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Applicant GlaxoSmithKline

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Dosing Regimen 1 inhalation once daily
Indication(s) Maintenance treatment of
airflow obstruction
Intended Population(s) COPD

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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

Clinical Review
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NDA 203-975
Anoro Ellipta (umeclidinium and vilanterol)

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 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

At the time of this review, the recommended regulatory action from a clinical perspective for umeclidinium/vilanterol (UMEC/VI) 62.5 mcg/25 mcg one inhalation once daily for the long-term, once-daily, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) is Approval. The demonstration of replicate evidence of efficacy as a bronchodilator, along with an acceptable safety profile, warrants the recommendation of Approval. This recommendation is preliminary and subject to change after the Pulmonary-Allergy Drugs Advisory Committee discussion of this application scheduled for September 10, 2013.

1.2 Risk Benefit Assessment

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 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.

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. (b) (4)

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 to 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.

In conclusion, the clinical development program for UMEC/VI 62.5 mcg/25 mcg in COPD provides replicate evidence of a bronchodilatory effect that is both statistically significant and likely to be clinically meaningful; the program also establishes the contribution of the monotherapies to the combination. Small numerical imbalances favoring placebo in adverse events pertaining to cardiac ischemia are noted for the primary efficacy trials only; the safety profile is acceptable. While approved LAMA and LABA monotherapy products for COPD are available in the United States, there are no approved LAMA/LABA combination products, and so UMEC/VI provides an additional treatment option for COPD. This benefit/risk profile for UMEC/VI is favorable.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No recommendations for postmarketing risk management activities are made.

1.4 Recommendations for Postmarket Requirements and Commitments

No recommendations for postmarketing requirements are made; however, this recommendation is preliminary and subject to change after the Pulmonary-Allergy Drugs Advisory Committee discussion of this application scheduled for September 10, 2013.

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 trifenate 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
		Acidinium bromide	Tudorza Pressair
Combination	Short-acting anti-cholinergic/ Short-acting beta-adrenergic agonist	Ipratropium bromide/Albuterol sulfate	Combivent 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 literature¹⁻² and in open public forums.³ In January 2010 FDA provided a Follow-Up⁴ 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 Spiriva 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 (acclidinium 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 acclidinium 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 acclidinium.

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 2010⁷ that they would require manufacturers to revise their drug labels to

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.

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/DrugSafetyInformationforHealthcareProfessionals/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

include updated guidelines for the use of LABA in asthma, and in April 2011⁸ announced that they would require manufacturers of LABAs to conduct five randomized, 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	<ul style="list-style-type: none">• preIND January 31, 2007• Teleconference March 24, 2010: dose and dosing interval in COPD discussed
UMEC	104,479	<ul style="list-style-type: none">• preIND May 26, 2009
UMEC/VI	106,616	<ul style="list-style-type: none">• EOP2 October 29, 2010: dose and dosing interval discussed• preNDA January 18, 2012
FFVI	77,955	<ul style="list-style-type: none">• EOP2 March 31, 2009 (asthma program), June 17, 2009 (COPD program), June 8, 2010 (asthma program)
SOBDA*		<ul style="list-style-type: none">• 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

called Long-Acting Beta-Agonists (LABAs), February 18, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm>; accessed August 3, 2013.

⁸FDA 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.

2.6 Other Relevant Background Information

The original application proposed UMEC/VI 62.5 mcg/25 mcg.

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3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was appropriately indexed and complete to permit review.

An Office of Scientific Investigations (OSI) consult was requested as the product includes a new molecular entity (NME). A center effect analysis was conducted by the primary statistical reviewer for the two placebo-controlled trials. This analysis took into account the magnitude of the treatment effect for the primary endpoint, the number of patients, and the percent dropout per site. While no one site appeared likely to drive efficacy results, based on the analysis the clinical recommendation was for audit of site 087869 (Trial DB2113373) and of site 086085 (Trial DB2113361), as they were characterized by a high enrollment, large percentage of dropouts, and a large effect size. The inspection of site 087869 (Trial DB2113373) found no significant regulatory violations and a Form FDA 483 (list of investigational observations) was not issued; the OSI team concluded that the study appeared to have been conducted adequately and the data generated by this site was acceptable. The inspection of site 086085 (Trial DB2113361) identified minor deficiencies (failure to prepare or maintain adequate case histories) that resulted in the issuing of a Form FDA 483; however, it is unlikely that these deficiencies impacted the data reliability of the trial.

3.2 Compliance with Good Clinical Practices

The application includes a statement that all trials were undertaken in accordance with the standard operating procedures of GlaxoSmithKline, which comply with the principles of Good Clinical Practice (GCP), that all trials were conducted with the approval of Ethics Committees or Institutional Review Boards, and that informed consent was obtained for all subjects.

