. Study DB2113359 (359) was a 52-week, randomized, double-blind, parallel-group, placebo-controlled trial to evaluate the safety and tolerability of UMEC/VI.

Finally, we briefly comment on several studies used to support the dose selection of umeclidinium and vilanterol. Studies AC4113589 (589), AC4113073 (73), AC4115321 (321), and AC4115408 (408) were randomized, double-blind, placebo-controlled trials that evaluated multiple doses of the UMEC monotherapy. Studies B2C111045 (45), HZA113310 (310), and B2C109575 (575) were randomized, double-blind, placebo-controlled, dose-ranging trials for the VI monotherapy.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted datasets were of acceptable quality and were adequately documented. We were able to reproduce the results of all key primary and secondary analyses.

3.2 Evaluation of Efficacy

3.2.1 Study Design

3.2.1.1 Primary Efficacy Studies

Studies 361, 373, 360, and 374 were designed to evaluate the 24-week efficacy of the once-daily bronchodilator UMEC/VI for treatment of airflow obstruction in COPD. The four studies were largely similar in design, with the exception of the treatment arms included. All were phase 3, multicenter, randomized, double-blind, parallel-group clinical trials in COPD patients with an extensive smoking history (≥10 pack-years), moderate-to-severe airflow obstruction (percent predicted $FEV_1 \leq 70\%$ and $FEV_1/FVC < 0.7$ post-salbutamol), and dyspnea (score of ≥2 on the Modified Medical Research Council Dyspnea Scale). Concomitant use of systemic corticosteroids or additional long-acting bronchodilators was prohibited, but patients were permitted to use inhaled corticosteroids at a stable dose ≤1000mg/day and study-provided salbutamol for as-needed relief medication.

There was a 1- to 2-week run-in period, followed by a 24-week double-blind treatment period. Visits occurred at Days 1 and 2, Weeks 4, 8, 12, 16, and 24, and 1 day after Week 24 (Day 169). All patients provided serial FEV_1 measurements at 15 and 30 minutes, and 1, 3, 6, 23, and 24 hours after dosing on Day 1 and Week 24, and at 15 and 30 minutes, and 1, 3, and 6 hours after dosing on Weeks 4 and 12. A subset of about 200 patients in each of Studies 361 and 373 provided more comprehensive 24-hour serial spirometry assessments, as well as 24-hour Holter monitoring, at Day 1, and Weeks 12 and 24.

Withdrawal ***from the treatment*** was equivalent to withdrawal ***from the study*** because patients who stopped taking the therapy early were not followed up for safety and efficacy assessment for the remainder of the 24-week treatment period. The protocol categorized primary reasons for early withdrawal from the study as follows: adverse event, withdrawal of consent, loss to follow-up, protocol deviation, lack of efficacy (e.g., COPD exacerbation), protocol-defined stopping criteria, and study termination. The many potential reasons for stopping treatment, combined with the fact that the applicant did not continue to collect information on patients who stopped therapy early, led to substantial missing data in efficacy and safety analyses (see 3.2.4.4 for further discussion). Patients who stopped treatment early were scheduled for an early withdrawal visit soon thereafter, but pulmonary function assessments were not performed.

The primary endpoint was change from baseline in predose trough FEV_1 on Day 169, where trough FEV_1 was defined as the mean of values obtained 23 and 24 hours after the dose of study treatment administered on Day 168 (Week 24). The lone secondary endpoint was the weighted mean FEV_1 0–6 hours postdose on Day 168. The weighted mean is time-weighted, calculated by dividing the area under the 0–6 hour postdose FEV_1 curve (using measurements at baseline, 15 and 30 minutes, 1, 3, and 6 hours, and the trapezoidal rule) by the time of observation. Mean SOBDA score on Week 24 was specified as a secondary endpoint in the original protocol, but was later changed to an "Other Efficacy Endpoint." Additional endpoints included trough and weighted mean FEV_1 at earlier time points, mean Transition Dyspnea Index (TDI) focal score, rescue salbutamol use, time to first COPD exacerbation, and several other spirometric outcomes.

Studies 361 and 373 were placebo-controlled trials with 3:3:3:2 randomization to UMEC/VI, UMEC, VI, and placebo, respectively. Different doses of UMEC were used in these two studies: 125 mcg in Study 361 and 62.5 mcg in Study 373 (for both the UMEC/VI combination and the UMEC monotherapy). In each study, a total sample size of 1463 patients was planned to provide 90% power to detect a 58 mL mean difference between the combination and either monotherapy, or a 68 mL difference between any active treatment and placebo (presuming about 30% missing data).

Studies 360 and 374 were tiotropium-controlled trials with 1:1:1:1 randomization to one of four treatment arms. In Study 360, the treatment arms were UMEC/VI 125/25 mcg, UMEC 62.5/25 mcg, VI 25 mcg, and tiotropium. In Study 374, the treatment arms were UMEC/VI 125/25 mcg, UMEC 62.5/25 mcg, UMEC 125 mcg, and tiotropium. In each study, a total sample size of 832 patients was planned to provide 98% power to detect a 100 mL mean difference between two of the treatment groups (presuming about 30% missing data).

3.2.1.2 Additional Studies

Studies 417 and 418 were phase 3, multicenter, randomized, double-blind, placebo-controlled, 2-period (12 weeks per period), incomplete block, cross-over clinical trials to evaluate the efficacy of UMEC/VI and its components with respect to both exercise endurance and lung function. The studies were identical

in design and conducted in COPD patients with an extensive smoking history, moderate-to-severe airflow obstruction and dyspnea, and lung hyperinflation (resting functional residual capacity (FRC) ≥120% of predicted normal). Concomitant use of systemic corticosteroids or additional long-acting bronchodilators was prohibited, but patients were permitted to use inhaled corticosteroids at a stable dose ≤1000mg/day and study-provided salbutamol for as-needed relief medication. A sample size of 312 was planned, and subjects were randomized to receive a sequence consisting of two of the following treatments: UMEC/VI 62.5/25, UMEC/VI 125/25, UMEC 62.5, UMEC 125, VI 25, or placebo. The studies consisted of a 12- to 21-day run-in period, followed by two 12-week treatment periods that were separated by a 2-week washout period. As in the other phase 3 studies, patients who stopped treatment early were also withdrawn from the study, and a number of reasons for early withdrawal were listed in the protocol (e.g., adverse event and lack of efficacy).

The co-primary endpoints were change from period baseline in exercise endurance time (EET) and trough FEV_1 at 12 weeks. The term co-primary indicates that statistical significance (at the typical two-sided 5% level) needed to be achieved on ***both*** endpoints for the trial to be considered positive. Trough FEV_1 at 12 weeks was defined as the value obtained 24 hours after dosing on Day 84, and EET was measured 3 hours postdose on Day 84 using the endurance shuttle walk test (ESWT). The incremental shuttle walk test (ISWT) was performed during the run-in and washout periods to determine the walking speed at which to conduct the ESWT in each patient during the subsequent treatment period. Secondary efficacy endpoints included measures of lung volume (inspiratory capacity, functional residual capacity, residual volume), and 3-hour postdose FEV_1 at Week 12.

Study 359 was a randomized, double-blind, parallel-group, placebo-controlled, 52-week clinical trial to evaluate the safety and tolerability of UMEC/VI. The plan was for a total sample size of 500 subjects to be randomized 2:2:1 to UMEC/VI 125/25, UMEC 125, or placebo. The primary objective was to evaluate safety, so no primary efficacy endpoints were specified, although spirometry measurements were obtained at randomization and Months 1, 3, 6, 9, and 12. As in the primary efficacy studies, the protocol listed several reasons for a patient to withdraw from the study. Possible reasons included adverse event, lack of efficacy, and protocol-defined stopping criteria based on electrocardiogram (ECG), Holter, or other laboratory abnormalities.

Studies 589, 73, 321, and 408 were randomized, double-blind, placebo-controlled trials evaluating multiple doses of the UMEC monotherapy in COPD. Study 589 was a 28-day parallel-group trial, Study 73 was an incomplete block, 3-period (14 days per period) cross-over trial, Study 321 was an incomplete block, 3-period (7 days per period) cross-over trial, and Study 408 was a 12-week, phase 3, parallel-group trial. Doses of UMEC in these trials ranged from 15.6 to 1000 mcg once daily, with some intermediate twice-daily doses evaluated as well.

Studies 45, 310, and 575 were randomized, double-blind, placebo-controlled, dose-ranging trials for the VI monotherapy. Study 45 was a 28-day parallel-group trial in COPD, Study 310 was a 5-period (7 days per period) cross-over trial in asthma, and Study 575 was a 28-day parallel-group trial in asthma. Doses of VI ranged from 3 mcg to 50 mcg once daily, with a 6.25 mcg twice-daily dose evaluated as well.

3.2.2 Statistical Methodologies

3.2.2.1 Primary Efficacy Studies

In Studies 361, 373, 360, and 374, the primary efficacy analysis was based on a mixed effects model for repeated measures (MMRM) to compare treatment groups with respect to the mean change from baseline

in trough FEV_1 at Day 169. The model used FEV_1 measurements at Days 2, 28, 56, 84, 112, 168, and 169, and included the following covariates: treatment group, baseline FEV_1, center group, smoking status, visit (categorical variable), visit-by-baseline FEV_1 interaction, and visit-by-treatment group interaction. Variance estimation was based on an unstructured covariance matrix, which does not presume a particular correlation structure for repeated FEV_1 measurements within patients over time. The MMRM model has important assumptions, including constant variance, normality of errors, and normality of random intercepts. Residuals plots suggested some departures from constant variance and normality. Therefore, we also fit simple linear regression models (using only baseline and Day 169 data) to estimate treatment effects, with adjustment for baseline FEV_1, center group, and smoking status, and the use of robust Huber-White standard errors. These analyses, which do not rely on assumptions of normality or constant variance, produced nearly identical estimates (results not shown) to the primary analyses.

The analysis of the secondary endpoint, weighted mean FEV_1 0–6 hours postdose (assessed at Days 1, 28, 84, and 168), was based on the same mixed effects model for repeated measures as the primary analysis. Analyses of other continuous endpoints, such as SOBDA score, SGRQ score, and mean daily rescue medication use, were based on analogous MMRM models. The treatment effect on time to first exacerbation was evaluated using a Cox proportional hazards model adjusting for smoking status and center group, with the exact method to handle ties. Analyses of binary endpoints (e.g. proportion of responders based on some threshold change) were based on logistic regression models adjusting for baseline value, smoking status, and center group.

The applicant used sequential step-down closed testing procedures to control the false positive rate across the multiple comparisons in each study. In Studies 361 and 373, the following treatment comparisons were performed in order: (1) UMEC/VI versus placebo; (2) UMEC versus placebo; (3) VI versus placebo; (4) UMEC/VI versus VI; and (5) UMEC/VI versus UMEC. These analyses were performed first for the primary endpoint (trough FEV_1), and then for the secondary endpoint (weighted mean FEV_1). In Studies 360 and 374, the following treatment comparisons were performed in order: (1) UMEC/VI versus tiotropium; (2) UMEC/VI versus vilanterol (Study 360) or UMEC (Study 374). Analyses were performed first for the high dose (UMEC/VI 125/25) with respect to both the primary and secondary endpoints, and then for the low dose (UMEC/VI 62.5/25). The applicant did not control for multiplicity across other efficacy endpoints (e.g., SGRQ, SOBDA, rescue medication use, exacerbation rate) in any of the studies. Efficacy analyses for Study 360 excluded one study center (with 20 subjects) at which the applicant identified significant deviations from Good Clinical Practice (GCP). Results were similar when the center was included.

The applicant performed a number of prespecified sensitivity analyses based on multiple imputation to explore the potential effect of missing data. The applicant's Missing at Random (MAR) approach assumes that data are missing at random and bases multiple imputation on mean and covariance estimation performed separately within each treatment arm. The Copy Differences from Control (CDC) approach assumes that changes over time in future outcomes in patients who withdraw from all treatment arms are similar to those future changes observed among completers in the control group. The Last Mean Carried Forward (LMCF) approach assumes that a constant mean trend over time (0 mL/year) or constant mean rate of decline (-25 mL/year), starting with the last observed value, would have occurred in all subjects following withdrawal. All imputation models used the same covariates to help estimate missing outcome data as were included in the primary MMRM model.

The underlying assumptions of these three imputation approaches are likely not scientifically plausible. If the estimand of interest is the effectiveness of the assigned treatment in all randomized participants, then the MAR, CDC, and LMCF approaches all essentially assume that any observed treatment effect before

dropout would have persisted in patients, even after they stopped taking the therapy. This is unlikely, because bronchodilators are generally considered symptomatic and not disease-modifying therapies, and their effects on FEV_1 likely do not persist more than a few days after patients stop using them.

We find more merit in two additional sensitivity analyses provided by the applicant in response to an information request. Both the Copy Reference (CR) and Jump to Reference (J2R) approaches multiply impute missing data using estimated means in the control group. This is justifiable scientifically under the assumption that patients who stop taking the therapy will no longer benefit from it in the future, and thus will tend to have outcomes similar to those in the control group (in particular, the subset of control patients with similar baseline characteristics). The difference in the two methods is that the CR approach presumes patients who withdraw from the active arm were on the control (rather than the active) treatment before dropout; the resulting positive residuals before withdrawal leads to imputed values that slowly (rather than quickly) trend towards the estimated mean on the control arm. Given that the majority of withdrawals occurred at or before Day 112, and therefore at least two months before the primary efficacy assessment, we would expect any treatment effect observed before dropout to have gone completely away during the time following treatment discontinuation. Therefore, we focus on the Jump to Reference approach in assessing questions about the effectiveness of the treatments in all randomized participants (often called the intention-to-treat or de facto estimand). Although the scientific justification of the Jump to Reference approach seems reasonable, it is important to note that any such sensitivity analysis still relies on untestable assumptions about unobserved data. More information about the different multiple imputation models used by the applicant can be found at www.missingdata.org.uk.

Analyses of SOBDA were based on weekly mean scores (reported in patient electronic diaries), which were considered non-missing if at least four of the seven days had non-missing daily mean scores. The Week 24 mean score was defined as the mean of the daily scores occurring between Day 163 and either Day 169 or the day before the Day 168 visit, whichever came first. Because many Day 168 visits were scheduled a few days early, several patients did not have four days of SOBDA diary entries during Week 24. Therefore, this definition resulted in substantial missing data in SOBDA analyses.

The mean number of rescue medication puffs per day and percentage of rescue-free days over 24 weeks were considered non-missing if at least half of the daily electronic diary entries between Day 2 and Day 169 (or the day before the Day 169 visit) were non-missing. As a result, patients who completed regular daily diary entries for at least 12 weeks but dropped out early would still contribute data to analyses of rescue medication use over 24 weeks. These analyses will only reliably estimate mean differences in rescue medication use over 24 weeks if a patient's rescue medication use prior to dropout accurately reflects his or her rescue use after study withdrawal (and if data from patients without at least 12 weeks of diary entries are missing at random).

3.2.2.2 Additional Studies

In Studies 417 and 418, the primary efficacy analyses were based on MMRM models to compare treatment groups with respect to the mean change from baseline in EET, and trough FEV_1, at Week 12. For EET, the model used measurements at Day 2, and Weeks 6 and 12, and included the following covariates: treatment group, period baseline walking speed, mean baseline walking speed (mean of two period baseline speeds), period, center group, smoking status, visit (categorical variable), visit-by-mean walking speed interaction, and visit-by-treatment group interaction. Variance estimation was based on an unstructured covariance matrix. An analogous model was used for FEV_1.

Comparisons of the two doses of the combination product (UMEC/VI 62.5/25 and UMEC/VI 125/25) against placebo were designated as primary, with a step-down testing procedure starting with the high dose comparisons (for both EET and FEV_1) to account for multiplicity. Comparisons of the combination against placebo with respect to secondary efficacy endpoints, as well as comparisons of the monotherapies against placebo, and of the combination product against the monotherapies, were also of interest, but multiplicity was not controlled across these additional analyses. We performed additional supportive analyses in the subgroup of patients who completed both 12-week treatment periods.

Study 359 was a safety trial and therefore did not have prespecified primary efficacy analyses. However, exploratory efficacy analyses were conducted for trough FEV_1, rescue puffs per day, and time to exacerbation using the same methods as in the four 24-week primary efficacy trials.

3.2.3 Dose Selection

Separate dose-ranging studies were conducted for UMEC and VI to support the selection of the dose and dosing interval for both the monotherapies and UMEC/VI combination product in the primary efficacy studies. Data on the efficacy of different doses of UMEC are available from phase 2 Studies 321, 73, and 589, and from phase 3 Study 408 (Table 1). The results suggested no additional improvement in FEV_1 at doses greater than 125 mcg. In addition, adverse events were more common at doses of 250 mcg and above. The results suggest that the 62.5 and 125 mcg doses selected for phase 3 study were reasonable.

Study 321 was the only clinical trial that evaluated doses lower than 62.5 mcg. In the 6 hours postdose at Day 1, there was clear separation in efficacy between all once-daily UMEC doses and placebo (Figure 1). UMEC 15.6 mcg demonstrated the smallest improvement in FEV_1 and UMEC 125 mcg demonstrated the largest improvement, while the intermediate 31.25 and 62.5 mcg time-response profiles were largely overlapping. There was a similar dose-response pattern in the 24 hours postdose at Day 7 (Figure 2). At both Day 1 and Day 7, the time-response profile of the approved LAMA tiotropium was comparable to those of the once-daily 62.5 and 125 mcg UMEC doses selected for phase 3 study. These trends are also evident when examining mean differences in trough FEV_1 at Day 8 (Figure 3). Figure 4 and Figure 5 present time-response profiles at Days 1 and 7, respectively, for both once- and twice-daily doses of UMEC. Average FEV_1 improvements over time on twice-daily UMEC 15.6 and 31.25 mcg were similar to that of once-daily UMEC 62.5 mcg. This trend was also evident in comparisons of trough FEV_1 at Day 8 (Figure 6).

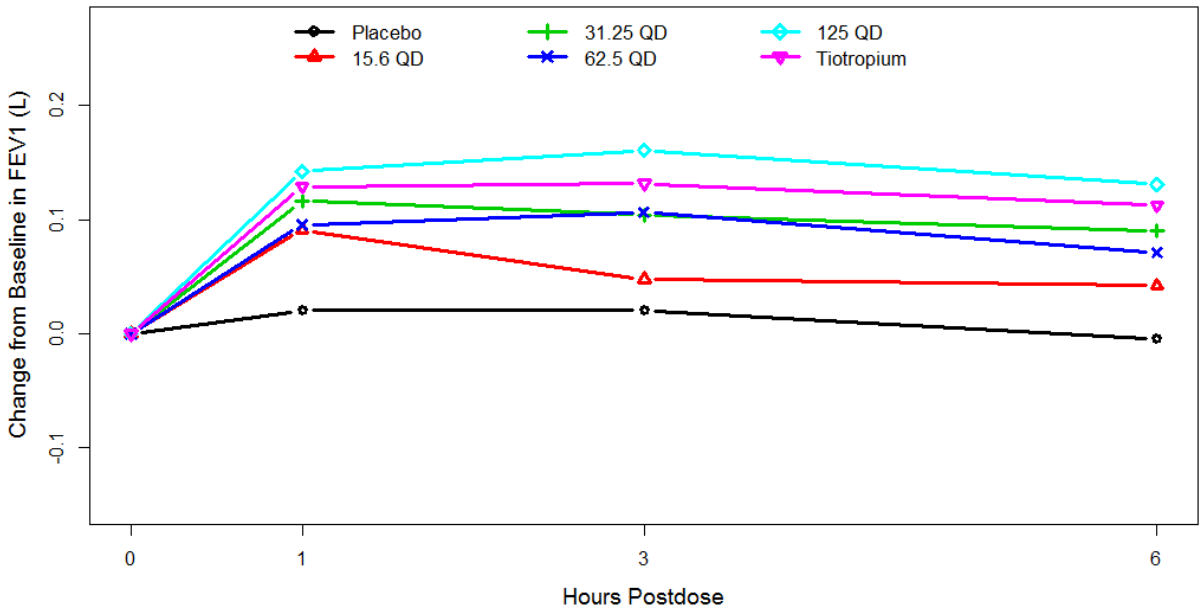
Data on the efficacy of different once-daily doses of VI are available from phase 2 Study 45 in COPD, as well as phase 2 Studies 575 and 310 in asthma (Table 2). These results were reviewed as part of the Breo Ellipta development program and are summarized in the reviews of that application, as well as in the label. In summary, results from Study 45 suggested greater benefit for 25 and 50 mcg VI, as compared to lower doses. Results from the asthma studies did not show a clear separation between the 12.5 and 25 mcg doses with respect to trough FEV_1, but analyses of a number of secondary efficacy endpoints suggested some added benefit for the 25 mcg dose. Both Study 45 and Study 575 results suggested that a greater improvement in mean trough FEV_1 may be possible with VI 50 mcg, as compared to the selected 25 mcg dose.

Table 1. Differences from Placebo in Mean Change from Baseline in Trough FEV_1 for Different Once-Daily Doses of the Umeclidinium Monotherapy in Studies 321, 73, 589, and 408

	Difference from Placebo for LS Mean Change from Baseline in Trough FEV_1 (L) (95% CI) by once daily UMEC dose (mcg) [a]						
Study	**15.6**	**31.25**	**62.5**	**125**	**250**	**500**	**1000**
AC4115321 at Day 8	0.113 (0.058, 0.168)	0.101 (0.045, 0.158)	0.124 (0.068, 0.179)	0.183 (0.127, 0.239)			
AC4113073 at Day 15			0.128 (0.060, 0.196)	0.147 (0.077, 0.216)	0.095 (0.027, 0.162)	0.140 (0.074, 0.205)	0.186 (0.113, 0.259)
AC4113589 at Day 29				0.159 (0.088, 0.229)	0.168 (0.099, 0.238)	0.150 (0.080, 0.220)	
AC4115408 at Day 85			0.127 (0.052, 0.202)	0.152 (0.076, 0.229)			

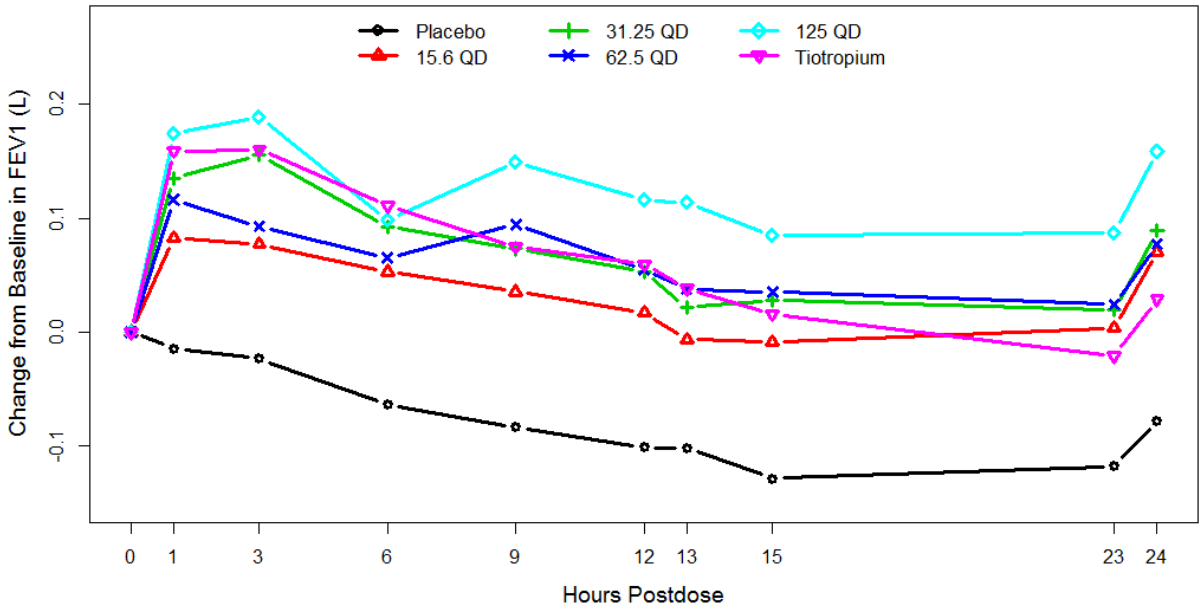
Source: Table 2, Clinical Overview

Figure 1. Postdose 6-Hour Serial Mean Change from Baseline in FEV_1 at Day 1 for Different Once-Daily Umeclidinium Doses, and Tiotropium, in Study 321



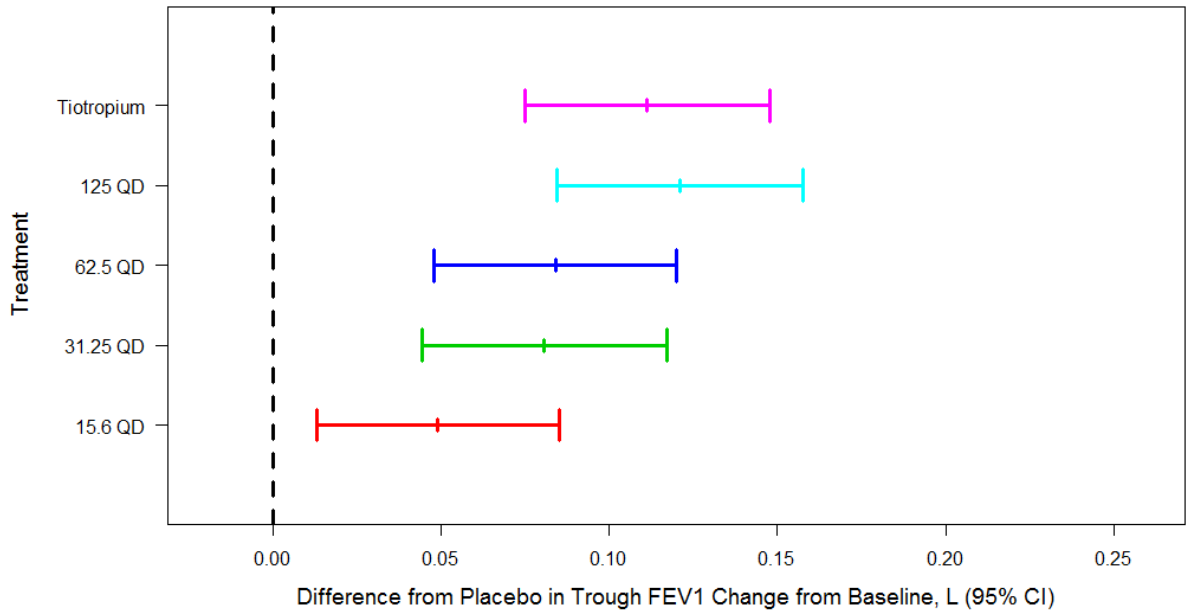
Abbreviations: QD = once-daily, BD = twice-daily

Figure 2. Postdose 24-Hour Serial Mean Change from Baseline in FEV_1 at Day 7 for Different Once-Daily Umeclidinium Doses, and Tiotropium, in Study 321



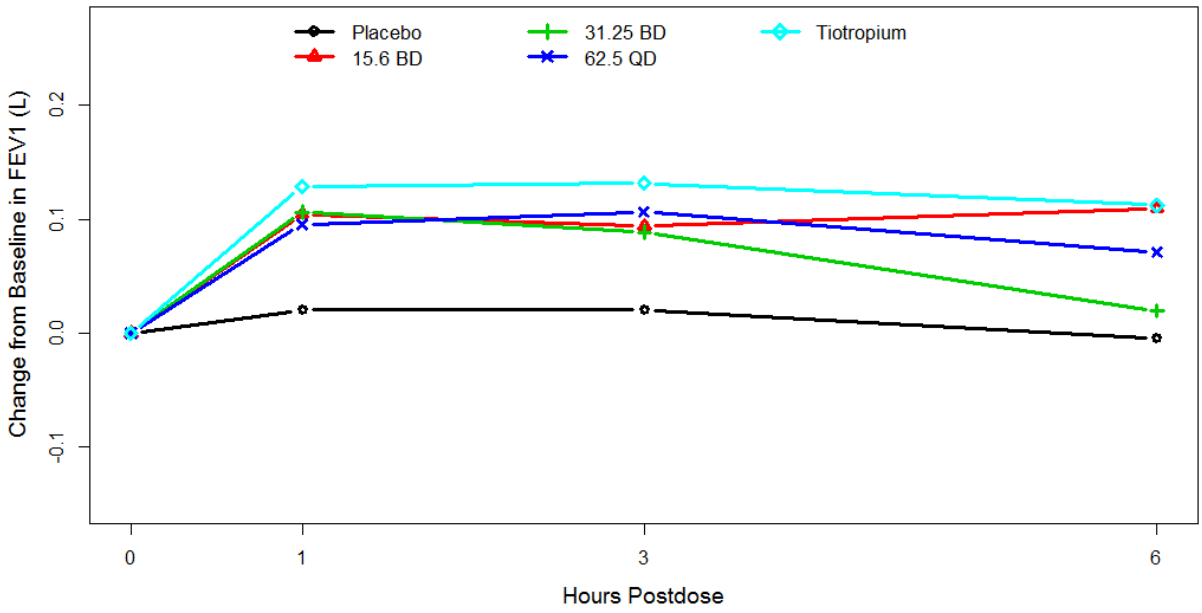
Abbreviations: QD = once-daily, BD = twice-daily

Figure 3. Difference from Placebo in Mean Change from Baseline in Postdose 0-6 Hour Weighted Mean FEV_1 at Day 1 for Different Once-Daily Umeclidinium Doses, and Tiotropium, in Study 321



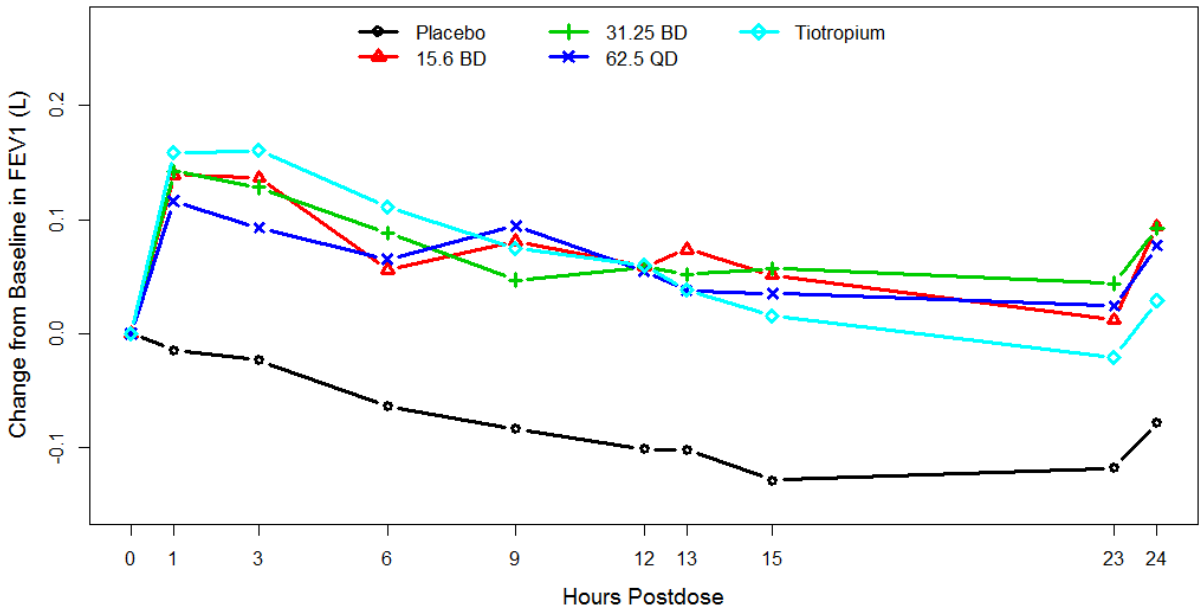
Estimates from mixed effects model adjusting for period baseline, mean period baseline, and period, with random subject effect
Abbreviations: QD = once-daily, BD = twice-daily

Figure 4. Postdose 6-Hour Serial Mean Change from Baseline in FEV_1 at Day 1 for Different Once- and Twice-Daily Umeclidinium Doses, and Tiotropium, in Study 321



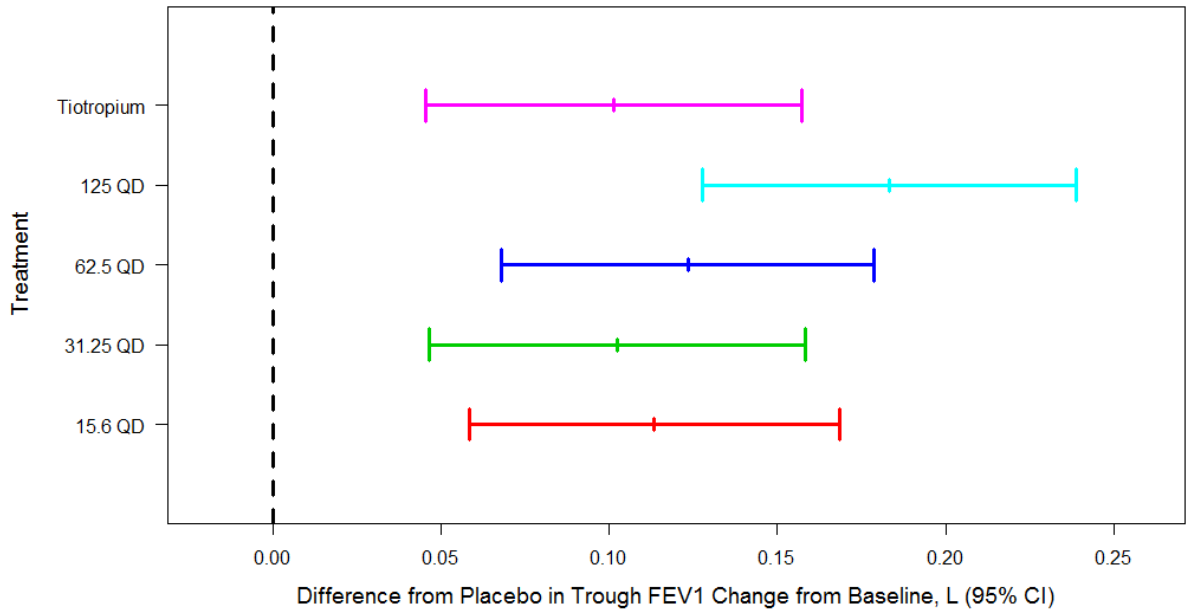
Abbreviations: QD = once-daily, BD = twice-daily

Figure 5. Postdose 24-Hour Serial Mean Change from Baseline in FEV_1 at Day 7 for Different Once- and Twice-Daily Umeclidinium Doses, and Tiotropium, in Study 321



Abbreviations: QD = once-daily, BD = twice-daily

Figure 6. Difference from Placebo in Mean Change from Baseline in Trough FEV_1 at Day 8 for Different Once-Daily Umeclidinium Doses, and Tiotropium, in Study 321



Estimates from mixed effects model adjusting for period baseline, mean period baseline, and period, with random subject effect
Abbreviations: QD = once-daily, BD = twice-daily

Table 2. Differences from Placebo in Mean Change from Baseline in Trough FEV_1 for Different Once-Daily Doses of the Vilanterol Monotherapy in Studies 45, 575, and 310

	Difference from Placebo for LS Mean Change from Baseline in Trough FEV_1 (L) (95% CI) by once daily VI dose (mcg) [a]				
Study	**3**	**6.25**	**12.5**	**25**	**50**
COPD					
B2C111045 at Day 29	0.092 (0.039,0.144)	0.098 (0.046, 0.150)	0.110 (0.057,0.162)	0.137 (0.085, 0.190)	0.165 (0.112,0.217)
Asthma					
B2C109575 at Day 28	0.064 (-0.036, 0.164)	0.069 (-0.029, 0.168)	0.130 (0.030, 0.230)	0.121 (0.023, 0.220)	0.162 (0.062, 0.261)
HZA113310 at Day 7		0.094 (0.049, 0.140)	0.102 (0.057, 0.147)	0.125 (0.080, 0.170)	

Source: Table 3, Clinical Overview

3.2.4 Patient Disposition, Demographic and Baseline Characteristics

Baseline characteristics were similar across the primary efficacy Studies 361, 373, 360, and 374, which consisted of 1,489, 1,532, 843, and 869 patients, respectively (Appendix: Table 21, Table 22, Table 23, and Table 24). The combined study population was predominantly male (68%), White (84%), and older in age (mean 63 years). Twenty-five percent of patients were treated at U.S. sites. Only 3% and 9% of patients were Black and Asian, respectively. Within U.S. sites, 10% of patients were Black. Ninety percent of subjects had percent predicted FEV_1 30–80%, 50% of subjects were current smokers, and 49% used inhaled corticosteroids. Patients were enrolled at 153, 163, 91, and 95 different centers from several countries around the world in Studies 361, 373, 360, and 374, respectively. There were no large imbalances in baseline characteristics across the treatment arms in the four studies.

As described previously, the design of the primary efficacy studies was such that subjects who stopped treatment early would also be withdrawn from the study. There were many prespecified reasons for withdrawal, such as adverse event, lack of efficacy (e.g., COPD exacerbation), and protocol deviation. As a result, there was substantial patient dropout. The proportions of subjects withdrawing from the four trials over time are displayed by treatment group in Figure 7, Figure 8, Figure 9, and Figure 10. In Studies 361, 373, 360, and 374, 25%, 23%, 17%, and 23% of patients failed to complete the 24-week treatment period, respectively. Dropout rates tended to be slightly higher on placebo than the other treatment arms in Studies 361 and 373, with the differences primarily attributable to greater placebo dropout because of lack of efficacy (Table 3 and Table 4). The most common reasons for study withdrawal across all four studies were adverse event, lack of efficacy, protocol-defined stopping criteria, and withdrawal of consent.

Figure 7. Proportion of Patients Withdrawing Early over Time in Study 361

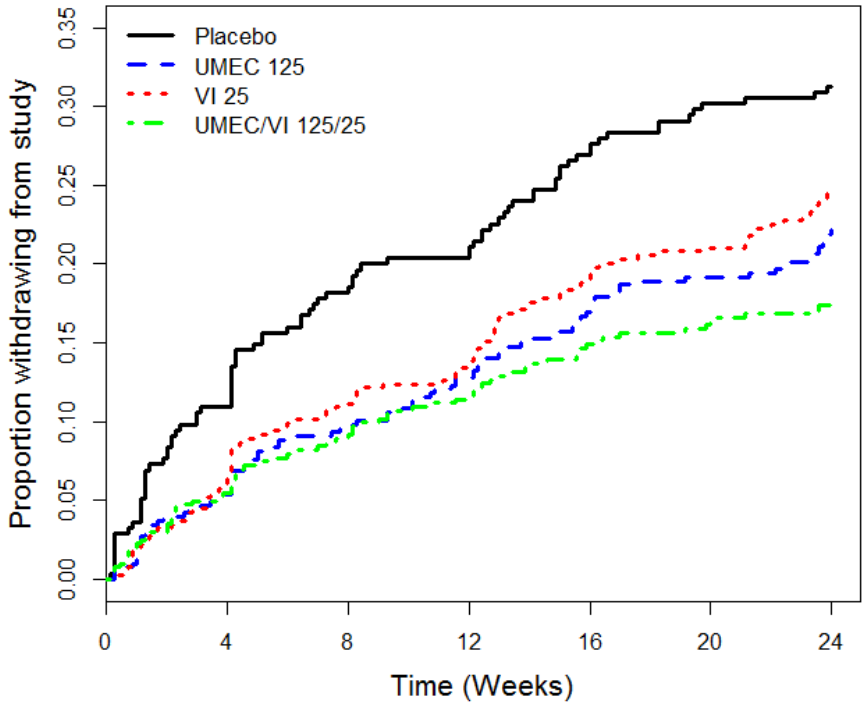


Figure 8. Proportion of Patients Withdrawing Early over Time in Study 373

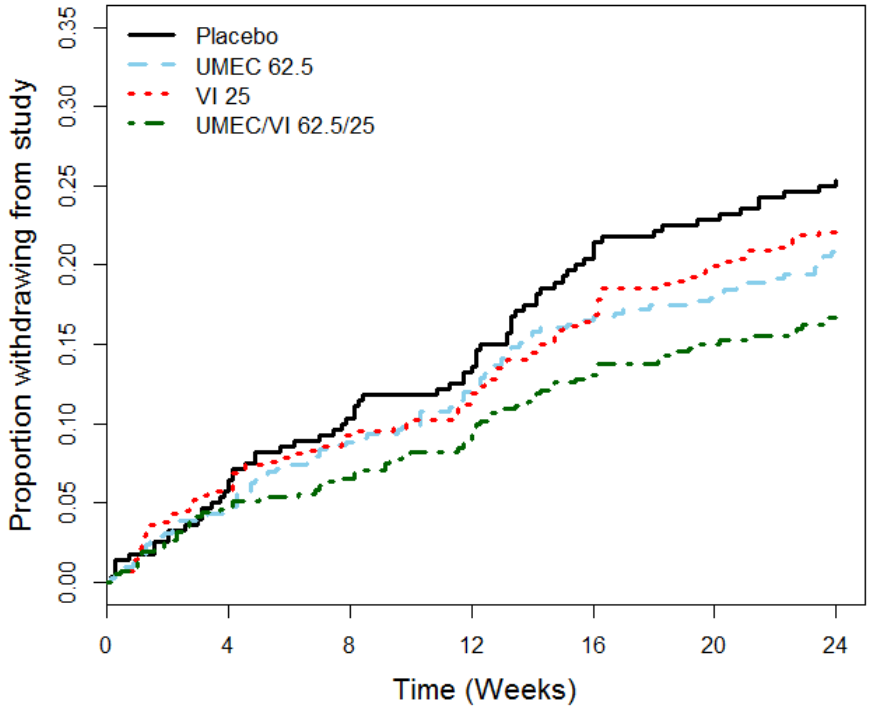


Figure 9. Proportion of Patients Withdrawing Early over Time in Study 360

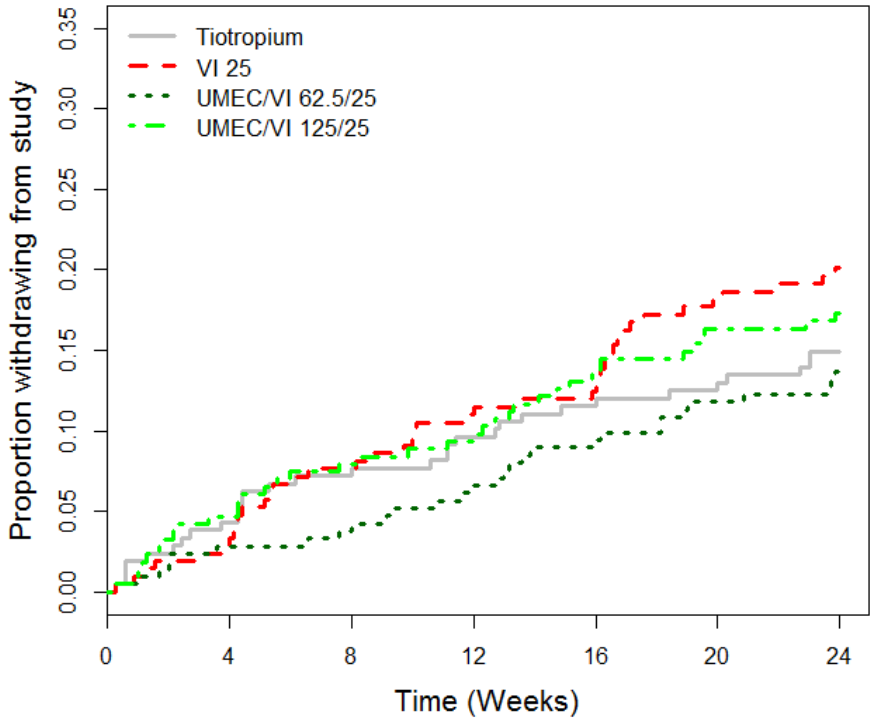


Figure 10. Proportion of Patients Withdrawing Early over Time in Study 374

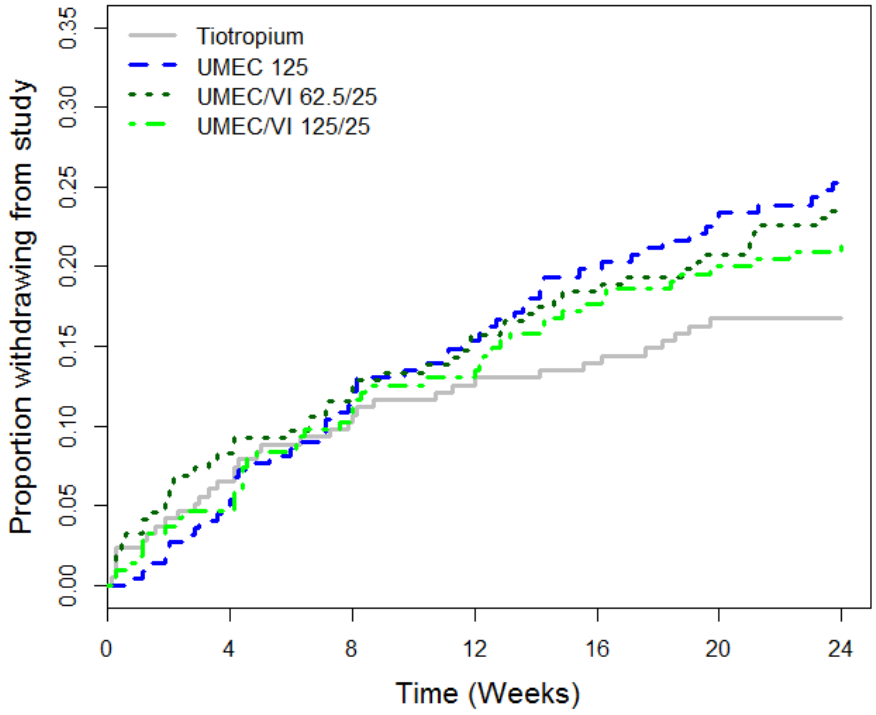


Table 3. Proportion of Patients Failing to Complete Study 361, by Reason for Withdrawal

	Placebo	UMEC 125	VI 25	UMEC/VI 125/25	Overall
Completed study	183 (67%)	312 (77%)	298 (74%)	325 (81%)	1118 (75%)
Did not complete study	92 (33%)	95 (23%)	106 (26%)	78 (19%)	371 (25%)
Adverse event	17 (6%)	24 (6%)	25 (6%)	18 (4%)	84 (6%)
Lack of efficacy	44 (16%)	38 (9%)	37 (9%)	24 (6%)	143 (10%)
Lost to follow-up	0 (0%)	2 (0%)	1 (0%)	3 (1%)	6 (0%)
Protocol deviation	4 (1%)	3 (1%)	11 (3%)	5 (1%)	23 (2%)
Protocol-defined stopping criteria	16 (6%)	15 (4%)	14 (3%)	13 (3%)	58 (4%)
Withdrew consent	11 (4%)	13 (3%)	18 (4%)	15 (4%)	57 (4%)

Table 4. Proportion of Patients Failing to Complete Study 373, by Reason for Withdrawal

	Placebo	UMEC 62.5	VI 25	UMEC/VI 62.5/25	Overall
Completed study	204 (73%)	324 (78%)	318 (76%)	332 (80%)	1178 (77%)
Did not complete study	76 (27%)	94 (22%)	103 (24%)	81 (20%)	354 (23%)
Adverse event	9 (3%)	34 (8%)	24 (6%)	23 (6%)	90 (6%)
Lack of efficacy	37 (13%)	20 (5%)	32 (8%)	20 (5%)	109 (7%)
Lost to follow-up	1 (0%)	0 (0%)	3 (1%)	2 (0%)	6 (0%)
Protocol deviation	4 (1%)	7 (2%)	5 (1%)	6 (1%)	22 (1%)
Protocol-defined stopping criteria	9 (3%)	13 (3%)	24 (6%)	15 (4%)	61 (4%)
Withdrew consent	16 (6%)	20 (5%)	15 (4%)	15 (4%)	66 (4%)

Table 5. Proportion of Patients Failing to Complete Study 360, by Reason for Withdrawal

	Tiotropium	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25	Overall
Completed study	177 (85%)	165 (79%)	181 (85%)	173 (81%)	696 (83%)
Did not complete study	31 (15%)	44 (21%)	31 (15%)	41 (19%)	147 (17%)
Adverse event	9 (4%)	10 (5%)	10 (5%)	15 (7%)	44 (5%)
Lack of efficacy	7 (3%)	17 (8%)	9 (4%)	5 (2%)	38 (5%)
Lost to follow-up	1 (0%)	1 (0%)	0 (0%)	1 (0%)	3 (0%)
Protocol deviation	0 (0%)	7 (3%)	1 (0%)	4 (2%)	12 (1%)
Protocol-defined stopping criteria	5 (2%)	2 (1%)	3 (1%)	10 (5%)	20 (2%)
Withdrew consent	9 (4%)	7 (3%)	8 (4%)	6 (3%)	30 (4%)

Table 6. Proportion of Patients Failing to Complete Study 374, by Reason for Withdrawal

	Tiotropium	UMEC 125	UMEC/VI 62.5/25	UMEC/VI 125/25	Overall
Completed study	176 (82%)	165 (74%)	163 (75%)	166 (77%)	670 (77%)
Did not complete study	39 (18%)	57 (26%)	54 (25%)	49 (23%)	199 (23%)
Adverse event	11 (5%)	17 (8%)	20 (9%)	15 (7%)	63 (7%)
Lack of efficacy	13 (6%)	22 (10%)	12 (6%)	9 (4%)	56 (6%)
Lost to follow-up	2 (1%)	0 (0%)	1 (0%)	0 (0%)	3 (0%)
Protocol deviation	1 (0%)	1 (0%)	4 (2%)	4 (2%)	10 (1%)
Protocol-defined stopping criteria	6 (3%)	7 (3%)	8 (4%)	11 (5%)	32 (4%)
Withdrew consent	6 (3%)	10 (5%)	9 (4%)	10 (5%)	35 (4%)

Baseline characteristics in the cross-over Studies 417 and 418, and the long-term safety Study 359, were largely similar to those of the primary efficacy studies. One notable difference was that all patients in Studies 417 and 418 had lung hyperinflation, resulting in mean percent predicted normal FRC values of 153.6% and 151.6%, respectively. There were no noticeable imbalances in baseline characteristics across the randomized treatment arms in these three studies.