The application also notes significant deviations from GCP for investigator site 040688; 48 subjects from this site were involved in the UMEC/VI development program, and 25 subjects were involved in the development program of a related product, the fixed-dose combination fluticasone furoate and vilanterol inhalation powder (FF/VI). Impacted trials include one of the four primary efficacy trials (DB2113360), the long-term safety trial (DB2113359), one of the key UMEC dose-ranging and dosing interval trials (AC4115321), and two of the FF/VI trials (HZC102871, HZC112207). The Applicant reports that sensitivity analyses of efficacy data with and without these subjects were conducted for each of the efficacy studies (but not the long-term safety trial), and results were generally consistent with those for the overall population. In general, the efficacy results for Trial DB2113360 presented throughout this review exclude patients from investigator site 040688.

3.3 Financial Disclosures

The Applicant provided financial interest information for clinical investigators as per regulation. Information was available for all investigators upon commencement of their participation; one investigator (participating in Trial HZC102970) is noted to have had a financial interest in GSK. The Applicant concludes that the data generated by this investigator was unlikely to affect the outcome of the study, as they were responsible for <2% of total patient recruitment. Information was available for all except for seven principal investigators/former principle investigators at the end of their participation; in five cases this was the result of the individual being deceased or unable to sign due to a medical condition. In the remaining two cases, one investigator had retired and another was no longer in contact. The Applicant also notes that significant payments of other sorts were reported by seven investigators. The Applicant concludes that the data generated by these seven investigators was unlikely to affect the outcome of the studies in which they participated, as in each instance they were responsible for <2% of total patient recruitment.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The preliminary recommendation from the CMC review team is Approval pending inspections.

The drug product is a plastic inhaler with a light grey body, a red mouthpiece cover and a dose counter. The inhaler contains two double-foil blister strips. Each blister on one strip contains a white powder mix of umeclidinium (62.5 mcg, equivalent to 74.2 mcg of umeclidinium bromide), magnesium stearate (75 mcg), and lactose monohydrate (to 12.5 mcg). Each blister on the other strip contains a white powder mix of vilanterol (25 mcg, equivalent to 40 mcg of vilanterol trifenate), magnesium stearate (125 mcg), and lactose monohydrate (to 12.5 mcg). The to-be-marketed UMEC/VI 62.5 mcg/25 mcg formulation was used in all pivotal trials.

4.2 Clinical Microbiology

Approval of this application is recommended from the product quality microbiology team (see NDA 203-975 review by Dr. Erika Pfeiler, April 3, 2013).

4.3 Preclinical Pharmacology/Toxicology

The recommendation from the preclinical review is Approval (see NDA 203-973 review by Dr. Jane Sohn, NDA 203-975, June 25, 2013).

UMEC

The general toxicity of inhaled UMEC was evaluated in rats and dogs for 26 and 39 weeks, respectively. No observed adverse effect levels (NOAELs) were identified in both studies. Relevant target organs were the lung and tracheal bifurcation in the rat and the heart, lung, larynx, and nasal turbinates in the dog. Safety margins were 30 and 19 times the maximum recommended human dose (MRHD) on an area under the curve (AUC) basis for the rats and dogs, respectively.

Two-year carcinogenicity studies were conducted in rats and mice, and were both negative for test-article related tumors. Safety margins were 26 and 22 times the MRHD on an AUC basis for male and female mice, respectively. The safety margin in rats was 22 times the MRHD on an AUC basis.

Reproductive and developmental studies demonstrated no effect of umeclidinium on fertility in rats, and no teratogenicity in rats or rabbits.

VI

The preclinical program conducted in support of VI was evaluated and found to be adequate during the review of a related product, the fixed-dose combination fluticasone furoate and vilanterol (FF/VI) inhalation powder (Breo Ellipta, NDA 204-275) which received United States approval for use in COPD on May 10, 2013.

UMEC/VI

A 13-week toxicology study with the combination of umeclidinium and vilanterol was conducted in dogs. The nonclinical review found that the observed toxicity was consistent with the monoproducts, with no evidence of additive or synergistic toxicity with the combination.

UMEC/VI has been given a pregnancy C category rating, which is consistent with other inhaled products for COPD.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Umeclidinium is a long-acting muscarinic antagonist (anticholinergic). In the airways, it exhibits pharmacological effects through inhibition of M3-receptors at the smooth muscle leading to bronchodilation.

Vilanterol is a long-acting beta agonist, and acts by binding and activating beta-2-adrenergic receptors in the lungs, predominantly in bronchial smooth muscle, to promote bronchodilation.

4.4.2 Pharmacodynamics

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.