There was substantial patient dropout in Studies 417, 418, and 359. In Study 417, 95 (27%) of the 348 randomized subjects failed to remain in the study through both 12-week treatment periods. In Study 418, 96 (31%) of the 307 randomized subjects failed to do so. The most common reasons for dropout were adverse event and lack of efficacy. In Study 359, 220 (39%) of the 562 randomized subjects did not complete the 52-week study (Table 7). Dropout rates overall were similar across the placebo, UMEC 125, and UMEC/VI 125/25 treatment arms. There was greater study withdrawal on placebo than the active arms for lack of efficacy and for adverse event, but greater withdrawal on the active arms because of protocol-defined stopping criteria. In particular, there was greater withdrawal on both UMEC 125 (16%) and UMEC/VI 125/25 (16%) than placebo (7%) because of either ECG or Holter abnormalities.

Table 7. Proportion of Patients Failing to Complete Study 359, by Reason for Withdrawal

	Placebo	UMEC 125	UMEC/VI 125/25	Overall
Completed study	66 (61%)	133 (59%)	143 (63%)	342 (61%)
Did not complete study	43 (39%)	94 (41%)	83 (37%)	220 (39%)
Adverse event	13 (12%)	21 (9%)	17 (8%)	51 (9%)
Lack of efficacy	9 (8%)	3 (1%)	1 (1%)	13 (2%)
Protocol-defined stopping criteria[1]	8 (7%)	37 (16%)	36 (16%)	81 (14%)
ECG abnormality	0 (0%)	12 (5%)	13 (6%)	25 (4%)
Holter abnormality	8 (7%)	26 (11%)	26 (12%)	60 (11%)
Lab abnormality	0 (0%)	1 (0%)	0 (0%)	1 (0%)
Other	13 (12%)	33 (15%)	29 (13%)	75 (13%)

[1] Patients who dropped out because of protocol-defined stopping criteria could have had more than one abnormality

3.2.5 Results and Conclusions

We largely focus on findings from the four primary efficacy studies (Studies 361, 373, 360, and 374). We discuss comparisons of UMEC/VI and its components against placebo in 3.2.5.1, the contribution of each component to the efficacy of the combination in 3.2.5.2, and comparisons against the approved LAMA tiotropium in 3.2.5.3. We evaluate the results of sensitivity analyses to explore the potential impact of missing data in 3.2.5.4, and summarize findings from the cross-over Studies 417 and 418 and the long-term safety Study 359 in 3.2.5.5.

3.2.5.1 Primary Efficacy Studies: Placebo Comparisons

Data are available for treatment comparisons of UMEC/VI against placebo only from Studies 361 (at the 125/25 mcg dose) and 373 (at the 62.5/25 mcg dose). In each of these trials, treatment with the combination product resulted in a statistically significant, greater change from baseline in the mean trough FEV_1 at 24 weeks, as compared to placebo (Table 8). In Study 361, the estimated difference in mean trough FEV_1 change between UMEC/VI 125/25 and placebo was 0.238 L (95% confidence interval [CI]: 0.200, 0.276; $p<0.0001$). In Study 373, the estimated difference in mean trough FEV_1 change between UMEC/VI 62.5/25 and placebo was 0.167 L (95% CI: 0.128, 0.207; $p<0.0001$).

Observed effects of the combination product on trough FEV_1 were evident as early as Day 2 and then remained relatively constant over the 24-week treatment period (Figure 11 and Figure 12). There was also evidence of efficacy for UMEC/VI with respect to the secondary endpoint, 0–6 hour weighted mean FEV_1. Mean differences in weighted mean FEV_1 between the experimental treatments and placebo in Studies 361 and 373 were slightly larger than the analogous trough FEV_1 comparisons, with strong statistical evidence against the null hypothesis of no treatment effect (Table 8). In addition, data from the subset of patients with 24-hour serial FEV_1 assessments demonstrated consistently higher mean FEV_1 levels with the combination product than placebo throughout the 24 hours postdose (Figure 13 and Figure 14). Finally, empirical distribution plots, in which dropouts were treated as the worst potential outcomes, suggested benefits of UMEC/VI treatment with respect to summary measures of the FEV_1 distribution besides the mean, such as the median (Figure 15 and Figure 16). These figures can also be used to descriptively compare treatment groups with respect to the proportion achieving certain threshold changes in FEV_1 at 24 weeks, such as an improvements of at least 0.1 or 0.2 L.

UMEC/VI also showed trends toward benefit for additional non-spirometric endpoints of interest, including mean changes from baseline in the SOBDA and SGRQ scores at 24 weeks, mean puffs of rescue mediation per day, percent of rescue-free days, and exacerbation rate over 24 weeks (Table 9). In Study 373, 35 (13%) and 27 (7%) patients suffered a COPD exacerbation on placebo and UMEC/VI 62.5/25, respectively. The separation between the treatment groups in the proportions suffering an exacerbation over time was also evident in Kaplan Meier plots (Appendix: Figure 27 and Figure 28). The applicant did not control for multiplicity across these additional comparisons, but the strength of statistical evidence without adjustment was high ($p<0.005$ for all comparisons). Although these trends toward benefit may not be sufficient to support labeling claims, they do provide support for the observed treatment effect on the primary endpoint.

In summary, there was strong statistical evidence of beneficial effects of both UMEC/VI 62.5/25 and UMEC/VI 125/25, as compared to placebo, with respect to the primary and secondary endpoints, in addition to supportive trends across a range of other spirometric and non-spirometric endpoints of interest. However, it is important to note that there was evidence of superiority against placebo for the proposed 62.5/25 mcg dose of the combination product from only one of the primary efficacy studies (Study 373; see 5.1 for further discussion).

There was also statistical evidence of benefit for the umeclidinium and vilanterol monotherapies relative to placebo with respect to trough FEV_1 at 24 weeks (Table 8). The estimated difference in mean trough FEV_1 change between UMEC 125 and placebo was 0.160 L in Study 361, and the difference between UMEC 62.5 and placebo was 0.115 L in Study 373. There was replicate evidence of efficacy for UMEC 62.5 in phase 3 Study 408, where the estimated treatment effect on trough FEV_1 at 12 weeks was 0.127 L (95% CI: 0.052, 0.202; $p<0.001$). The estimated differences in mean trough FEV_1 change between VI 25 and placebo were 0.124 and 0.072 L in Studies 361 and 373, respectively. Efficacy of the monotherapies

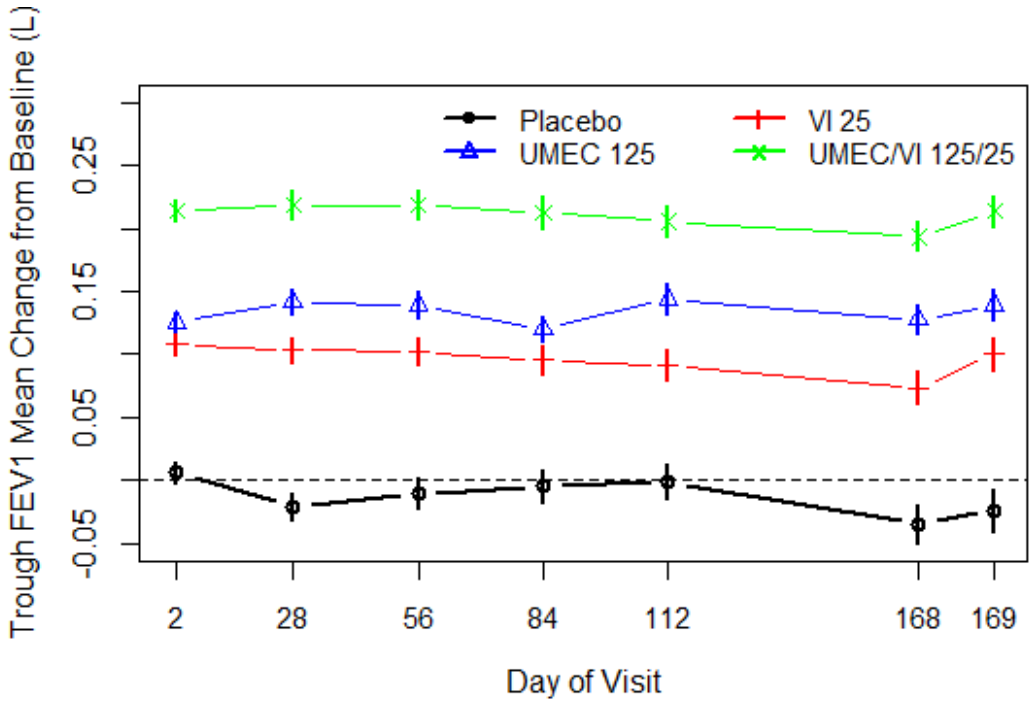
relative to placebo was also supported by comparisons of FEV_1 at earlier time points (Figure 11 and Figure 12), comparisons of 0–6 hour weighed mean FEV_1 (Table 8), and by comparisons of FEV_1 throughout the 24 hours postdose (Figure 13 and Figure 14). Evidence of benefits for the UMEC and VI monotherapies relative to placebo for additional non-spirometric endpoints of interest was generally not as strong as for the combination product, but estimates trended in the positive direction (Table 9).

Table 8. Comparisons of UMEC, VI, and UMEC/VI against Placebo with Respect to the Mean Changes from Baseline in Trough FEV_1 (Primary Endpoint) and 0–6 Hour Weighted Mean FEV_1 (Secondary Endpoint) at 24 Weeks in Studies 361 and 373

	Mean Change from Baseline in Trough FEV_1 (L)	Mean Difference[1] in Trough FEV_1 (L) (95% CI) p-value	Mean Change from Baseline in 0–6 Hour Weighted Mean FEV_1 (L)	Mean Difference[1] in 0–6 Hour Weighted Mean FEV_1 (L) (95% CI) p-value
Study 361				
Placebo	-0.031		-0.018	
UMEC 125	0.129	0.160 (0.122, 0.198) <0.0001	0.160	0.178 (0.141, 0.216) <0.0001
VI 25	0.093	0.124 (0.086, 0.162) <0.0001	0.127	0.145 (0.107, 0.182) <0.0001
UMEC/VI 125/25	0.207	0.238 (0.200, 0.276) <0.0001	0.269	0.287 (0.250, 0.324) <0.0001
Study 373				
Placebo	0.004		0.001	
UMEC 62.5	0.119	0.115 (0.076, 0.155) <0.0001	0.151	0.150 (0.110, 0.190) <0.0001
VI 25	0.076	0.072 (0.032, 0.112) 0.0004	0.123	0.122 (0.082, 0.162) <0.0001
UMEC/VI 62.5/25	0.171	0.167 (0.128, 0.207) <0.0001	0.243	0.242 (0.202, 0.282) <0.0001

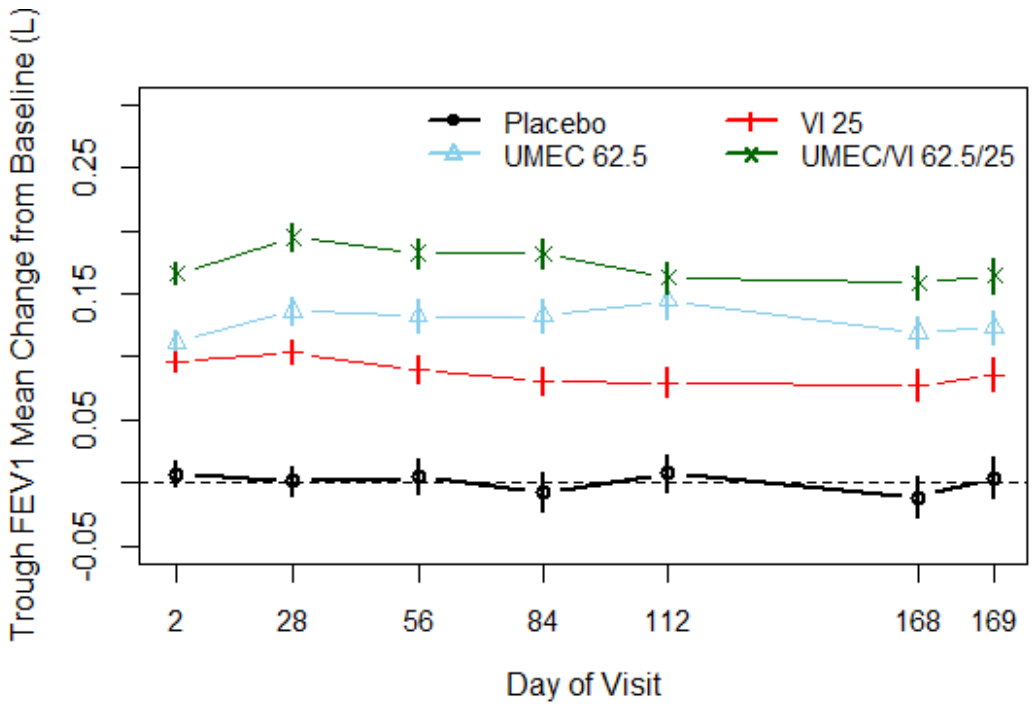
[1] Estimated differences, as compared to placebo, from linear mixed effects models with the following covariates: treatment group, baseline FEV_1, center group, smoking status, visit, visit-by-baseline FEV_1 interaction, and visit-by-treatment group interaction

Figure 11. Mean Change from Baseline in Trough FEV_1 over Time in Study 361



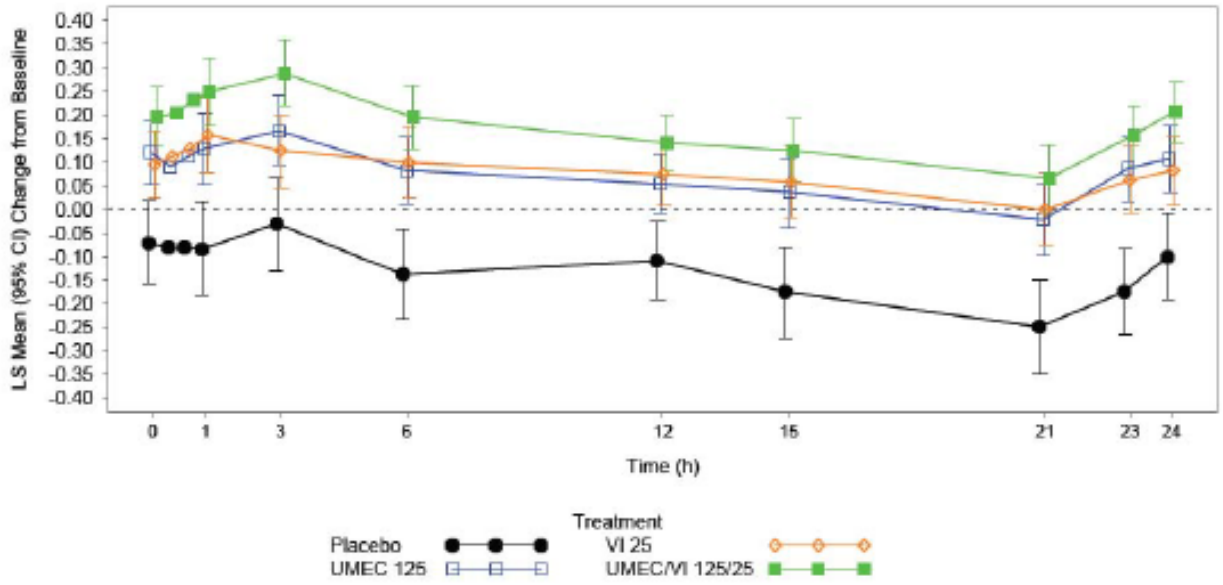
Unadjusted means based on observed data are displayed
Error bars represent ± 1 standard error

Figure 12. Mean Change from Baseline in Trough FEV_1 over Time in Study 373



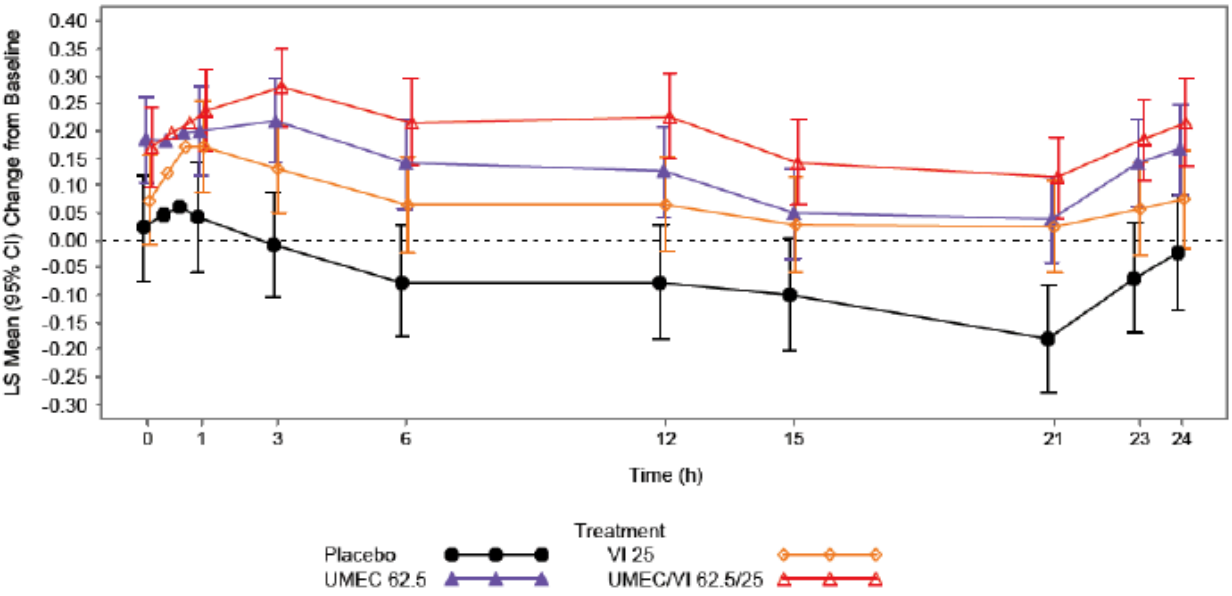
Unadjusted means based on observed data are displayed
Error bars represent ± 1 standard error

Figure 13. Mean Change from Baseline in Serial FEV_1 over 0 to 24 Hours Postdose at Day 168 in the Subset of Study 361 with 24-Hour measurements



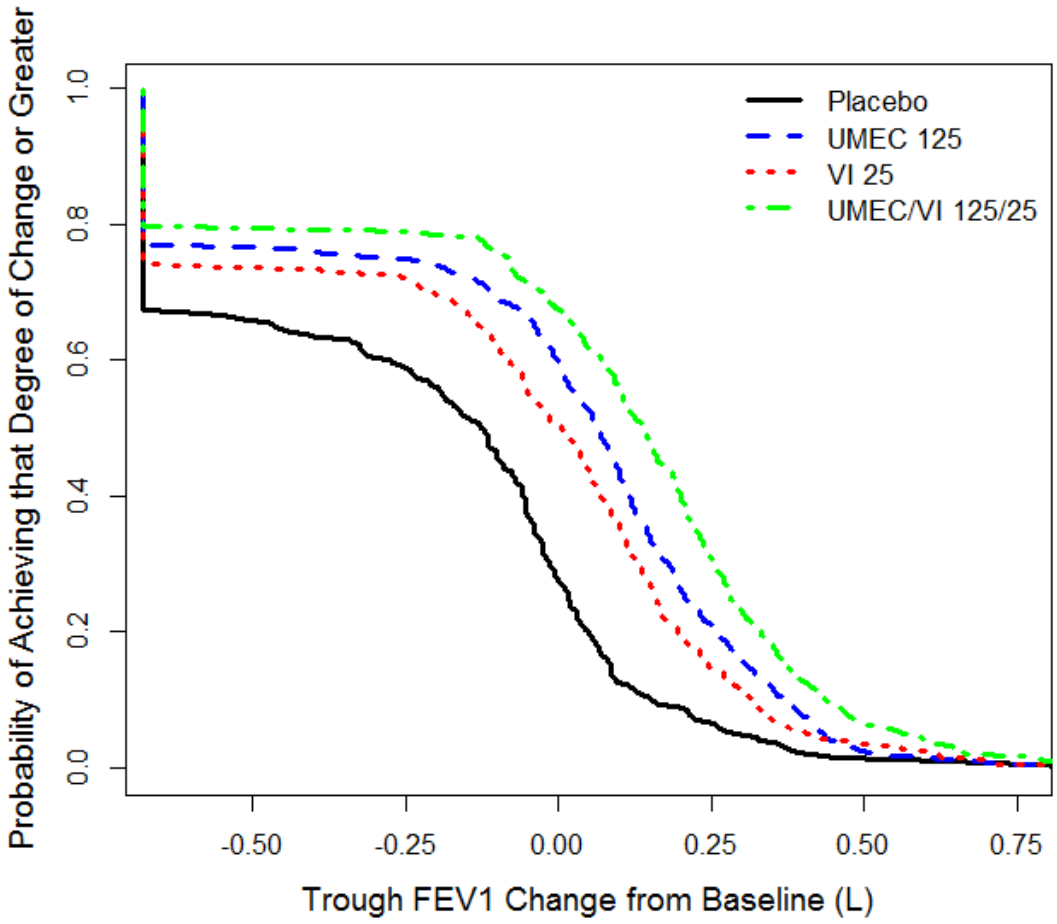
Source: Figure 15, Applicant's Clinical Study Report
Error bars represent 95% confidence intervals for the mean

Figure 14. Mean Change from Baseline in Serial FEV_1 over 0 to 24 Hours Postdose at Day 168 in the Subset of Study 373 with 24-Hour measurements



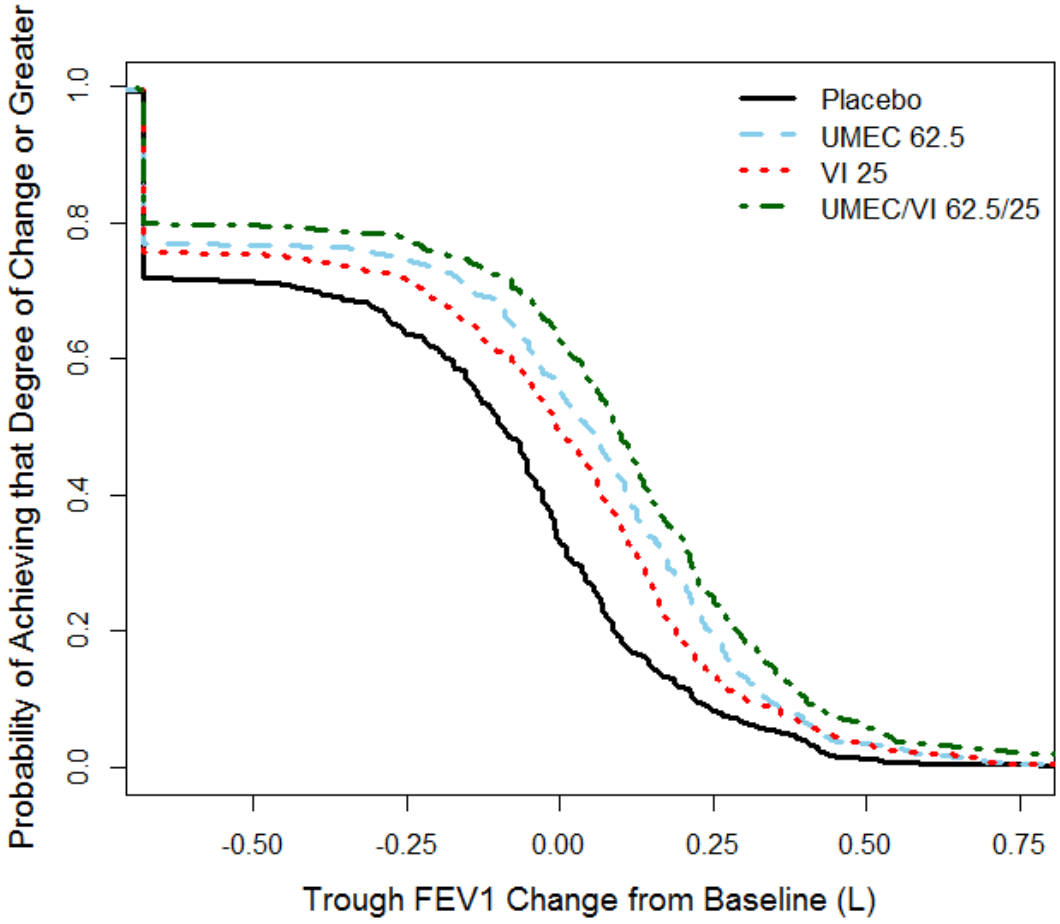
Source: Figure 15, Applicant's Clinical Study Report
Error bars represent 95% confidence intervals for the mean

Figure 15. Empirical Distribution Function for Change from Baseline in Trough FEV_1 at 24 Weeks in Study 361



Plot displays one minus the empirical distribution function
Early study withdrawal was considered the worst possible outcome

Figure 16. Empirical Distribution Function for Change from Baseline in Trough FEV_1 at 24 Weeks in Study 373



Plot displays one minus the empirical distribution function
Early study withdrawal was considered the worst possible outcome

Table 9. Comparisons against Placebo for Additional Supportive Endpoints in Studies 361 and 373

	Mean SOBDA Score at 24 Weeks[1] (95% CI)	Mean SGRQ Score at 24 Weeks[1] (95% CI)	Mean Rescue Puffs per Day over 24 Weeks[1] (95% CI)	Mean Percent Rescue-Free Days over 24 Weeks[1] (95% CI)	Exacerbation Rate over 24 Weeks[2] (95% CI)
Study 361					
UMEC 125	-0.08 (-0.17, 0.02)	-0.31 (-2.47, 1.85)	-0.84 (-1.29, -0.39)	9.17 (3.51, 14.84)	0.50 (0.35, 0.93)
VI 25	-0.03 (-0.13, 0.06)	-0.87 (-3.05, 1.30)	-0.79 (-1.24, -0.34)	9.56 (3.85, 15.26)	0.52 (0.32, 0.83)
UMEC/VI 125/25	-0.15 (-0.24, -0.06)	-3.60 (-5.76, 1.44)	-1.49 (-1.94, -1.04)	16.74 (11.08, 22.41)	0.36 (0.21, 0.60)
Study 373					
UMEC 62.5	-0.10 (-0.19, -0.00)	-4.69 (-7.07, 2.31)	-0.27 (-0.77, 0.22)	8.40 (3.17, 13.62)	0.60 (0.37, 0.96)
VI 25	-0.14 (-0.24, -0.05)	-5.19 (-7.58, 2.80)	-0.92 (-1.41, -0.43)	13.55 (8.32, 18.78)	0.71 (0.45, 1.12)
UMEC/VI 62.5/25	-0.17 (-0.26, -0.08)	-5.51 (-7.89, -3.13)	-0.83 (-1.32, -0.34)	12.51 (7.31, 17.71)	0.48 (0.29, 0.79)

[1] Estimated differences, as compared to placebo, from linear mixed effects models with the following covariates: treatment group, baseline value, center group, smoking status, visit, visit-by-baseline interaction, and visit-by-treatment group interaction
[2] Estimated hazard ratios, as compared to placebo, from Cox proportional hazards models with the following covariates: treatment group, center group, smoking status

3.2.5.2 Primary Efficacy Studies: Contributions of Components to Efficacy of Combination

The contributions of the components to the efficacy of a combination product can be established by comparisons of the combination to each monotherapy. The contribution of UMEC was evaluated through a comparison between UMEC/VI and VI, and the contribution of VI was evaluated through a comparison between UMEC/VI and UMEC (Table 10). There was consistent evidence of the contribution of UMEC to the efficacy of the combination product with respect to the primary endpoint of mean change from baseline in trough FEV_1 at 24 weeks (evidence for contribution of UMEC 62.5 to UMEC/VI 62.5/25 from Studies 373 and 360, evidence for contribution of UMEC 125 to UMEC/VI 125/25 from Studies 361 and 374). Evidence was not as strong for the contribution of vilanterol to the efficacy of the combination. There was statistical evidence of a contribution of VI to the combination product at the proposed dose, UMEC/VI 62.5/25, in Study 373 (difference in mean trough FEV1: 0.052 L, p=0.0021). There was evidence of a contribution of VI to the efficacy of the higher dose combination product in Study 361, but not in Study 374.

The contributions of both the UMEC and VI components were supported by analyses of the secondary endpoint 0–6 hour weighted mean FEV_1 (Table 10). There was also some separation between the

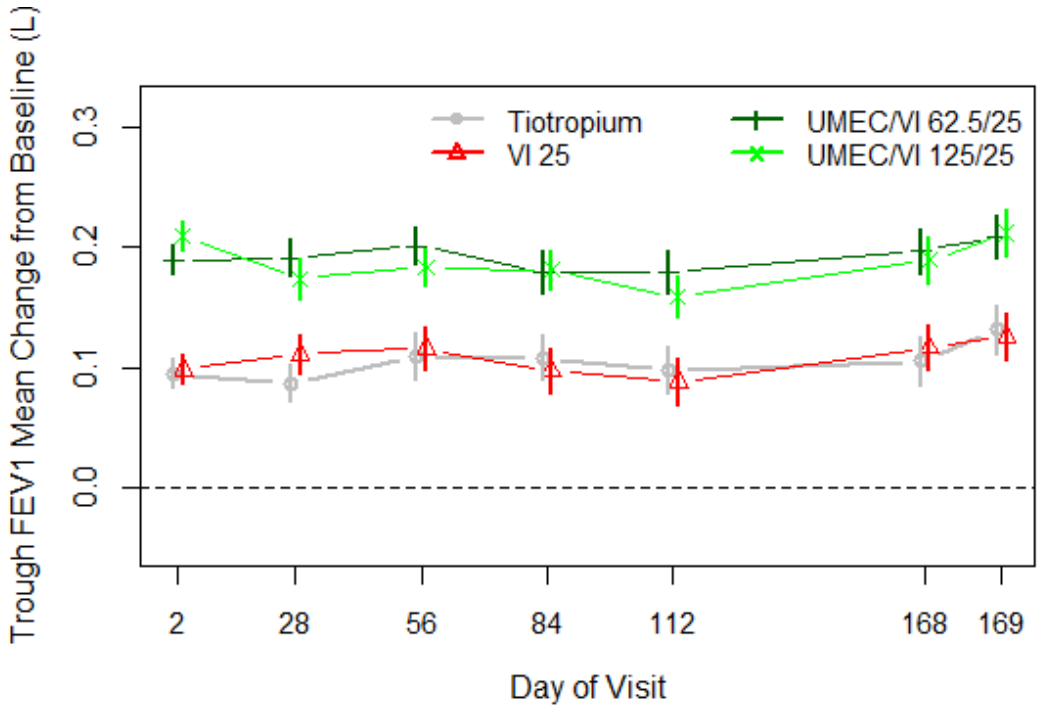
monotherapy and combination treatment arms in descriptive figures presenting trough FEV_1 at earlier time points (Figure 17 and Figure 18), in addition to empirical FEV_1 distribution functions (Figure 19 and Figure 20). There was not consistent evidence, however, for the contribution of the components with respect to other non-spirometric endpoints of interest (Table 11), although estimates generally trended in the direction of benefit (for the efficacy of the combination relative to the monotherapies).

Table 10. Contributions of the Umeclidinium and Vilanterol Components to the Efficacy of the Combination Product with Respect to the Mean Changes from Baseline in Trough FEV_1 (Primary Endpoint) and 0–6 Hour Weighted Mean FEV_1 (Secondary Endpoint) at 24 Weeks in Studies 361, 373, 360, and 374

	Mean Difference[1] in Trough FEV_1 (L) (95% CI) p-value	Mean Difference[1] in 0–6 Hour Weighted Mean FEV_1 (L) (95% CI) p-value
Study 361		
UMEC 125 Contribution (UMEC/VI 125/25 vs. VI 25)	0.114 (0.081, 0.148) <0.0001	0.142 (0.109, 0.175) <0.0001
VI 25 Contribution (UMEC/VI 125/25 vs. UMEC 125)	0.079 (0.046, 0.112) <0.0001	0.109 (0.076, 0.141) <0.0001
Study 373		
UMEC 62.5 Contribution (UMEC/VI 62.5/25 vs. VI 25)	0.095 (0.060, 0.130) <0.0001	0.120 (0.084, 0.155) <0.0001
VI 25 Contribution (UMEC/VI 62.5/25 vs. UMEC 62.5)	0.052 (0.017, 0.087) 0.0021	0.092 (0.056, 0.127) <0.0001
Study 360		
UMEC 62.5 Contribution (UMEC/VI 62.5/25 vs. VI 25)	0.088 (0.037, 0.139) 0.0007	0.077 (0.025, 0.128) 0.0035
UMEC 125 Contribution (UMEC/VI 125/25 vs. VI 25)	0.093 (0.041, 0.144) 0.0004	0.088 (0.037, 0.140) 0.0008
Study 374		
VI 25 Contribution (UMEC/VI 125/25 vs. UMEC 125)	0.037 (-0.012, 0.087) 0.142	0.076 (0.029, 0.122) 0.0014

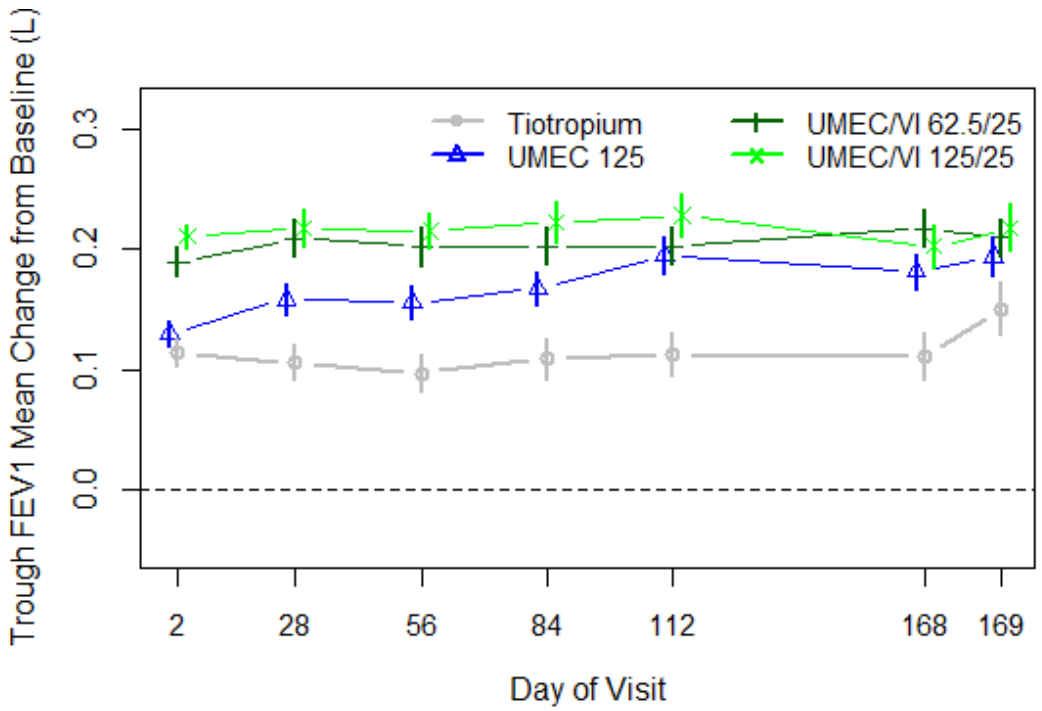
[1] Estimate differences, comparing the combination to monotherapy, from linear mixed effects models with the following covariates: treatment group, baseline FEV_1, center group, smoking status, visit, visit-by-baseline FEV_1 interaction, and visit-by-treatment group interaction

Figure 17. Mean Change from Baseline in Trough FEV_1 over Time in Study 360



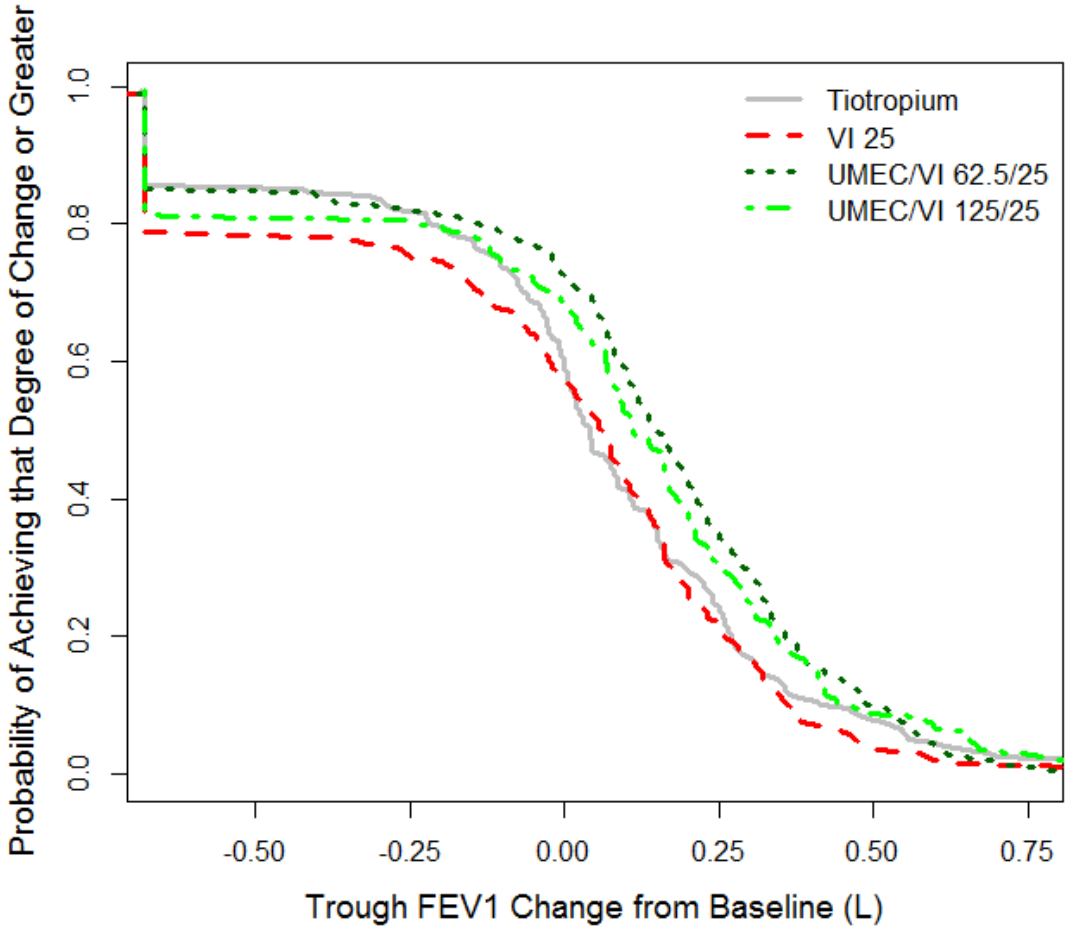
Unadjusted means based on observed data are displayed
Error bars represent ± 1 standard error

Figure 18. Mean Change from Baseline in Trough FEV_1 over Time in Study 374



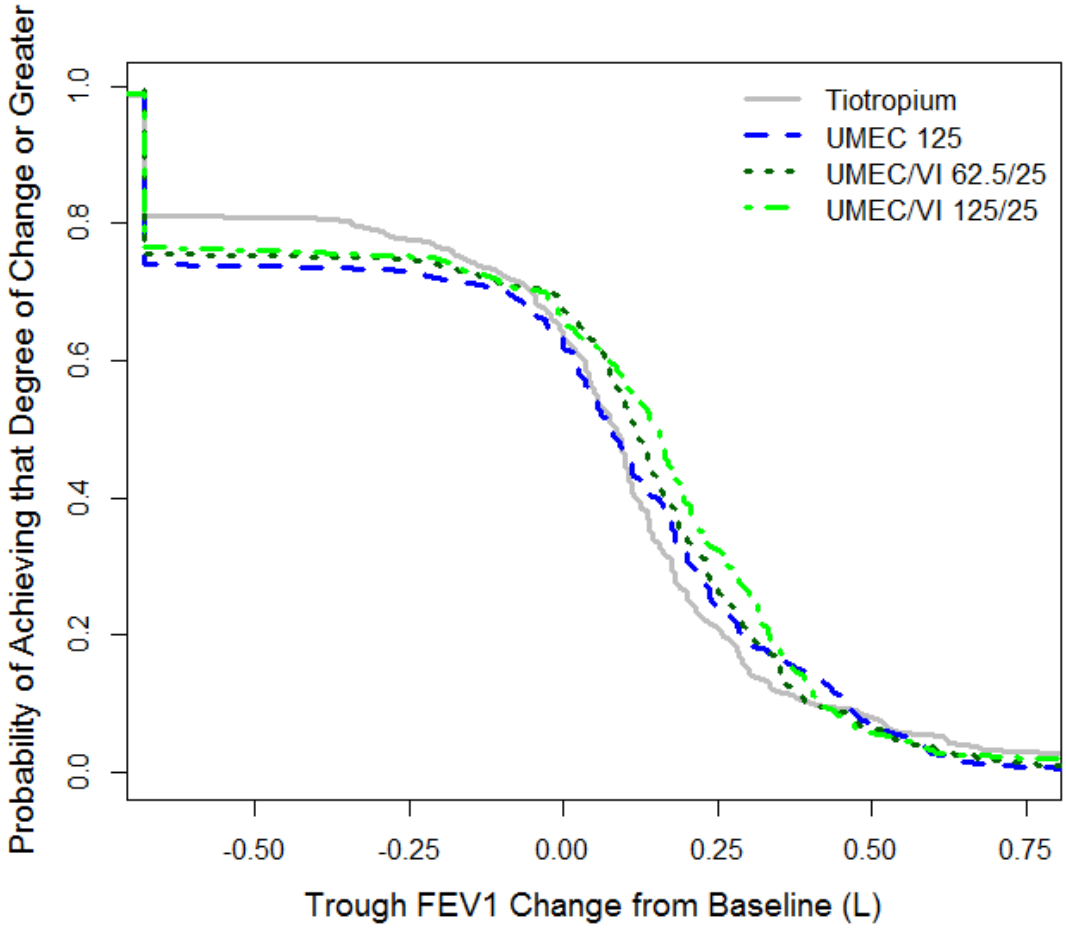
Unadjusted means based on observed data are displayed
Error bars represent ± 1 standard error

Figure 19. Empirical Distribution Function for Change from Baseline in Trough FEV_1 at 24 Weeks in Study 360



Plot displays one minus the empirical distribution function
Early study withdrawal was considered the worst possible outcome

Figure 20. Empirical Distribution Function for Change from Baseline in Trough FEV_1 at 24 Weeks in Study 374



Plot displays one minus the empirical distribution function
Early study withdrawal was considered the worst possible outcome

Table 11. Contributions of the Umeclidinium and Vilanterol Components to the Efficacy of the Combination Product with Respect to Additional Supportive Endpoints in Studies 361, 373, 360, and 374

	Mean SOBDA Score at 24 Weeks[1] (95% CI)	Mean SGRQ Score at 24 Weeks[1] (95% CI)	Mean Rescue Puffs per Day over 24 Weeks[1] (95% CI)	Mean Percent Rescue-Free Days over 24 Weeks[1] (95% CI)	Exacerbation Rate over 24 Weeks[2] (95% CI)
Study 361					
UMEC 125 (UMEC/VI 125/25 vs. VI 25)	-0.12 (-0.20, -0.04)	-2.72 (-4.59, -0.86)	-0.70 (-1.09, -0.31)	7.19 (2.22, 12.16)	0.69 (0.40, 1.18)
VI 25 (UMEC/VI 125/25 vs. UMEC 125)	-0.07 (-0.15, 0.01)	-3.29 (-5.13, -1.44)	-0.65 (-1.04, -0.26)	7.57 (2.64, 12.50)	0.71 (0.42, 1.22)
Study 373					
UMEC 62.5 (UMEC/VI 62.5/25 vs. VI 25)	-0.03 (-0.11, 0.05)	-0.32 (-2.41, 1.78)	0.09 (-0.35, 0.53)	-1.04 (-5.68, 3.60)	0.68 (0.42, 1.11)
VI 25 (UMEC/VI 62.5/25 vs. UMEC 62.5)	-0.08 (-0.16, 0.01)	-0.82 (-2.90, 1.27)	-0.55 (-0.99, -0.11)	4.11 (-0.53, 8.76)	0.80 (0.48, 1.33)
Study 360					
UMEC 62.5 (UMEC/VI 62.5/25 vs. VI 25)	-0.02 (-0.14, 0.10)	1.42 (-1.46, 4.30)	-0.25 (-0.83, 0.32)	0.32 (-6.63, 7.28)	0.75 (0.37, 1.52)
UMEC 125 (UMEC/VI 125/25 vs. VI 25)	-0.02 (-0.14, 0.10)	-0.74 (-3.68, 2.20)	-0.22 (-0.80, 0.35)	1.61 (-5.41, 8.63)	0.64 (0.30, 1.37)
Study 374					
VI 25 (UMEC/VI 125/25 vs. UMEC 125)	-0.14 (-0.26, -0.03)	-2.12 (-4.80, 0.57)	-1.12 (-1.75, -0.49)	12.60 (5.35, 19.84)	0.63 (0.34, 1.17)

[1] Estimated differences, comparing the combination to monotherapy, from linear mixed effects models with the following covariates: treatment group, baseline value, center group, smoking status, visit, visit-by-baseline interaction, and visit-by-treatment group interaction

[2] Estimated hazard ratios, comparing the combination to monotherapy, from Cox proportional hazards models with the following covariates: treatment group, center group, smoking status

3.2.5.3 Primary Efficacy Studies: Tiotropium Comparisons

Data are available from Studies 360 and 374 for comparisons of UMEC/VI, and the monotherapy components, to the LAMA tiotropium. In Study 360, both UMEC/VI 62.5/25 and UMEC/VI 125/25 showed statistically significant, greater improvements in trough FEV_1 than tiotropium (Table 12; differences of 0.088 and 0.093 L, respectively). However, in Study 374, statistical significance was not achieved for the UMEC 125 versus UMEC/VI 125/25 comparison, which came before the tiotropium comparisons in the sequential multiple testing framework. Therefore, Study 374 ***did not*** provide replicate evidence for the superiority of the combination product (at either dose) to tiotropium. In addition, other non-spirometric endpoints of interest did not provide additional support for a benefit of the combination product relative to tiotropium (Table 13). In particular, the estimated effects of UMEC/VI 62.5/25 mcg on SOBDA and SGRQ in Studies 360 and 374 were similar to those of tiotropium, and actually trended in the wrong direction for exacerbation rate (hazard ratio: 1.86; 95% CI: 0.97, 3.56).

Table 12. Comparisons against Tiotropium with Respect to the Mean Changes from Baseline in Trough FEV_1 (Primary Endpoint) and 0–6 Hour Weighted Mean FEV_1 (Secondary Endpoint) at 24 Weeks in Studies 360 and 374

	Mean Change from Baseline in Trough FEV_1 (L)	Mean Difference[1] in Trough FEV_1 (L) (95% CI) p-value	Mean Change from Baseline in 0–6 Hour Weighted Mean FEV_1 (L)	Mean Difference[1] in 0–6 Hour Weighted Mean FEV_1 (L) (95% CI) p-value
Study 360				
Tiotropium	0.121		0.181	
VI 25	0.121	0.000 (-0.052, 0.051) 0.995	0.178	-0.005 (-0.057, 0.047) 0.853
UMEC/VI 62.5/25	0.211	0.088 (0.038, 0.139) 0.0006	0.254	0.072 (0.021, 0.123) 0.0060
UMEC/VI 125/25	0.209	0.093 (0.042, 0.144) 0.0004	0.263	0.083 (0.032, 0.135) 0.0015
Study 374				
Tiotropium	0.149		0.18	
UMEC 125	0.186	0.037 (-0.012, 0.086) 0.138	0.206	0.026 (-0.020, 0.072) 0.273
UMEC/VI 62.5/25	0.208	0.060 (0.010, 0.109) 0.018	0.276	0.096 (0.050, 0.142) <0.0001
UMEC/VI 125/25	0.223	0.074 (0.025, 0.123) 0.0031	0.282	0.101 (0.055, 0.148) <0.0001

[1] Estimate differences, as compared to tiotropium, from linear mixed effects models with the following covariates: treatment group, baseline FEV_1, center group, smoking status, visit, visit-by-baseline FEV_1 interaction, and visit-by-treatment group interaction

Table 13. Comparisons against Tiotropium for Additional Supportive Endpoints in Studies 360 and 374

	Mean SOBDA Score at 24 Weeks[1] (95% CI)	Mean SGRQ Score at 24 Weeks[1] (95% CI)	Mean Rescue Puffs per Day over 24 Weeks[1] (95% CI)	Mean Percent Rescue-Free Days over 24 Weeks[1] (95% CI)	Exacerbation Rate over 24 Weeks[2] (95% CI)
Study 360					
VI 25	0.02 (-0.10, 0.14)	-0.67 (-3.60, 2.26)	-0.41 (-0.99, 0.16)	5.66 (-1.36, 12.69)	1.56 (0.73, 3.33)
UMEC/VI 62.5/25	-0.00 (-0.12, 0.12)	0.75 (-2.12, 3.63)	-0.67 (-1.24, -0.10)	5.98 (-0.96, 12.93)	1.16 (0.53, 2.56)
UMEC/VI 125/25	-0.00 (-0.12, 0.12)	-1.41 (-4.34, 1.52)	-0.64 (-1.22, -0.06)	7.27 (0.23, 14.31)	1.00 (0.43, 2.31)
Study 374					
UMEC 125	0.02 (-0.10, 0.13)	1.38 (-1.28, 4.05)	0.03 (-0.59, 0.65)	2.49 (-4.63, 9.62)	1.82 (0.95, 3.49)
UMEC/VI 62.5/25	-0.08 (-0.20, 0.03)	-0.17 (-2.85, 2.52)	-0.58 (-1.21, 0.04)	5.16 (-2.08, 12.39)	1.86 (0.97, 3.56)
UMEC/VI 125/25	-0.13 (-0.24, -0.02)	-0.74 (-3.41, 1.93)	-1.09 (-1.72, -0.46)	15.09 (7.83, 22.35)	1.15 (0.56, 2.35)

[1] Estimated differences, as compared to tiotropium, from linear mixed effects models with the following covariates: treatment group, baseline value, center group, smoking status, visit, visit-by-baseline interaction, and visit-by-treatment group interaction
[2] Estimated hazard ratios, as compared to tiotropium, from Cox proportional hazards models with the following covariates: treatment group, center group, smoking status

3.2.5.4 Primary Efficacy Studies: Potential Effect of Missing Data

As described in detail in 3.2.3, there were substantial missing data in the primary efficacy studies. Dropout rates ranged from 15% to 33%, depending on the treatment arm and study. We used a number of approaches to investigate the potential effect of missing data on the reliability of efficacy results. First, we explored whether patients who dropped out were similar to patients who completed the 24-week studies. Patients who would go on to withdraw early tended to have slightly greater disease burden at baseline than patients who would go on to complete the 24-week primary efficacy studies (Table 14). For example, 14% of dropouts had GOLD Stage IV COPD at baseline, as compared to 9% of completers. Demographic characteristics were largely similar between dropouts and completers. These trends were also evident when each study was evaluated separately.

We also examined trends in trough FEV_1 before dropout within each treatment arm. Figure 21 displays average pulmonary function over time by dropout pattern, i.e., by the final visit at which FEV_1

measurements were available, for the placebo-controlled Studies 361 and 373. Two general patterns were evident: (1) in all treatment arms, patients' pulmonary function tended to be relatively constant, or in slight decline, across the visits immediately preceding withdrawal; and (2) patients on the active treatment arms (both the monotherapies and combination product) tended to have better pulmonary function than placebo patients (both placebo completers and dropouts) before study withdrawal. These patterns were also generally observed within each study separately.

Based on these trends, it seems unlikely that patients treated with UMEC/VI who withdrew from the study early went on to have substantially worse lung function at 24 weeks than patients treated with placebo who dropped out. This is reassuring, especially in combination with the observation of greater dropout on placebo because of lack of efficacy (including COPD exacerbation) than on the experimental treatment arms. However, these patterns also highlight important deficiencies in the primary MMRM model, as well as the majority of the sensitivity analyses proposed by the applicant.

If the estimand of interest is the hypothetical effectiveness of the assigned treatment ***if all patients could tolerate and adhere to the combination product***, then the estimated treatment effect from the MMRM model may provide a reliable estimate of the truth. However, if the estimand of interest is the effectiveness of the assigned treatment in all randomized participants, ***at real world achievable adherence and tolerability***, the MMRM model likely does not produce a reliable estimate of the truth. The MMRM model, as well as the three missing data sensitivity analyses (MAR, CDC, LMCF) originally proposed by the applicant, essentially assumes that the observed treatment effect before dropout would have persisted in patients, even after they stopped taking the therapy. Because bronchodilators are generally considered symptomatic and not disease-modifying therapies, and their effects on FEV_1 likely do not persist more than a few days after patients stop using them, this assumption is not plausible scientifically.

Therefore, we focused on the Jump to Reference multiple imputation method, which essentially presumes that dropouts on all treatment arms would have had outcomes similar to those that were observed among completers (with similar baseline characteristics) ***in the control group*** (placebo in Studies 361 and 373, and tiotropium in Studies 360 and 374). Under the Jump to Reference approach, statistical significance was maintained for all relevant treatment comparisons (both against placebo and for contributions of the components). However, estimated magnitudes of treatment effect were approximately 20–30% smaller than those based on the primary MMRM model (Table 15 and Table 16). For example, in Study 373, the estimated mean improvement in FEV_1 on UMEC/VI 62.5/25, relative to placebo, was 0.132 L (95% CI: 0.092, 0.173), as compared to 0.167 L (95% CI: 0.128, 0.207) in the primary analysis. Estimated treatment effects of UMEC, VI, and UMEC/VI on weighted mean FEV_1 and SGRQ were also attenuated toward the null by about 20–30% in sensitivity analyses (Table 17). Estimated effects on SOBDA score were attenuated by up to 50% because of the substantial missing data (e.g., 50% missing Week 24 data in Study 373). The greater missing data on SOBDA as compared to other efficacy endpoints was in part attributable to the algorithm used by the applicant to compute the Week 24 mean score (see 3.2.2.1).

Although the scientific justification of the Jump to Reference assumptions seems reasonable, this and all other potential missing data sensitivity analyses rely on untestable assumptions about unobserved data. In addition, none of the sensitivity analyses conducted by the applicant allow for the possibility that dropouts on active treatment could have experienced ***worse*** outcomes after discontinuation than dropouts on control. That being said, the observed trend toward greater FEV_1 on active treatment than placebo before dropout (Figure 21) somewhat mitigates this concern, at least with respect to pulmonary function. There remains the possibility that dropouts from the active treatment arms could have gone on to experience ***worse*** outcomes with respect to important safety endpoints (see 3.3).

Table 14. Baseline Characteristics, Stratified According to Whether Patients Completed the Study, Based on Integrated Data from Studies 361, 373, 360, and 374

	Completer[1] (N=3650)	Dropout (N=1051)	Overall (N=4733)
Female	1141 (31%)	354 (34%)	1505 (32%)
Age	63.1 (8.6)	63.8 (9.1)	63.3 (8.7)
Race			
White	3076 (84%)	893 (85%)	3995 (84%)
Black	84 (2%)	40 (4%)	127 (3%)
Asian	328 (9%)	94 (9%)	425 (9%)
Other	162 (4%)	24 (2%)	186 (4%)
Hispanic/Latino	305 (8%)	75 (7%)	382 (8%)
BMI (kg/m^2)	26.8 (5.8)	26.6 (5.8)	26.8 (5.8)
Current Smoker	1823 (50%)	497 (47%)	2343 (50%)
FEV_1	1.3 (0.5)	1.1 (0.5)	1.2 (0.5)
GOLD Stage ($ppFEV_1$)			
Stage II (50-80%)	1764 (49%)	408 (39%)	2184 (46%)
Stage III (30-50%)	1535 (42%)	486 (47%)	2034 (43%)
Stage IV (<30%)	338 (9%)	150 (14%)	494 (10%)
Chronic Bronchitis	2427 (66%)	658 (63%)	3106 (66%)
Emphysema	2153 (59%)	688 (65%)	2860 (60%)
Duration of COPD, years			
<1	331 (9%)	73 (7%)	407 (9%)
1,5	1379 (38%)	356 (34%)	1751 (37%)
5,10	1073 (29%)	322 (31%)	1405 (30%)
10,15	556 (15%)	204 (19%)	762 (16%)
15-20	163 (4%)	49 (5%)	212 (4%)
20-25	92 (3%)	25 (2%)	118 (2%)
>25	56 (2%)	22 (2%)	78 (2%)
Inhaled Corticosteroid Use	1775 (49%)	517 (49%)	2306 (49%)
Reversible to Salbutamol	1122 (31%)	317 (30%)	1452 (31%)
Reversible to Salbutamol and Ipratropium	1961 (54%)	534 (51%)	2512 (53%)
At United States site	854 (23%)	329 (31%)	1196 (25%)

Abbreviations: BMI = body mass index, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second

[1] Patients classified as completers if they had a Day 169 visit. Numbers differ slightly from Tables 1-4, which were based on investigator reporting.

Figure 21. Mean Change from Baseline in Trough FEV_1 by Treatment Group over Time, Stratified by Dropout Pattern, Based on Integrated Data from Studies 361 and 373

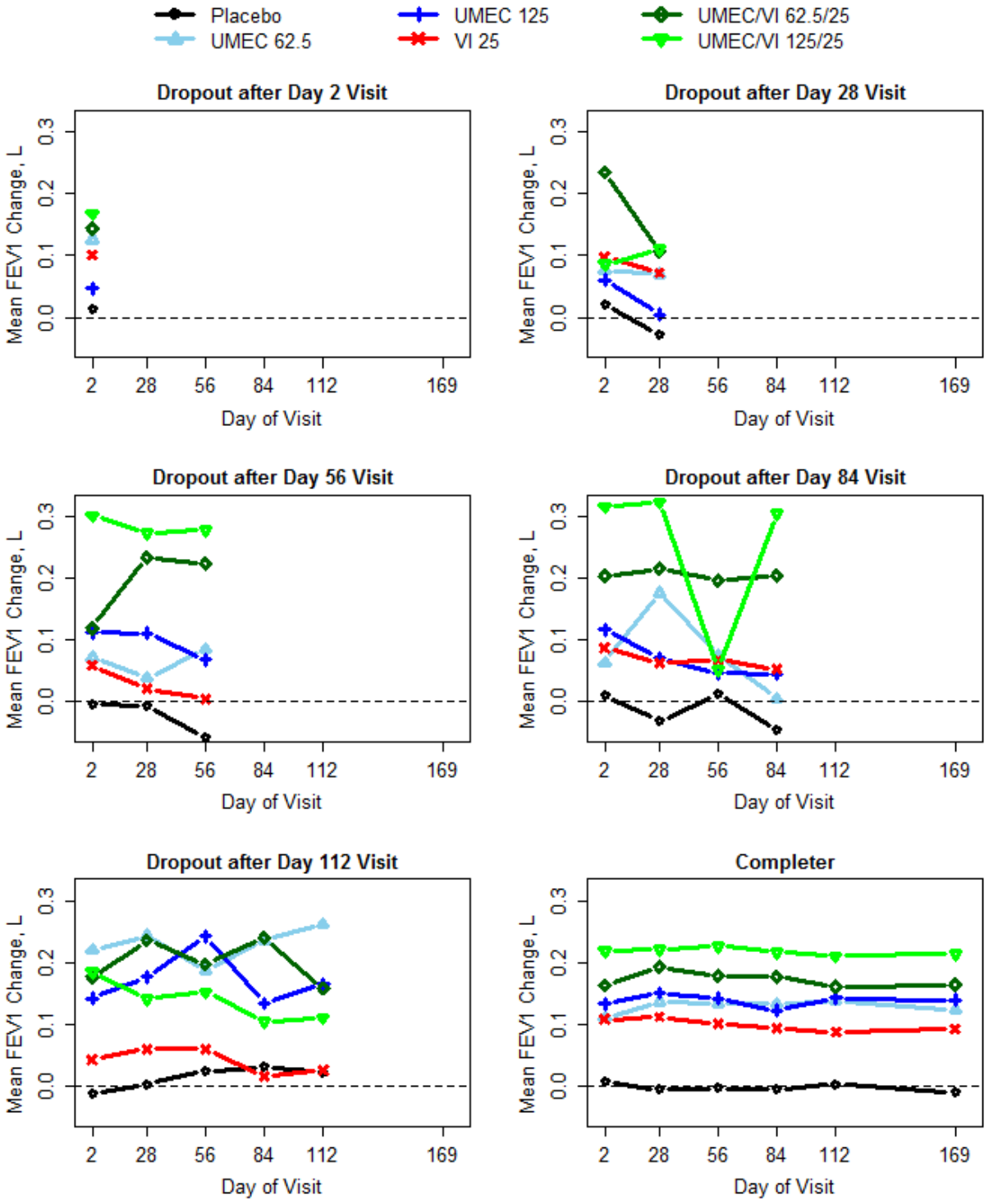


Table 15. Exploring the Potential Effect of Missing Data: Results for the Primary Endpoint Trough FEV_1 with the Primary Mixed Effects Analysis as Compared to a Multiple Imputation Sensitivity Analysis in Studies 361 and 373

	Study 361: Mean Difference in Trough FEV_1 (L) (95% CI)		Study 373: Mean Difference in Trough FEV_1 (L) (95% CI)	
	Primary	**Sensitivity[1]**	**Primary**	**Sensitivity[1]**
Placebo Comparisons				
UMEC 62.5			0.115 (0.076, 0.155)	0.089 (0.049, 0.129)
UMEC 125	0.160 (0.122, 0.198)	0.122 (0.083, 0.162)		
VI 25	0.124 (0.086, 0.162)	0.092 (0.052, 0.131)	0.072 (0.032, 0.112)	0.053 (0.013, 0.093)
UMEC/VI 62.5/25			0.167 (0.128, 0.207)	0.132 (0.092, 0.173)
UMEC/VI 125/25	0.238 (0.200, 0.276)	0.192 (0.153, 0.231)		
Contributions to Combination				
UMEC 62.5 Contribution			0.095 (0.060, 0.130)	0.079 (0.044, 0.115)
UMEC 125 Contribution	0.114 (0.081, 0.148)	0.100 (0.065, 0.135)		
VI 25 Contribution	0.079 (0.046, 0.112)	0.070 (0.035, 0.104)	0.052 (0.017, 0.087)	0.043 (0.008, 0.079)

[1] Based on multiple imputation and the Jump to Reference model

Table 16. Exploring the Potential Effect of Missing Data: Results for the Primary Endpoint Trough FEV_1 with the Primary Mixed Effects Analysis as Compared to a Multiple Imputation Sensitivity Analysis in Studies 360 and 374

	Study 360: Mean Difference in Trough FEV1 (L) (95% CI)		Study 374: Mean Difference in Trough FEV1 (L) (95% CI)	
	Primary	**Sensitivity[1]**	**Primary**	**Sensitivity[1]**
Tiotropium Comparisons				
UMEC/VI 62.5/25	0.088 (0.038, 0.139)	0.078 (0.027, 0.129)	0.060 (0.010, 0.109)	0.046 (-0.003, 0.095)
UMEC/VI 125/25	0.093 (0.042, 0.144)	0.071 (0.019, 0.123)	0.074 (0.025, 0.123)	0.057 (0.008, 0.106)
Contributions to Combination				
UMEC 62.5 Contribution	0.088 (0.037, 0.139)	0.078 (0.026, 0.129)		
UMEC 125 Contribution	0.093 (0.041, 0.144)	0.071 (0.019, 0.123)		
VI 25 Contribution			0.037 (-0.012, 0.087)	0.029 (-0.020, 0.078)

[1] Based on multiple imputation and the Jump to Reference model

Table 17. Exploring the Potential Effect of Missing Data: Results for Secondary and Additional Endpoints with the Primary Mixed Effects Analysis as Compared to a Multiple Imputation Sensitivity Analysis in Studies 361 and 373

	Mean Difference in 0-6 Hour Weighted Mean FEV_1 at 24 Weeks (L) (95% CI)		Mean Difference in SOBDA Score at 24 Weeks (95% CI)		Mean Difference in SGRQ Score at 24 Weeks (95% CI)	
	Primary	**Sensitivity[1]**	**Primary**	**Sensitivity[1]**	**Primary**	**Sensitivity[1]**
Study 361: Placebo Comparisons						
UMEC 125	0.178 (0.141, 0.216)	0.136 (0.096, 0.175)	-0.08 (-0.17, 0.02)	-0.04 (-0.14, 0.05)	-0.31 (-2.47, 1.85)	-0.25 (-2.39, 1.88)
VI 25	0.145 (0.107, 0.182)	0.107 (0.067, 0.146)	-0.03 (-0.13, 0.06)	-0.02 (-0.12, 0.08)	-0.87 (-3.05, 1.30)	-0.68 (-2.83, 1.48)
UMEC/VI 125/25	0.287 (0.250, 0.324)	0.226 (0.186, 0.265)	-0.15 (-0.24, -0.06)	-0.10 (-0.19, 0.00)	-3.60 (-5.76, 1.44)	-3.02 (-5.17, -0.88)
Study 373: Placebo Comparisons						
UMEC 62.5	0.150 (0.110, 0.190)	0.116 (0.075, 0.157)	-0.10 (-0.19, -0.00)	-0.05 (-0.15, 0.04)	-4.69 (-7.07, 2.31)	-3.74 (-6.12, -1.37)
VI 25	0.122 (0.082, 0.162)	0.090 (0.049, 0.131)	-0.14 (-0.24, -0.05)	-0.07 (-0.17, 0.02)	-5.19 (-7.58, 2.80)	-4.12 (-6.50, -1.74)
UMEC/VI 62.5/25	0.242 (0.202, 0.282)	0.194 (0.153, 0.235)	-0.17 (-0.26, -0.08)	-0.10 (-0.19, -0.01)	-5.51 (-7.89, -3.13)	-4.54 (-6.92, -2.17)

[1] Based on multiple imputation and the Jump to Reference model

3.2.5.5 Additional Phase 3 Studies

In the cross-over Studies 417 and 418, treatment with UMEC/VI 125/25 resulted in statistically significantly greater mean changes from baseline in trough FEV_1 than placebo (Table 18 and Table 19). There was evidence of benefit on FEV_1 for UMEC/VI 62.5/25 over placebo in Study 418, but the same comparison failed to achieve statistical significance in Study 417 because it was positioned after the high dose EET comparison (which failed – see Table 19) in the statistical multiple testing hierarchy. Estimated magnitudes of treatment effect on FEV_1 for the two doses of combination product were similar to those observed in the primary efficacy studies.

There was not replicate evidence of benefit for UMEC/VI (at either dose) relative to placebo with respect to the co-primary endpoint exercise endurance time (Table 18 and Table 19). In Study 418, patients treated with UMEC/VI 62.5/25 had a statistically significant 69 second greater mean change from baseline in EET than those on placebo (95% CI: 25, 114 s; p=0.003). However, in Study 417, there was not statistical evidence of benefit for UMEC/VI 62.5/25 (estimated difference in means: 22 s; 95% CI: -14, 58 s; p=0.23). In addition, the estimated magnitude of benefit for the combination product (at either dose) in Studies 417 and 418 did not attain the minimal clinically important difference (70 seconds) approximated by the sponsor before the trial.

We also evaluated whether pulmonary function data from Studies 417 and 418 provided support for the contribution of vilanterol to the efficacy of the combination product. Such comparisons were not included in the multiple testing framework and therefore are only considered supportive. In both studies (Table 18 and Table 19), there was support for a contribution of VI 25 to the efficacy of the combination at the lower 62.5/25 dose (estimate mean differences in FEV_1 of 0.124 and 0.099 L), but not at the higher 125/25 dose.

The 52-week Study 359 only included placebo, UMEC 125, and UMEC/VI 125/25 treatment arms, and was designed to evaluate safety and tolerability, so no primary efficacy analyses were prespecified. Nevertheless, efficacy results were generally supportive of findings in the primary efficacy studies. Treatment with UMEC/VI 125/25 resulted in 0.197 L (95% CI: 0.121, 0.272) and 0.231 L (95% CI: 0.153, 0.310) greater mean trough FEV_1 changes at 6 and 12 months, respectively, as compared to placebo. In addition, there were lower rates of first COPD exacerbation (hazard ratio: 0.4; 95% CI: 0.3, 0.8) and daily rescue medication use (difference in mean puffs per day: -1.0; 95% CI: -1.4, -0.5) on the combination product, as compared to placebo.

Table 18. Treatment Effects on the Co-Primary Endpoints Exercise Endurance Time (EET) and Trough FEV_1 at 12 Weeks in the Cross-Over Study 417

	Mean Difference[1] in EET (s) (95% CI) p-value	**Mean Difference[1] in Trough FEV_1 (L) (95% CI) p-value**
Placebo Comparisons		
UMEC 62.5	26.5 (-25.9, 78.9) 0.32	0.087 (0.030, 0.143) 0.003
UMEC 125	13.1 (-38.9, 65.1) 0.62	0.140 (0.084, 0.197) 0.03
VI 25	-10.0 (-55.5, 35.4) 0.67	0.099 (0.050, 0.148) <0.0001
UMEC/VI 62.5/25	21.9 (-14.2, 58.0) 0.23	0.211 (0.172, 0.249) <0.0001
UMEC/VI 125/25	32.4 (-3.9, 68.8) 0.08	0.169 (0.129, 0.209) <0.0001
Contributions to Combination		
UMEC 62.5 Contribution (UMEC/VI 62.5/25 vs. VI 25)	31.9 (-14.1, 77.9) 0.17	0.111 (0.062, 0.161) <0.0001
UMEC 125 Contribution (UMEC/VI 125/25 vs. VI 25)	42.4 (-3.8, 88.7) 0.07	0.070 (0.019, 0.120) 0.007
VI 25 Contribution (UMEC/VI 62.5/25 vs. UMEC 62.5)	-4.6 (-57.6, 48.4) 0.86	0.124 (0.067, 0.182) <0.0001
VI 25 Contribution (UMEC/VI 125/25 vs. UMEC 125)	19.3 (-33.4, 71.9) 0.47	0.029 (-0.028, 0.086) 0.32

[1] Estimates from linear mixed effects models with the following covariates: treatment group, period baseline value, mean of period baseline values, period, center group, smoking status, visit, visit by mean baseline value interaction, and visit-by-treatment group interaction

Table 19. Treatment Effects on the Co-Primary Endpoints Exercise Endurance Time (EET) and Trough FEV_1 at 12 Weeks in the Cross-Over Study 418

	Mean Difference[1] in EET (s) (95% CI) p-value	Mean Difference[1] in Trough FEV_1 (L) (95% CI) p-value
Placebo Comparisons		
UMEC 62.5	25.0 (-41.0, 91.1) 0.46	0.144 (0.086, 0.203) <0.0001
UMEC 125	74.7 (6.0, 143.4) 0.03	0.256 (0.193, 0.318) <0.0001
VI 25	30.6 (26.8, 88.0) 0.30	0.112 (0.061, 0.163) <0.0001
UMEC/VI 62.5/25	69.4 (24.5, 114.4) 0.003	0.243 (0.202, 0.284) <0.0001
UMEC/VI 125/25	65.8 (20.3, 111.3) 0.005	0.261 (0.220, 0.303) <0.0001
Contributions to Combination		
UMEC 62.5 Contribution (VI 25 vs. UMEC/VI 62.5/25)	38.8 (-18.9, 96.5) 0.19	0.132 (0.081, 0.183) <0.0001
UMEC 125 Contribution (VI 25 vs. UMEC/VI 125/25)	35.2 (-22.7, 93.1) 0.23	0.150 (0.098, 0.201) <0.0001
VI 25 Contribution (UMEC 62.5 vs. UMEC/VI 62.5/25)	44.4 (-21.8, 110.6) 0.19	0.099 (0.041, 0.157) 0.0009
VI 25 Contribution (UMEC 125 vs. UMEC/VI 125/25)	-8.9 (-77.8, 60.1) 0.80	0.006 (-0.055, 0.067) 0.85

[1] Estimates from linear mixed effects models with the following covariates: treatment group, period baseline value, mean of period baseline values, period, center group, smoking status, visit, visit by mean baseline value interaction, and visit-by-treatment group interaction

3.3 Evaluation of Safety

Dr. Jennifer Pippins, the Medical Reviewer, conducted the safety evaluation, and the reader is referred to Dr. Pippins' review for detailed information on the safety profile of UMEC/VI. We also conducted some additional analyses to further explore a potential cardiovascular safety signal. The applicant prespecified a number of adverse events (AEs) of special interest based on potential pharmacologic class effects of LAMAs and LABAs. One group of special interest consisted of cardiovascular adverse events, including acquired long QT interval, cardiac arrhythmias, cardiac failure, cardiac ischemia, hypertension, sudden death, and stroke. All serious adverse event (SAE) narratives were adjudicated by an independent, blinded adjudication committee. The applicant also classified events according to the major adverse cardiac events (MACE) criteria. MACE included adjudicated cardiovascular death, non-fatal stroke AEs of special interest, and non-fatal cardiac ischaemia AEs of special interest.

We compared treatment groups with respect to adjudicated cardiovascular serious adverse events and MACE, using unadjusted incidence rates, Kaplan Meier plots, and Cox proportional hazards regression analyses. We combined UMEC 62.5 and 125 into one UMEC group, and combined UMEC/VI 62.5/25

and 125/25 into one UMEC/VI group, because of the small numbers of events within groups and the lack of a consistent dose-response. We report findings both for the primary efficacy studies, and based on data from all phase 3 studies (Studies 361, 373, 360, 374, 359, 408, and the first treatment periods of Studies 417 and 418). Analyses based on pooled data across randomized clinical trials can be influenced by confounding by study if randomization ratios and outcome risks differ across studies. This concern is somewhat mitigated here because the patient populations were very similar across the primary efficacy studies. In addition, we adjusted for study as a covariate in regression models.

Many of the numbers of events and event rates presented here differ from those in the Clinical Briefing Document, and in the applicant's Briefing Document, because: (1) our analyses include post-treatment events, which were generally captured if they occurred in the week (±2 days) following a patient's 24-week or early withdrawal visit, whereas the other documents only consider on-treatment data; (2) our analyses of CVD SAEs only include adjudicated events, whereas the other documents largely focus on event reports prior to adjudication; and (3) our analyses of data from "All phase 3 studies" include results from only the first treatment periods of cross-over Studies 417 and 418, whereas the applicant's results include data from the second treatment periods, as well.

Incidence rates of MACE were largely similar across the treatment arms (Table 20). There also was no evidence of a safety signal for MACE based on comparisons of the proportions of patients with events over time (Figure 22 and Figure 23), nor was there evidence in regression analyses (hazard ratio for UMEC/VI versus placebo in the primary efficacy studies: 1.2 [95% CI: 0.5, 2.7]; hazard ratio in all phase 3 studies: 0.8 [95% CI: 0.4, 1.5]). Similar results were observed when evaluating a narrow definition of MACE that only included cardiovascular death, non-fatal stroke AEs of special interest, and non-fatal myocardial infarction AEs of special interest (e.g., see Table 20).

Despite the lack of evidence for MACE, there was the suggestion of a possible trend toward greater cardiovascular risk on UMEC, VI, and UMEC/VI, as compared to both placebo and tiotropium, when evaluating cardiovascular-related serious adverse events in the primary efficacy studies. This imbalance was evident when examining incidence rates (Table 20) and proportions with events over times (Figure 24), as well as in regression analyses (hazard ratio: 1.9; 95% CI: 0.5, 6.7). However, these trends largely went away when including data from all phase 3 studies (Table 20 and Figure 25; hazard ratio: 1.0 [95% CI: 0.4, 2.3]). Of note, the long-term, placebo-controlled safety Study 359 was the primary additional source of data in analyses that included all phase 3 studies. In Study 359, the only trial to include Holter monitoring in all randomized subjects, there was greater dropout on UMEC 125 (16%) and UMEC/VI 125/25 (16%) than placebo (7%) because of ECG and/or Holter abnormalities.

Finally, it is important to note that missing data clouds the interpretability of safety analyses. It is reassuring that dropout rates because of adverse events on the active arms (6-7% in the primary efficacy studies) were similar to the rate on placebo (5%). However, because patients were not followed up after treatment discontinuation for a complete 24-week safety evaluation, we cannot rule out the possibility that (1) differences in patient characteristics between dropouts on the placebo and active arms induce bias in safety comparisons, or (2) the active treatments have residual effects that increase risk of adverse events after patients stop taking them.

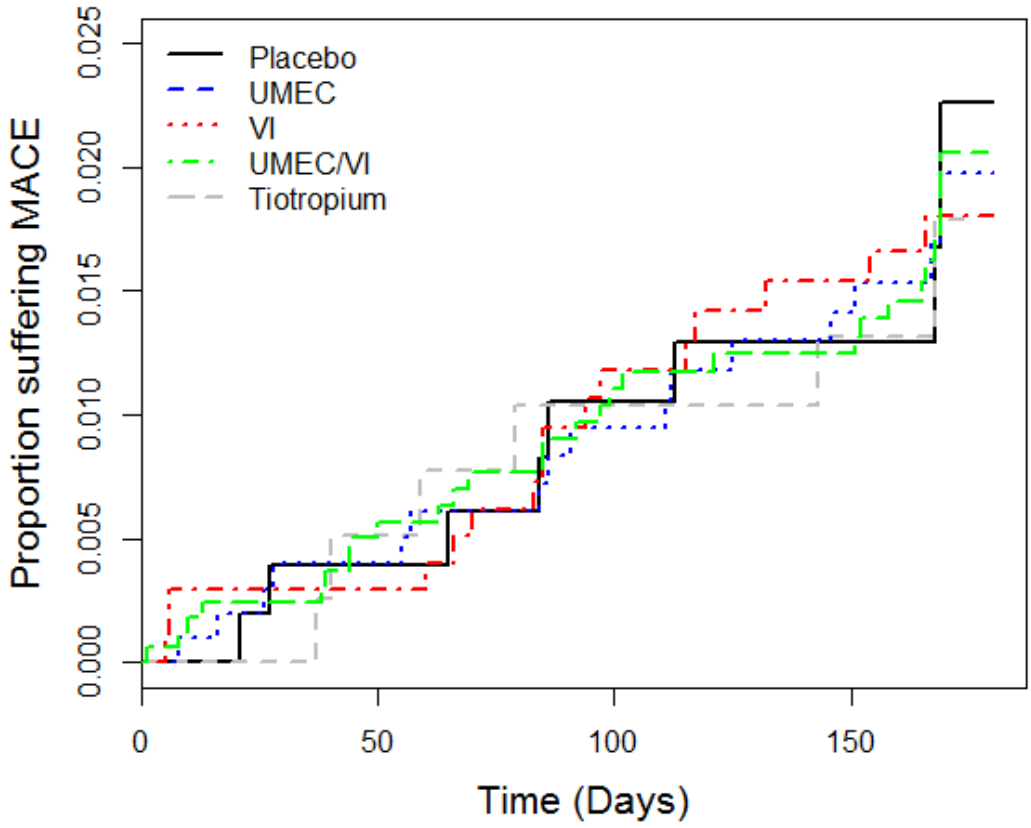
Table 20. Numbers of MACE and Adjudicated Cardiovascular Serious Adverse Events, and Unadjusted Pooled Incidence Rates, by Treatment Group and Source of Data

All Phase 3 Studies[1] (N=6,156)					
Endpoint	**Placebo (N=910)**	**UMEC[2] (N=1,512)**	**VI (N=1,111)**	**UMEC/VI[3] (N=2,200)**	**Tiotropium (N=423)**
MACE (broad)[4]	17 (51)	23 (37)	16 (38)	35 (38)	6 (35)
MACE (narrow)[5]	6 (18)	9 (14)	7 (16)	10 (11)	1 (6)
Adjudicated Cardiovascular SAE	8 (24)	20 (32)	15 (35)	22 (23)	2 (12)
Primary Efficacy Studies (N=4,733)					
Endpoint	**Placebo (N=555)**	**UMEC[2] (N=1,047)**	**VI (N=1,034)**	**UMEC/VI[3] (N=1,674)**	**Tiotropium (N=423)**
MACE (broad)[4]	8 (39)	16 (39)	16 (39)	27 (40)	6 (35)
MACE (narrow)[5]	3 (14)	5 (12)	7 (17)	8 (12)	1 (6)
Adjudicated Cardiovascular SAE	3 (14)	15 (36)	15 (37)	17 (25)	2 (12)

Cell contents are number of events (incidence rate, per 1,000 person-years)
Abbreviations: MACE = major adverse cardiac events; SAE = serious adverse event

[1] All Phase 3 Studies = Studies 361, 373, 360, 374, 359, 408, and the first treatment periods of Studies 417 and 418
[2] Combines the UMEC 62.5 and 125 mcg treatment groups
[3] Combines the UMEC/VI 62.5/25 and 125/25 mcg treatment groups
[4] MACE (broad) includes adjudicated cardiovascular death, non-fatal stroke adverse events of special interest, and non-fatal cardiac ischaemia adverse events of special interest
[5] MACE (narrow) includes adjudicated cardiovascular death, non-fatal stroke adverse events of special interest, and non-fatal myocardial infarction adverse events of special interest

Figure 22. Proportion Suffering MACE over Time by Treatment Group Based on Data from the Primary Efficacy Studies

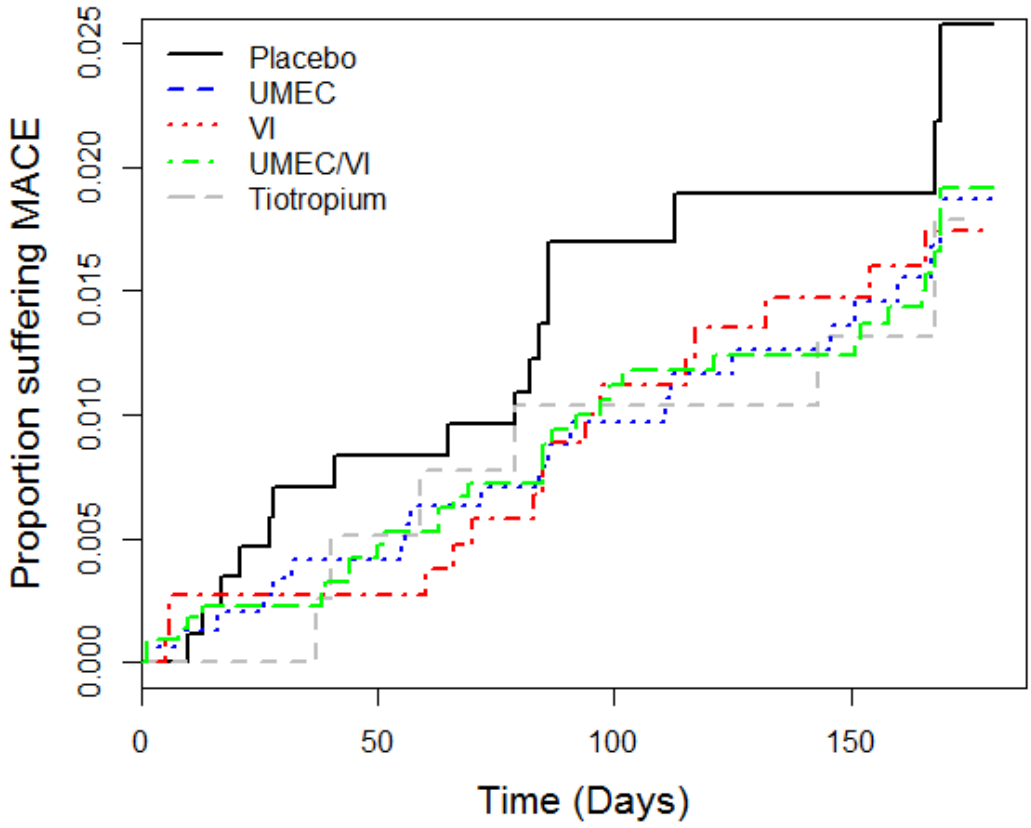


Number at risk

Placebo	555	474	426	398
Tiotropium	423	385	366	355
UMEC	1047	944	865	826
VI	1034	932	863	808
UMEC/VI	1674	1529	1437	1377

Abbreviations: MACE = major adverse cardiac events

Figure 23. Proportion Suffering MACE over Time by Treatment Group Based on Data from all Phase 3 Studies



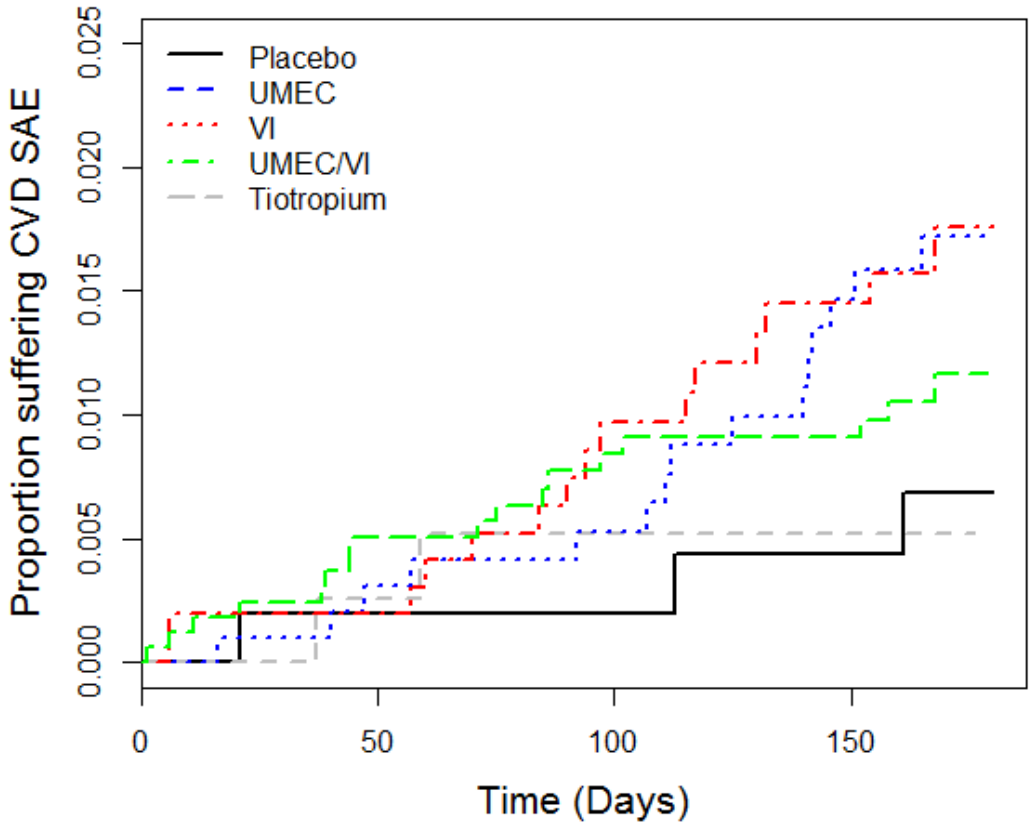
Number at risk

Placebo	910	780	512	479
Tiotropium	423	385	366	355
UMEC	1512	1357	1045	996
VI	1111	1000	863	808
UMEC/VI	2200	2019	1639	1562

Abbreviations: MACE = major adverse cardiac events

All Phase 3 Studies = Studies 361, 373, 360, 374, 359, 408, and the first treatment periods of Studies 417 and 418

Figure 24. Proportion Suffering Adjudicated Cardiovascular Serious Adverse Events over Time by Treatment Group Based on Data from Primary Efficacy Studies

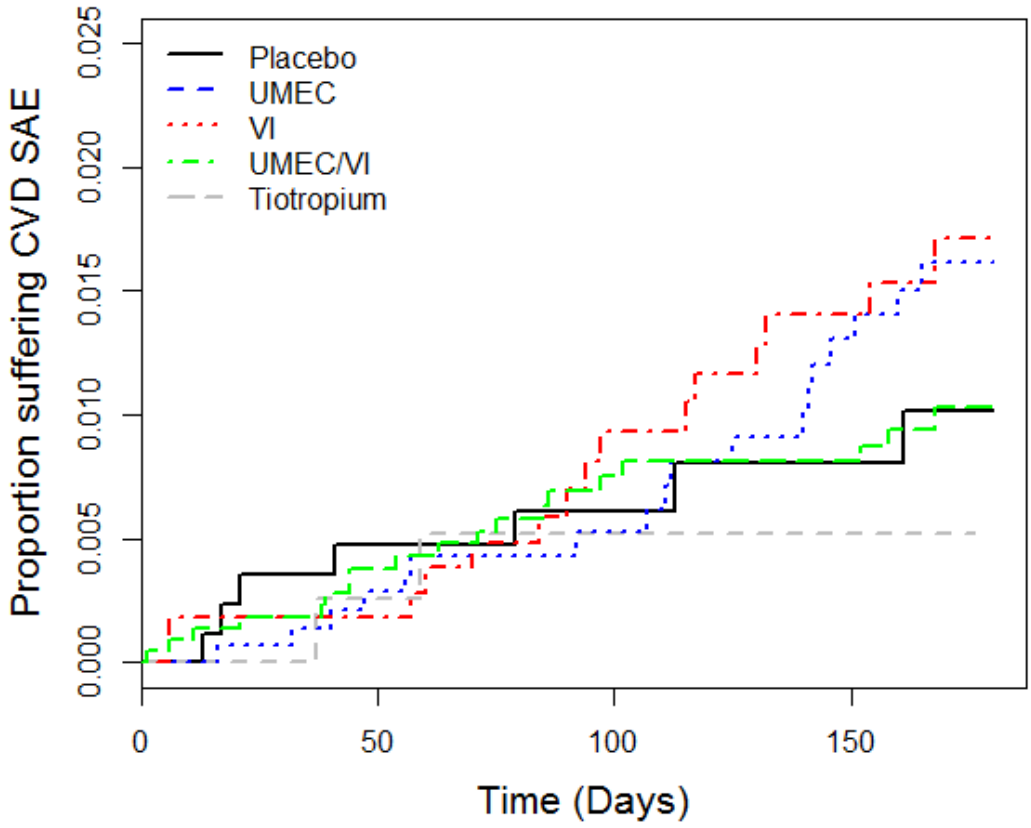


Number at risk

Placebo	555	475	430	401
Tiotropium	423	386	368	357
UMEC	1047	944	867	825
VI	1034	933	864	810
UMEC/VI	1674	1529	1436	1378

Abbreviations: CVD SAE = cardiovascular serious adverse event

Figure 25. Proportion Suffering Adjudicated Cardiovascular Serious Adverse Events over Time by Treatment Group Based on Data from all Phase 3 Studies



Number at risk

Placebo	910	783	517	483
Tiotropium	423	386	368	357
UMEC	1512	1358	1048	996
VI	1111	1001	864	810
UMEC/VI	2200	2019	1638	1563

Abbreviations: CVD SAE = cardiovascular serious adverse event

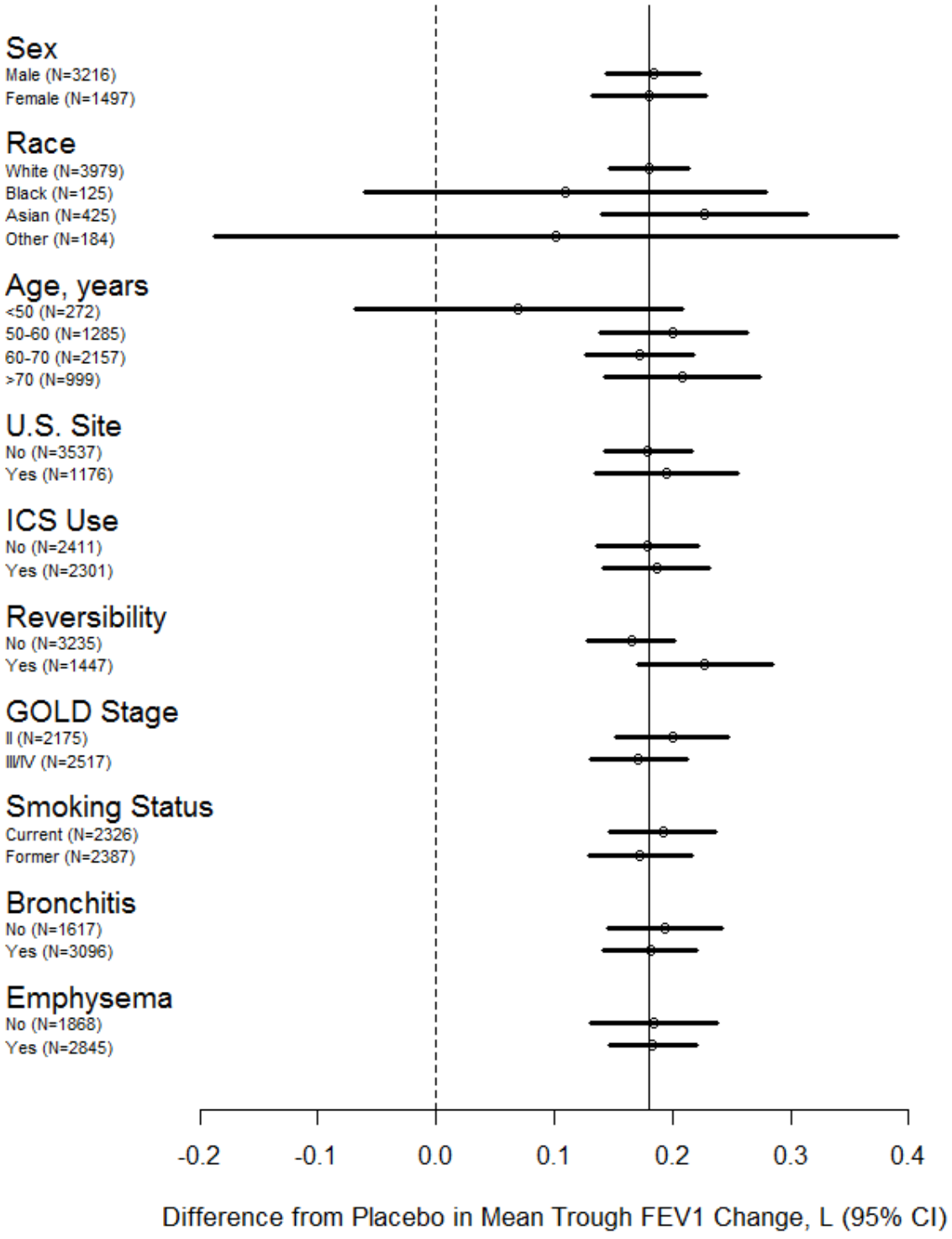
All Phase 3 Studies = Studies 361, 373, 360, 374, 359, 408, and the first treatment periods of Studies 417 and 418

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Figure 26 presents the results of subgroup analyses by a number of demographic and baseline characteristics based on integrated data from the primary efficacy studies. We conducted subgroup analyses by sex, race (White, Black, Asian, or Other), age (<50, 50–60, 60–70, >70 years), geographic region (Non-U.S., U.S.), inhaled corticosteroid use (ICS) use, reversibility to salbutamol (defined by post-salbutamol FEV_1 at least 12% and 200 mL greater than pre-salbutamol FEV_1), COPD GOLD stage, smoking status, chronic bronchitis, and emphysema. Estimated differences in mean trough FEV_1 comparing UMEC/VI 62.5/25 with placebo were largely consistent across these subgroups. Similar results were observed when restricting to Study 373, the only trial containing both placebo and UMEC 62.5/25 treatment arms. Of note, the limited number of Black subjects led to large variability in the estimated treatment effect in this subgroup (see wide confidence interval in Figure 26).

The suggestion in Figure 26 of possible differences in treatment effect by race and age was not replicated when we examined the higher 125/25 dose. The tendency for a larger observed treatment effect within the subset of patients demonstrating reversibility to salbutamol at baseline, however, was consistent across doses and studies. Importantly, the estimated treatment effect in patients who did not demonstrate reversibility, although smaller in magnitude, was still statistically significantly greater than zero.

Figure 26. Estimated Treatment Effect of UMEC/VI 62.5/25 on Mean Tough FEV_1 at 24 Weeks, Stratified by Different Subgroups, Based on Integrated Data from Studies 360, 361, 373, and 374



Estimates based on linear regression models adjusting for baseline FEV_1, smoking status, center grouping, and study
Subgroup sample sizes (N) based on complete integrated cohort, not subset receiving placebo or UMEC/VI 62.5/25

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During this statistical review, we identified the following important issues:

- Potential effect of missing data on the reliability of efficacy results

This issue was discussed in detail in 3.2.4.4. There were substantial missing data in the primary efficacy studies, with dropout rates ranging from 15% to 33%, depending on the treatment arm and study. If the estimand of interest is the effectiveness of the assigned treatment in all randomized participants, at real world achievable adherence and tolerability, the MMRM model likely does not provide a reliable estimate of the truth. The MMRM model, as well as the three missing data sensitivity analyses (MAR, CDC, LMCF) originally proposed by the applicant, essentially assumes that the observed treatment effect before dropout would have persisted in patients, even after they stopped taking the therapy. Because bronchodilators are generally considered symptomatic and not disease-modifying therapies, and their effects on FEV_1 likely do not persist more than a few days after patients stop using them, this assumption is not plausible scientifically.

Therefore, we gave importance to a sensitivity analysis that multiply imputed missing data under the assumption that dropouts on all treatment arms would have had outcomes similar to those that were observed among completers (with similar baseline characteristics) ***in the control group***. Statistical significance was maintained for all relevant treatment comparisons, but estimated magnitudes of treatment effect were approximately 20-30% smaller than those based on the primary MMRM model. None of the sensitivity analyses proposed by the applicant allow for the possibility that dropouts on active treatment could have experienced ***worse* o**utcomes after discontinuation than dropouts on control. However, the observed trend toward greater FEV_1 on active treatment than placebo before dropout somewhat mitigates this concern, at least with respect to pulmonary function.

The presence of missing data also clouds the interpretation of safety comparisons. It is reassuring that dropout rates because of adverse events on the active arms (6-7% in the primary efficacy studies) were similar to the rate on placebo (5%). However, because patients were not followed up after treatment discontinuation for a complete 24-week safety evaluation, we cannot rule out the possibility that (1) differences in patient characteristics between dropouts on the placebo and active arms induce bias in safety comparisons, or (2) the active treatments have residual effects that increase risk of adverse events after patients stop taking them.

- Quantity of evidence of effectiveness for UMEC/VI at the proposed 62.5/25 mcg dose

From the four primary efficacy studies, a direct comparison between the proposed 62.5/25 mcg dose of UMEC/VI and placebo is possible only from Study 373. Therefore, we must evaluate whether results from this single study, combined with supportive data from additional studies, meet the standard for substantial evidence of effectiveness. The FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* indicates situations in which a single study of a new treatment may be combined with independent substantiation from related, supportive study data to provide evidence of effectiveness. In particular, the Guidance notes that supportive data may come from studies of a different dose, studies in a slightly different patient population, or from studies of the

monotherapies when evaluating a combination product, depending on the quality and outcomes of such related studies.

Therefore, we must evaluate the totality of the evidence in support of a UMEC/VI treatment effect on FEV_1. First, we note that there was ***strong*** statistical evidence ($p<0.0001$) of a treatment effect in the single study evaluating UMEC/VI 62.5/25 versus placebo with respect to 24-week mean change in FEV_1. Second, there was supportive evidence for FEV_1 improvement from a number of related studies. In the primary efficacy Study 360, there was evidence of superiority over the approved active comparator tiotropium (estimate=0.088 L; p=0.0006). In addition, in Study 418, which was a cross-over study designed to evaluate both FEV_1 and exercise endurance time (in a slightly different patient population than the primary efficacy studies), there was a statistically significant treatment effect on trough FEV_1 at 12 weeks (estimate=0.243 L; $p<0.0001$). Third, there was strong statistical evidence ($p<0.0001$) of efficacy for the higher UMEC/VI 125/25 dose (which consistently showed similar benefit over placebo as the proposed 62.5/25 dose) in Study 361. Finally, the efficacy of UMEC/VI was also supported by trends toward benefit on additional non-spirometric endpoints of interest, including mean changes from baseline in the SOBDA and SGRQ scores at 24 weeks, mean puffs of rescue mediation per day, and exacerbation rate over 24 weeks (although the evidence for these endpoints may not be sufficient to support labeling).

- Quantity of evidence of the contribution of vilanterol to the effectiveness for UMEC/VI

From the four primary efficacy studies, a direct comparison between UMEC/VI 62.5/25 and UMEC 62.5 to evaluate the contribution of VI 25 at the proposed dose of the combination product is possible only from Study 373. Therefore, we must evaluate whether results from this single study, combined with supportive data from additional studies, meet the standard for substantial evidence of effectiveness.

First, it is important to note that there was ***strong*** statistical evidence in the single study evaluating the contribution of VI with respect to 24-week mean change in FEV_1 (p=0.0021). Second, there was some limited supportive evidence from related studies. There was statistical evidence of the contribution of VI to the higher 125/25 mcg dose of the UMEC/VI combination product in Study 361 (estimate=0.079 L; $p<0.0001$) but not Study 374 (estimate=0.037 L; p=0.142). There was also some support from comparisons of UMEC/VI 62.5/25 to UMEC 62.5 in the cross-over Studies 417 and 418 (estimated mean differences of 0.124 and 0.099 L, respectively), although these comparisons were not among those in the prespecified framework to account for multiple testing. Finally, there was evidence of a treatment effect for the VI 25 monotherapy, relative to placebo, in Studies 361 (estimate=0.124 L; $p<0.0001$) and 373 (estimate=0.072 L; p=0.0004).

- Dose selection and evidence of effectiveness for UMEC

Data to support the dose selection, safety, and effectiveness of vilanterol were reviewed as part of the Breo Ellipta program. However, umeclidinium is a new molecular entity, and therefore requires a more comprehensive evaluation. The findings of UMEC dose-ranging studies in COPD suggested that the 62.5 and 125 mcg doses selected for phase 3 study were reasonable, although there was little separation in efficacy between UMEC 31.25 and 62.5 mcg in Study 321. From the four primary efficacy studies, a direct comparison between UMEC 62.5 and placebo is possible only from Study 373. In Study 373, the estimated difference in mean trough FEV_1 change between UMEC 6.25 and placebo was 0.115 L (95% CI: 0.076, 0.155; $p<0.0001$). The efficacy of UMEC was also supported by trends toward benefit (relative to placebo) with respect to additional non-spirometric endpoints of interest, including mean changes from baseline in the SOBDA and SGRQ scores at 24 weeks, mean puffs of rescue mediation per day, and exacerbation rate over 24 weeks. There was also evidence of efficacy in phase 3 Study 408,

where the estimated treatment effect of UMEC 62.5 on trough FEV_1 at 12 weeks was 0.127 L (95% CI: 0.052, 0.202; p<0.001).

5.2 Collective Evidence

In the only one of the four primary efficacy studies (Study 373) that included both placebo and UMEC/VI 62.5/25 mcg treatment arms, the combination product provided a statistically significant 0.167 L (95% confidence interval: 0.128, 0.207) improvement over placebo in the primary endpoint, 24-week mean change from baseline in trough FEV_1. There was also independent, supportive evidence of a treatment effect on FEV_1 from a 12-week phase 3 cross-over study, from comparisons against the active comparator tiotropium, and from results for the higher 125/25 mcg dose. The effectiveness of UMEC/VI 62.5/25 was also supported by trends toward benefit with respect to several additional endpoints, including trough FEV_1 at earlier time points, weighted mean FEV_1, SGRQ score, SOBDA score, daily rescue medication use, and rate of COPD exacerbation. Missing data sensitivity analyses demonstrated consistent evidence of superiority to placebo, but provided estimated treatment effect sizes of approximately 20–30% less than the primary analyses.

There was evidence of the contribution of UMEC 62.5 mcg to the efficacy of the UMEC/VI 62.5/25 mcg combination product in Studies 360 and 373. There was evidence of the contribution of VI 25 mcg to the efficacy of the combination in only a single study (Study 373), but there was supportive evidence from independent, related study data. Supportive data included results from Study 361 for the higher 125/25 mcg dose, exploratory analyses from two phase 3 cross-over studies, and findings of efficacy relative to placebo for the VI monotherapy. There was also replicate evidence of efficacy, relative to placebo, for the UMEC monotherapy, which is a new molecular entity.

The complete safety evaluation was conducted by Dr. Jennifer Pippins, the Medical Reviewer, but we performed additional analyses to explore potential cardiovascular safety signals. Rates of MACE were similar across the treatment arms, but an analysis of cardiovascular-related serious adverse events in the primary efficacy studies suggested a possible trend toward greater risk on the UMEC, VI, and UMEC/VI treatment arms, as compared to placebo and tiotropium. This imbalance in the rates of cardiovascular-related SAEs was not evident in analyses that included data from all of the phase 3 studies.

6 REFERENCES

FDA guidance for industry, 1998, Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products.

7 APPENDIX

Table 21. Baseline Characteristics in Study 361

	Placebo (N = 275)	UMEC 125 (N = 407)	VI 25 (N = 404)	UMEC/VI 125/25 (N = 403)	Overall (N = 1489)
Female	100 (36%)	137 (34%)	139 (34%)	139 (34%)	515 (35%)
Age (years)	62.2 (8.5)	63.1 (8.5)	62.8 (8.8)	63.4 (8.1)	62.9 (8.5)
Race					
White	238 (87%)	363 (89%)	354 (88%)	359 (89%)	1314 (88%)
Black	9 (3%)	4 (1%)	7 (2%)	4 (1%)	24 (2%)
Asian	27 (10%)	40 (10%)	42 (10%)	39 (10%)	148 (10%)
Other	1 (0%)	0 (0%)	1 (0%)	1 (0%)	3 (0%)
Hispanic/Latino	1 (0%)	0 (0%)	0 (0%)	2 (0%)	3 (0%)
BMI (kg/m^2)	26.5 (6.1)	26.4 (5.8)	27.2 (6.0)	26.5 (5.1)	26.6 (5.8)
Current Smoker	143 (52%)	216 (53%)	210 (52%)	200 (50%)	769 (52%)
FEV_1 (L)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)
GOLD Stage ($ppFEV_1$)					
Stage II (50-80%)	121 (44%)	194 (48%)	207 (51%)	177 (44%)	699 (47%)
Stage III (30-50%)	132 (48%)	180 (44%)	159 (40%)	189 (47%)	660 (45%)
Stage IV (<30%)	21 (8%)	32 (8%)	36 (9%)	35 (9%)	124 (8%)
Chronic Bronchitis	199 (72%)	266 (65%)	273 (68%)	283 (70%)	1021 (69%)
Emphysema	160 (58%)	241 (59%)	230 (57%)	227 (56%)	858 (58%)
Duration of COPD, years					
<1	16 (6%)	39 (10%)	32 (8%)	29 (7%)	116 (8%)
1-5	94 (34%)	146 (36%)	167 (41%)	135 (33%)	542 (36%)
5-10	101 (37%)	117 (29%)	116 (29%)	131 (33%)	465 (31%)
10-15	48 (17%)	58 (14%)	70 (17%)	73 (18%)	249 (17%)
15-20	9 (3%)	25 (6%)	13 (3%)	11 (3%)	58 (4%)
20-25	3 (1%)	10 (2%)	3 (1%)	18 (4%)	34 (2%)
>25	4 (1%)	12 (3%)	3 (1%)	6 (1%)	25 (2%)
Inhaled Corticosteroid Use	138 (50%)	193 (47%)	191 (47%)	176 (44%)	698 (47%)
Reversible to Salbutamol	77 (28%)	132 (32%)	119 (29%)	133 (33%)	461 (31%)
Reversible to Salbutamol and Ipratropium	146 (53%)	228 (56%)	203 (50%)	213 (53%)	790 (53%)
At United States site	57 (21%)	87 (21%)	86 (21%)	86 (21%)	316 (21%)

Cell contents are mean (standard deviation) for continuous variables or frequency (percent) for categorical variables
Abbreviations: BMI = body mass index, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second

Table 22. Baseline Characteristics in Study 373

	Placebo (N = 280)	UMEC 62.5 (N = 418)	VI 25 (N = 421)	UMEC/VI 62.5/25 (N = 413)	Overall (N = 1532)
Female	85 (30%)	120 (29%)	136 (32%)	108 (26%)	449 (29%)
Age (years)	62.2 (9.0)	64.0 (9.2)	62.7 (8.5)	63.1 (8.7)	63.1 (8.9)
Race					
White	237 (85%)	354 (85%)	363 (86%)	348 (84%)	1302 (85%)
Black	9 (3%)	14 (3%)	9 (2%)	15 (4%)	47 (3%)
Asian	22 (8%)	35 (8%)	34 (8%)	35 (8%)	126 (8%)
Other	12 (4%)	15 (4%)	15 (4%)	15 (4%)	57 (4%)
Hispanic/Latino	25 (9%)	37 (9%)	36 (9%)	35 (8%)	133 (9%)
BMI (kg/m^2)	26.9 (5.9)	26.5 (5.6)	26.6 (5.9)	27.3 (6.0)	26.8 (5.9)
Current Smoker	150 (54%)	207 (50%)	199 (47%)	203 (49%)	759 (50%)
FEV_1 (L)	1.2 (0.5)	1.2 (0.5)	1.2 (0.5)	1.3 (0.6)	1.2 (0.5)
GOLD Stage ($ppFEV_1$)					
Stage II (50-80%)	119 (42%)	191 (46%)	197 (47%)	201 (49%)	708 (46%)
Stage III (30-50%)	133 (48%)	172 (41%)	179 (43%)	166 (40%)	650 (43%)
Stage IV (<30%)	28 (10%)	54 (13%)	44 (10%)	45 (11%)	171 (11%)
Chronic Bronchitis	182 (65%)	274 (66%)	260 (62%)	283 (69%)	999 (65%)
Emphysema	173 (62%)	271 (65%)	273 (65%)	236 (57%)	953 (62%)
Duration of COPD, years					
<1	20 (7%)	36 (9%)	36 (9%)	36 (9%)	128 (8%)
1-5	107 (38%)	151 (36%)	157 (37%)	160 (39%)	575 (38%)
5-10	82 (29%)	127 (30%)	115 (27%)	123 (30%)	447 (29%)
10-15	51 (18%)	70 (17%)	73 (17%)	63 (15%)	257 (17%)
15-20	9 (3%)	15 (4%)	19 (5%)	16 (4%)	59 (4%)
20-25	6 (2%)	10 (2%)	12 (3%)	9 (2%)	37 (2%)
>25	5 (2%)	9 (2%)	9 (2%)	6 (1%)	29 (2%)
Inhaled Corticosteroid Use	137 (49%)	219 (52%)	212 (50%)	212 (51%)	780 (51%)
Reversible to Salbutamol	91 (32%)	121 (29%)	155 (37%)	129 (31%)	496 (32%)
Reversible to Salbutamol and Ipratropium	146 (52%)	223 (53%)	230 (55%)	227 (55%)	826 (54%)
At United States site	78 (28%)	118 (28%)	117 (28%)	115 (28%)	428 (28%)

Cell contents are mean (standard deviation) for continuous variables or frequency (percent) for categorical variables
Abbreviations: BMI = body mass index, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second

Table 23. Baseline Characteristics in Study 360

	Tiotropium (N = 208)	VI 25 (N = 209)	UMEC/VI 62.5/25 (N = 212)	UMEC/VI 125/25 (N = 214)	Overall (N = 843)
Female	68 (33%)	66 (32%)	64 (30%)	63 (29%)	261 (31%)
Age (years)	62.6 (9.4)	63.2 (9.1)	63.0 (8.7)	62.9 (8.9)	62.9 (9.0)
Race					
White	177 (85%)	184 (88%)	182 (86%)	180 (84%)	723 (86%)
Black	6 (3%)	3 (1%)	7 (3%)	9 (4%)	25 (3%)
Asian	2 (1%)	0 (0%)	3 (1%)	1 (0%)	6 (1%)
Other	23 (11%)	22 (11%)	20 (9%)	24 (11%)	89 (11%)
Hispanic/Latino	23 (11%)	21 (10%)	24 (11%)	25 (12%)	93 (11%)
BMI (kg/m^2)	27.6 (5.5)	27.3 (5.7)	27.4 (6.1)	26.5 (5.1)	27.2 (5.6)
Current Smoker	99 (48%)	106 (51%)	98 (46%)	124 (58%)	427 (51%)
FEV_1 (L)	1.3 (0.5)	1.4 (0.5)	1.3 (0.5)	1.3 (0.5)	1.3 (0.5)
GOLD Stage ($ppFEV_1$)					
Stage II (50-80%)	96 (47%)	94 (46%)	104 (49%)	99 (47%)	393 (47%)
Stage III (30-50%)	87 (42%)	91 (44%)	85 (40%)	87 (41%)	350 (42%)
Stage IV (<30%)	23 (11%)	21 (10%)	22 (10%)	26 (12%)	92 (11%)
Chronic Bronchitis	149 (72%)	147 (70%)	147 (69%)	144 (67%)	587 (70%)
Emphysema	125 (60%)	116 (56%)	123 (58%)	129 (60%)	493 (58%)
Duration of COPD, years					
<1	20 (10%)	13 (6%)	20 (9%)	19 (9%)	72 (9%)
1,5	79 (38%)	73 (35%)	75 (35%)	74 (35%)	301 (36%)
5,10	54 (26%)	62 (30%)	63 (30%)	60 (28%)	239 (28%)
10,15	34 (16%)	40 (19%)	30 (14%)	38 (18%)	142 (17%)
15-20	14 (7%)	13 (6%)	11 (5%)	11 (5%)	49 (6%)
20-25	6 (3%)	7 (3%)	8 (4%)	10 (5%)	31 (4%)
>25	1 (0%)	1 (0%)	5 (2%)	2 (1%)	9 (1%)
Inhaled Corticosteroid Use	93 (45%)	84 (40%)	93 (44%)	103 (48%)	373 (44%)
Reversible to Salbutamol	47 (23%)	52 (25%)	57 (27%)	61 (29%)	217 (26%)
Reversible to Salbutamol and Ipratropium	99 (48%)	98 (47%)	113 (53%)	106 (50%)	416 (49%)
At United States site	53 (25%)	55 (26%)	59 (28%)	60 (28%)	227 (27%)

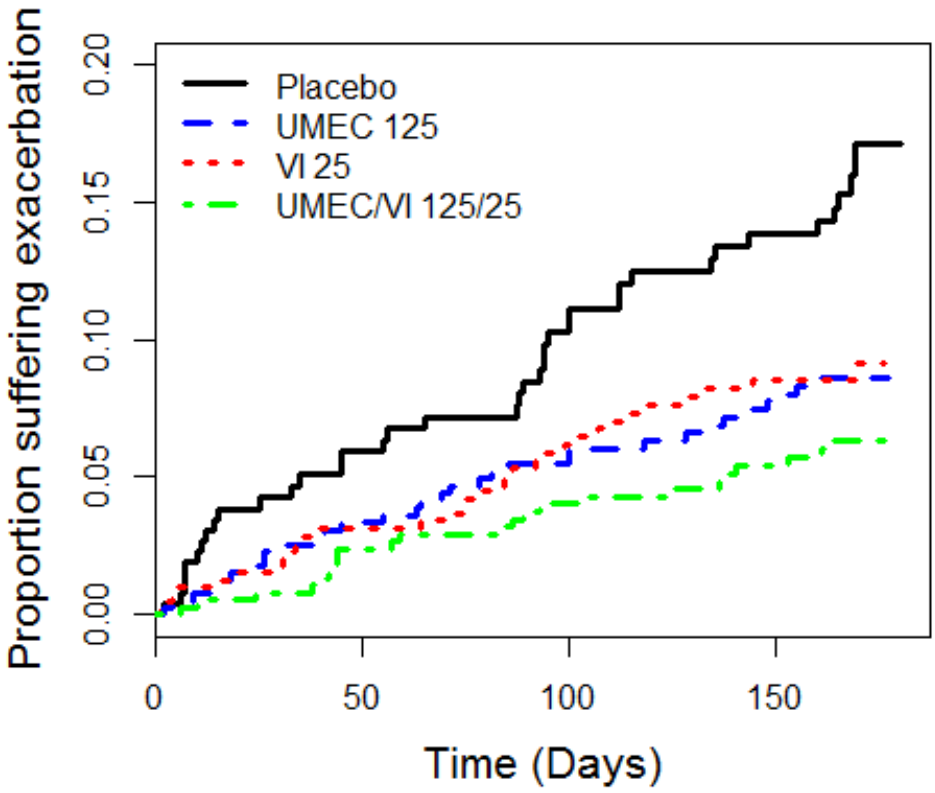
Cell contents are mean (standard deviation) for continuous variables or frequency (percent) for categorical variables
Abbreviations: BMI = body mass index, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second

Table 24. Baseline Characteristics in Study 374

	Tiotropium (N = 215)	UMEC 125 (N = 222)	UMEC/VI 62.5/25 (N = 217)	UMEC/VI 125/25 (N = 215)	Overall (N = 869)
Female	62 (29%)	74 (33%)	77 (35%)	67 (31%)	280 (32%)
Age (years)	65.2 (8.3)	64.5 (8.3)	65.0 (8.6)	63.8 (8.5)	64.6 (8.4)
Race					
White	163 (76%)	169 (76%)	164 (76%)	160 (74%)	656 (75%)
Black	8 (4%)	6 (3%)	8 (4%)	9 (4%)	31 (4%)
Asian	36 (17%)	37 (17%)	35 (16%)	37 (17%)	145 (17%)
Other	8 (4%)	10 (5%)	10 (5%)	9 (4%)	37 (4%)
Hispanic/Latino	38 (18%)	42 (19%)	38 (18%)	35 (16%)	153 (18%)
BMI (kg/m^2)	26.4 (6.1)	26.4 (5.7)	26.7 (6.1)	26.6 (5.8)	26.5 (5.9)
Current Smoker	102 (47%)	98 (44%)	92 (42%)	96 (45%)	388 (45%)
FEV_1 (L)	1.2 (0.4)	1.1 (0.4)	1.2 (0.5)	1.1 (0.5)	1.1 (0.5)
GOLD Stage ($ppFEV_1$)					
Stage II (50-80%)	103 (48%)	86 (39%)	106 (49%)	89 (42%)	384 (44%)
Stage III (30-50%)	83 (39%)	106 (48%)	83 (38%)	102 (48%)	374 (43%)
Stage IV (<30%)	28 (13%)	29 (13%)	27 (12%)	23 (11%)	107 (12%)
Chronic Bronchitis	120 (56%)	120 (54%)	134 (62%)	125 (58%)	499 (57%)
Emphysema	136 (63%)	152 (68%)	132 (61%)	136 (63%)	556 (64%)
Duration of COPD, years					
<1	16 (7%)	16 (7%)	28 (13%)	31 (14%)	91 (10%)
1,5	83 (39%)	96 (43%)	80 (37%)	74 (34%)	333 (38%)
5,10	65 (30%)	65 (29%)	53 (24%)	71 (33%)	254 (29%)
10,15	34 (16%)	22 (10%)	37 (17%)	21 (10%)	114 (13%)
15-20	12 (6%)	12 (5%)	10 (5%)	12 (6%)	46 (5%)
20-25	3 (1%)	7 (3%)	3 (1%)	3 (1%)	16 (2%)
>25	2 (1%)	4 (2%)	6 (3%)	3 (1%)	15 (2%)
Inhaled Corticosteroid Use	115 (53%)	124 (56%)	103 (47%)	113 (53%)	455 (52%)
Reversible to Salbutamol	60 (28%)	75 (34%)	64 (29%)	79 (37%)	278 (32%)
Reversible to Salbutamol and Ipratropium	110 (51%)	130 (59%)	115 (53%)	125 (58%)	480 (55%)
At United States site	55 (26%)	58 (26%)	59 (27%)	53 (25%)	225 (26%)

Cell contents are mean (standard deviation) for continuous variables or frequency (percent) for categorical variables
Abbreviations: BMI = body mass index, $ppFEV_1$ = percent predicted forced expiratory volume in 1 second

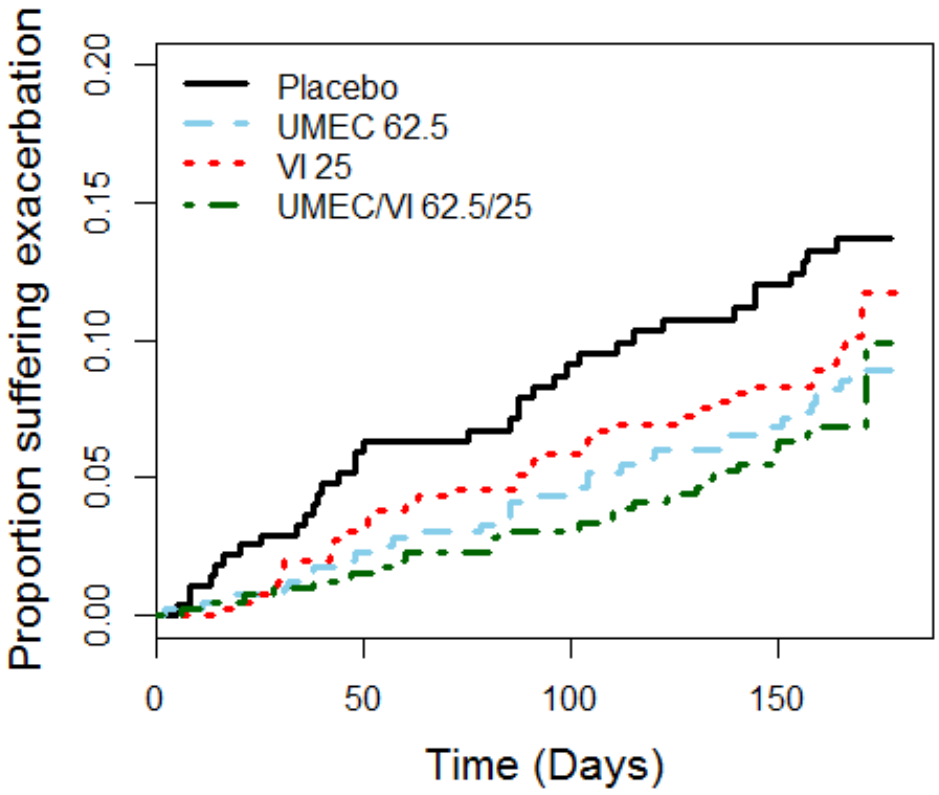
Figure 27. Proportion Suffering a COPD Exacerbation over Time in Study 361



Number at risk

Placebo	275	223	199	189
UMEC 125	407	368	337	324
VI 25	404	357	328	312
UMEC/VI 125/25	403	364	346	333

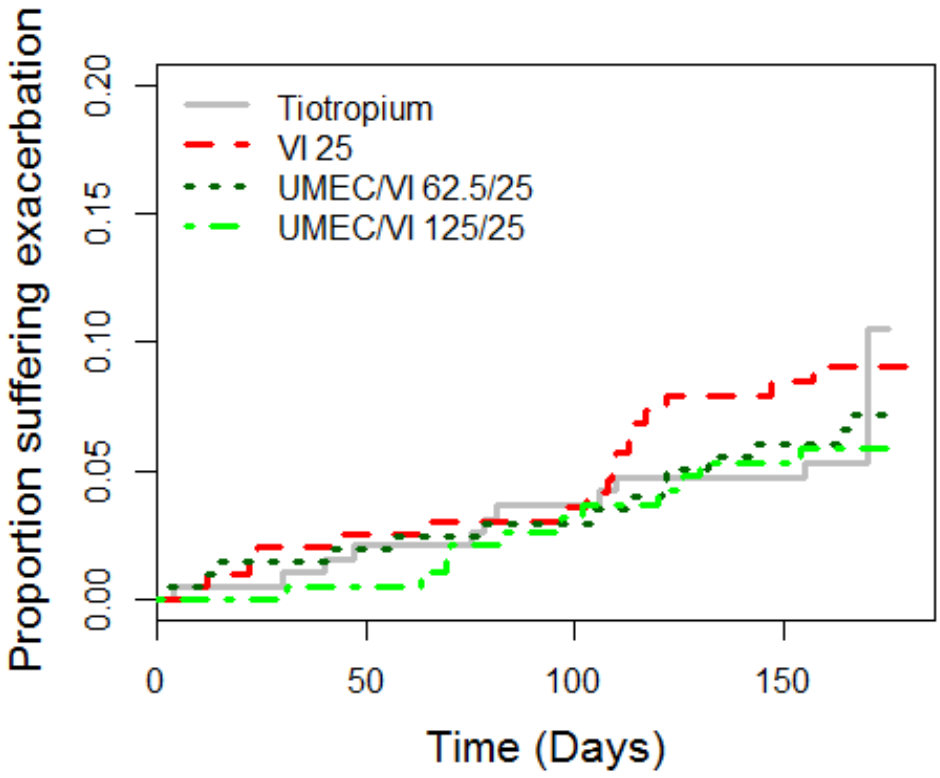
Figure 28. Proportion Suffering a COPD Exacerbation over Time in Study 373



Number at risk

Placebo	280	247	224	209
UMEC 62.5	418	378	349	334
VI 25	421	379	353	331
UMEC/VI 62.5/25	413	385	362	342

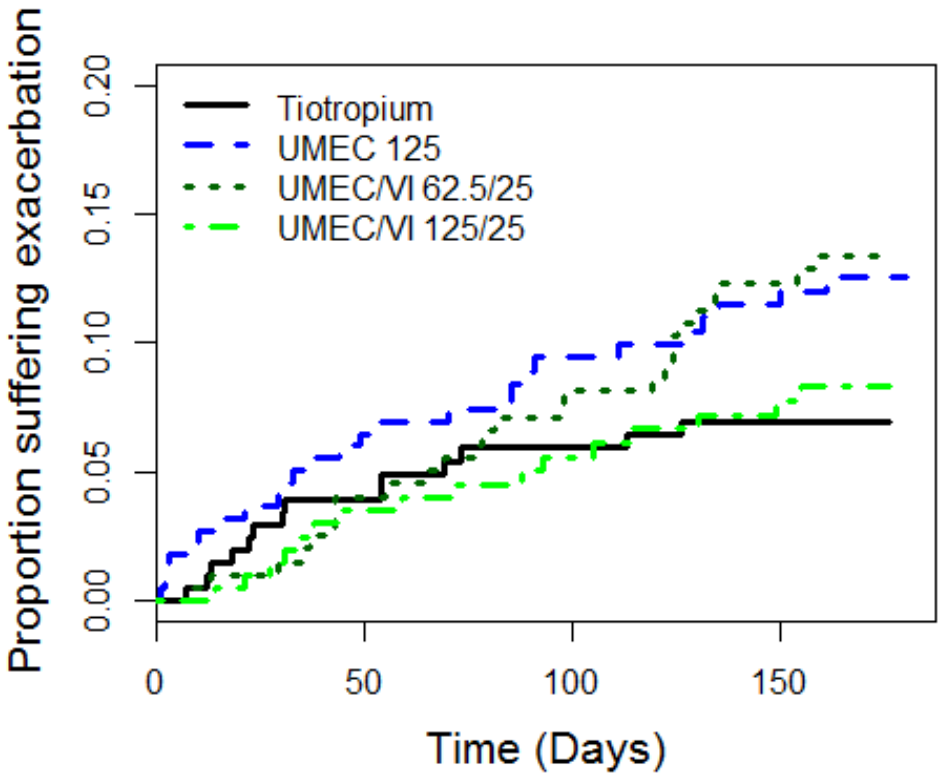
Figure 29. Proportion Suffering a COPD Exacerbation over Time in Study 360



Number at risk

Tiotropium	203	187	179	175
VI 25	205	189	178	166
UMEC/VI 62.5/25	207	198	188	181
UMEC/VI 125/25	208	192	179	173

Figure 30. Proportion Suffering a COPD Exacerbation over Time in Study 374



Number at risk

Tiotropium	215	194	185	179
UMEC 125	222	196	178	167
UMEC/VI 62.5/25	217	189	177	166
UMEC/VI 125/25	215	190	177	170

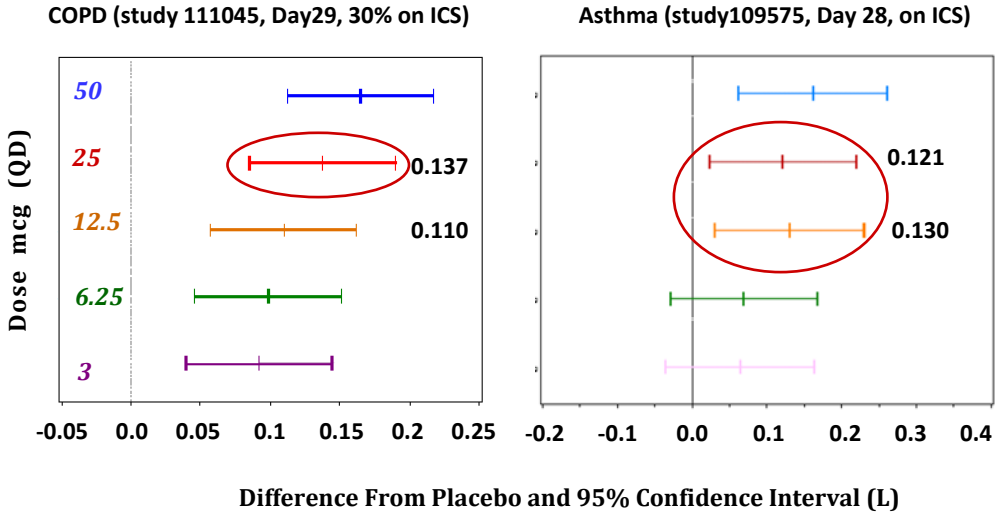
Clinical Pharmacology Summary

The clinical pharmacologystudies, including selection of dose, dosing frequency and timing of the dose, was conducted in patients with COPD as well as in patients with asthma.

Rationale for Dose and Dosing Frequency Selection
The proposed dose of UMEC/VI is 62.5/25 mcg once daily. Two dosing regimens, once daily doses of UMEC/VI 62.5/25 and 125/25 (mcg/mcg), were tested in Phase III studies in COPD patients. The dose regimens, including the selection of dose, dosing frequency and timing of the dose, was established in dose ranging studies in COPD population as well as in asthma patients.

Dose Selection
VI
The 25 mcg daily dose of VI was selected on the basis of results from a Phase 2 dose-ranging study in subjects with COPD (Study B2C111045), which tested a range of VI doses (3, 6.25, 12.5, 25 and 50 mcg once daily). Based upon the primary endpoint trough FEV1 (**Figure 1**) and secondary endpoint weighted mean FEV1 as well as the safety profile, 25 mcg was the appropriate dose. The 25 mcg dose was also supported by study B2C109575 in patients with asthma.

Figure 1. Effect of VI on lung function (trough FEV_1) across doses ranging from 3 mcg to 50 mcg QD



UMEC
The results for different UMEC doses on trough FEV_1 from four Phase 2 dose ranging studies in subjects with COPD are summarized in **Table 1**. Efficacy was observed with UMEC 62.5 mcg and near maximal efficacy with UMEC 125 mcg. Thus, the sponsor selected two doses of UMEC (62.5 and 125 mcg) for further evaluation in combination with VI in the COPD phase III program.

Table 1. Difference from Placebo for LS Mean Change from Baseline in Trough FEV1 (L) (95% CI)

	Difference from Placebo for LS Mean Change from Baseline in Trough FEV_1 (L) (95% CI) by once daily UMEC dose (mcg) [a]						
Study	**15.6**	**31.25**	**62.5**	**125**	**250**	**500**	**1000**
AC4115321 at Day 8	0.113 (0.058, 0.168)	0.101 (0.045, 0.158)	0.124 (0.068, 0.179)	0.183 (0.127, 0.239)			
AC4113073 at Day 15			0.128 (0.060, 0.196)	0.147 (0.077, 0.216)	0.095 (0.027, 0.162)	0.140 (0.074, 0.205)	0.186 (0.113, 0.259)
AC4113589 at Day 29				0.159 (0.088, 0.229)	0.168 (0.099, 0.238)	0.150 (0.080, 0.220)	
AC4115408 at Day 85			0.127 (0.052, 0.202)	0.152 (0.076, 0.229)			

Limited efficacy ← → toxicity

Following selection of doses for individual components of UMEC and VI, sponsor evaluated the efficacy of UMEC/VI 62.5/25 and 125/25 mcg in Phase III studies in COPD patients.

Dosing Frequency

Study AC4115321 supported the comparability of once and twice daily dosing for UMEC in subjects with COPD. The improvement of weighted mean FEV1 (0-24h) was similar with UMEC 31.25 mcg twice daily and UMEC 62.5 mcg once daily dosing(**Figure 2**). For VI, Study HZA113310 investigated once-daily vs. twice daily administration in subjects with persistent asthma. The improvement of weighted mean FEV1 (0-24h) was similar with VI 6.25 mcg twice daily and VI 12.5 mcg once daily dosing (**Figure 3**).

Figure 2. COPD; Change from baseline FEV1 (L) on Day 7; study AC4115321

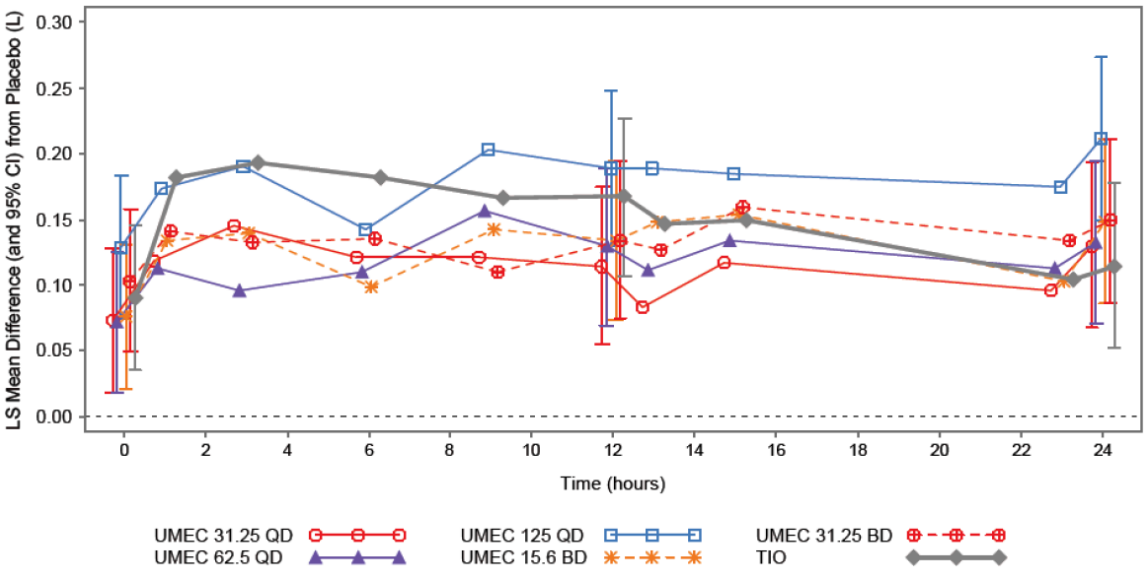
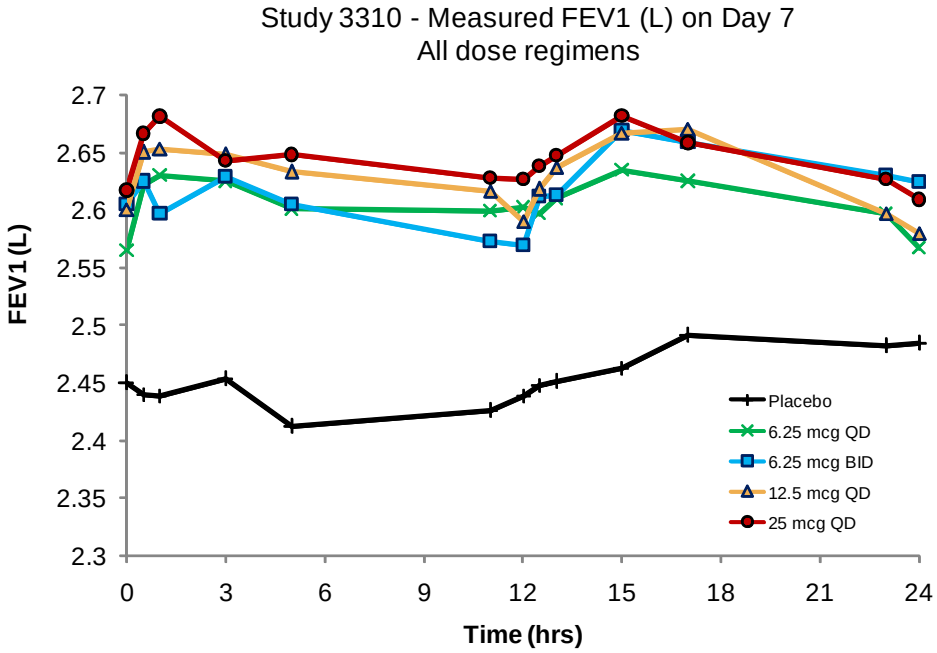


Fig 3. Effect of VI dosing on FEV1 in subjects with persistent asthma (study HZA113310)



Morning vs. evening dosing

All phase II and III studies used morning dosing. The timing of dosing is not specified in the proposed label.

PHARMACOKINETICS

Absorption

- The absolute systemic bioavailability for UMEC and VI was about 12.8% (based on

an earlier clinical formulation) and 26%, respectively. However, the systemic bioavailability of both UMEC and VI was low after oral administration (on average <1% and <2%, respectively). Therefore, systemic exposures for both inhaled UMEC and VI are primarily due to absorption of the inhaled portion of the dose delivered to the lung.

- T_{max} was reached by approximately 0.08-1 hours for both UMEC and VI following oral inhalation administration.
- The accumulation of C_{max} after once-daily dosing of orally-inhaled UMEC/VI 125/25 μg was 1.3 for UMEC and up to 2.4 fold for VI at Day 7. The assessment of accumulation of AUC is limited by low assay sensitivity.
- Systemic exposure for orally-inhaled UMEC/VI increased in proportion to the dose in the dose range of 125 to 500 μg for UMEC ($AUC_{tau,}$ C_{max}), and 25 to 100 mcg for VI (C_{max}).

Distribution

- The *in-vitro* plasma protein binding of UMEC and VI is independent of concentration with average values of 89% and 97%, respectively.
- Steady state volume of distribution (Vdss) for UMEC and VI following oral inhalation were 86 L and 165L, respectively.

Metabolism and Transporters

- *In-vitro* metabolism of UMEC is mediated primarily by CYP2D6. However, no clinically meaningful difference in systemic exposure to UMEC (500 mcg) was observed following repeat daily inhaled dosing to normal and CYP2D6 poor metabolizer subjects (Study AC4110106). Thus, no dose adjustment is recommended in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6 metabolism.
- VI is a substrate of CYP3A4.
- There are no known active metabolites for UMEC or VI.
- Both VI and UMEC are substrates of P-glycoprotein (P-gp).
- Based on in vitro studies, the potential for UMEC and VI to inhibit and induce metabolic enzymes is negligible at low inhalation doses.

Elimination

- In humans, UMEC is eliminated primarily by metabolism with metabolites excreting in feces (58%) and urine (22%). VI is also primarily eliminated by metabolism with metabolites excreting both in urine and feces (approximately 70% and 30% of the recovered radioactive dose, respectively).
- The apparent terminal elimination half-lives , following oral inhalation administration of UMEC/VI, are 11 hours for both UMEC and VI.

COPD vs. Healthy

- UMEC Cmax in COPD patients was <50% lower compared to Cmax in healthy subjects.

- VI Cmax in COPD patients was 62% lower while $AUC_{(0\text{-}24hr)}$ was 43% higher compared to that in healthy subjects.

POPULATION PHARMACOKINETIC ANALYSIS

Population PK models were developed to describe the UMEC and VI systemic exposure in subjects with COPD in Phase 3 studies DB2113361 and DB2113373. There were no covariates found in the population PK of UMEC and VI that warrant the dose adjustment of either component.

SPECIAL POPULATIONS

Renal Impairment

The effect of renal function on the PK of UMEC was evaluated in Studies DB2114636 (UMEC and UMEC/VI) and HZA113970 (VI).

- Following oral inhalation of UMEC 125 μg IH, UMEC plasma exposure for subjects with severe renal impairment was comparable with healthy controls. There was no difference in the *in-vitro* plasma protein binding of UMEC in healthy vs. severe renal impaired subjects.
- Systemic VI exposure is higher in severe renal impairment patients. At day 7 after continuous dosing of 25 mcg, subjects with severe renal impairment had a mean (90%CI) increase in VI $AUC_{(0\text{-}24hr)}$ by 56% (27%, 92%) and had similar VI C_{max} compared to subjects with normal renal function. Compared to healthy subjects, the increased VI exposure in severe renal impairment patients did not result in a significant increase in heart rate or decreases in serum potassium.
- No dose adjustments are recommended for subjects with renal impairment.

Hepatic Impairment

The effect of hepatic function on the PK of UMEC was evaluated in Study DB2114637 (UMEC and UMEC/VI) and Study HZA111789 (VI).

- Systemic UMEC and VI exposure in moderate hepatic impairment patients is comparable to that in healthy subjects. There was no evidence for reduced plasma protein binding of either UMEC or VI in plasma from subjects with varying degrees of hepatic impairment.
- No dose adjustments are recommended for subjects with hepatic impairment.

DRUG-DRUG INTERACTIONS (DDI)

Drug-Drug and Formulation Interactions

There were no clinically relevant differences (<20% difference between the geometric

means) in the pharmacokinetics of either UMEC or VI when administered in combination compared with administration alone.

Effect of co-administered drugs on UMEC/VI exposure

- Co-administration with ketoconazole, a strong CYP3A4 and potent P-gp inhibitor, resulted in modest increases in mean VI $AUC_{(0-t)}$ and C_{max} (by 65% and 22%, respectively). No dose adjustment is recommended for UMEC/VI when co-administered with ketoconazole.
- Co-administration with verapamil, a potent P-glycoprotein and moderate CYP3A4 inhibitor, resulted in no effect on VI C_{max} or AUC. No dose adjustment is recommended for UMEC/VI when co-administered with verapamil.
- There was no clinically significant difference in the systemic exposure to UMEC following 7 days of repeat dosing with inhaled doses up to 1000 mcg between normal metabolizer and CYP2D6 poor metabolizer. No dose adjustment is recommended in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6 metabolism.

Effect of UMEC/VI on exposure of co-administered drugs

- With low systemic exposures for both UMEC and VI after oral inhalation administration, potential for inhibition and induction of metabolic enzymes is negligible.

PHARMACOKINETIC/PHARMACODYNAMIC RELATIONSHIPS FOR SAFETY

UMEC/VI is administered by oral inhalation and efficacy is presumed to be driven by local effects in the lung. Systemic exposures of UMEC and VI are considered more relevant for safety.

Effect of UMEC/VI on QTc

QT effect for UMEC/VI was evaluated in a randomized, placebo-controlled, incomplete block, four-period crossover, repeat-dose study (DB2114635). In this study, subjects were given dry powder inhaler once daily for 10 days as placebo, UMEC 500 mcg, UMEC/VI 125/25 mcg, UMEC/VI 500/100 mcg. The active control was single oral dose of moxifloxacin 400 mg on Day 10. A dose representing 8-times the proposed upper therapeutic UMEC/VI dose (UMEC/VI 500/100 mcg) increased QTcF 8.2 msec (90% CI: 6.2, 10.2 msec) at 30 minutes, which was the largest increase observed. Subsequent QTcF differences from placebo declined rapidly.