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 2010	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 UMEC 250 P	3 periods per subject, 14 days per period	Trough FEV1
AC4115321	Dose-ranging, dosing	R, DB, PC, CO, incomplete	163	Once-daily: UMEC 15.6	3 periods per subject,	Trough FEV1

2011	interval	block		UMEC 31.25 UMEC 62.5 UMEC 125 Tio 18 (OL) P Twice-daily: UMEC 15.6 UMEC 31.25 P	7 days per period	
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

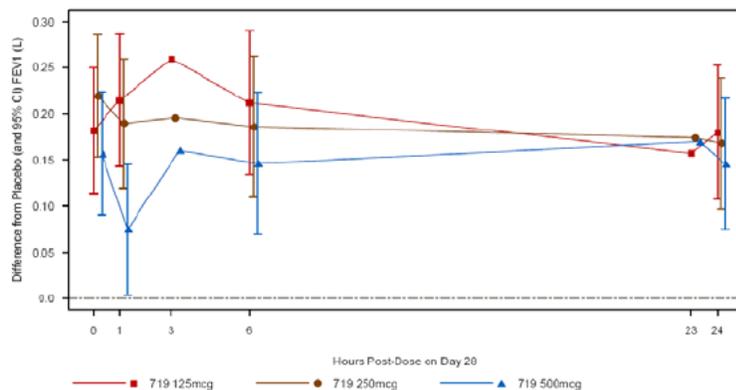
Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		Mean (SD)	LS Mean (SE)	Difference	95% CI	p-value
UMEC 500	71	1.320 (0.4242)	0.163 (0.025)	0.150	0.080, 0.220	<0.001
UMEC 250	72	1.480 (0.5772)	0.181 (0.025)	0.168	0.099, 0.238	<0.001
UMEC 125	71	1.466 (0.4737)	0.171 (0.025)	0.159	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	0.048	0.095	0.027,	0.006

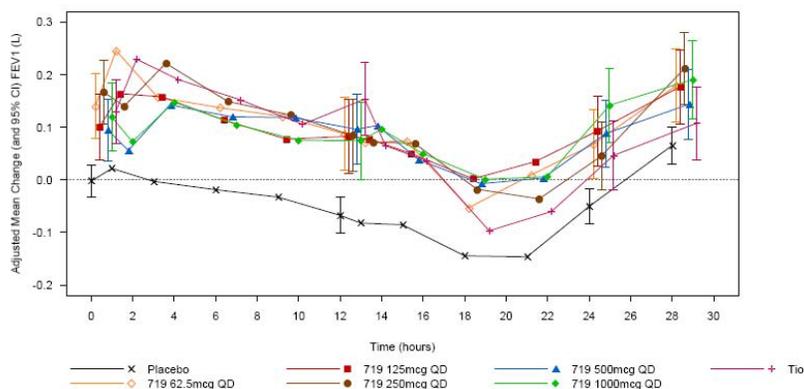
		(0.033)	(0.033)		0.162	
UMEC 125	34	1.542 (0.034)	0.099 (0.034)	0.147	0.077, 0.216	<0.001
UMEC 62.5	35	1.524 (0.033)	0.081 (0.033)	0.128	0.060, 0.196	<0.001
Tio 18	35	1.500 (0.033)	0.058 (0.033)	0.105	0.037, 0.173	0.003
Twice-daily						
UMEC 250	33	1.567 (0.034)	0.124 (0.034)	0.172	0.101, 0.242	<0.001
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).

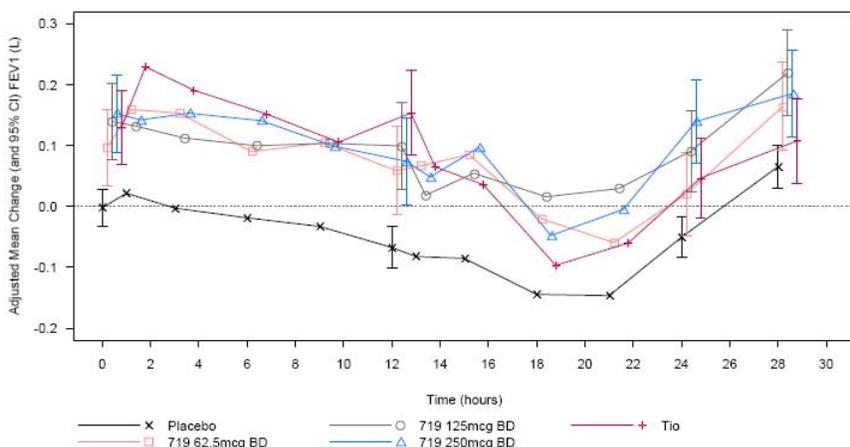
Results for an additional efficacy endpoint, 0-24 hour weighted mean FEV1 on Day 14, are supportive of the findings of the primary endpoint, with statistically significant results for each treatment group compared to placebo, and no clear dose ordering. Also consistent with the results for the primary 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)			

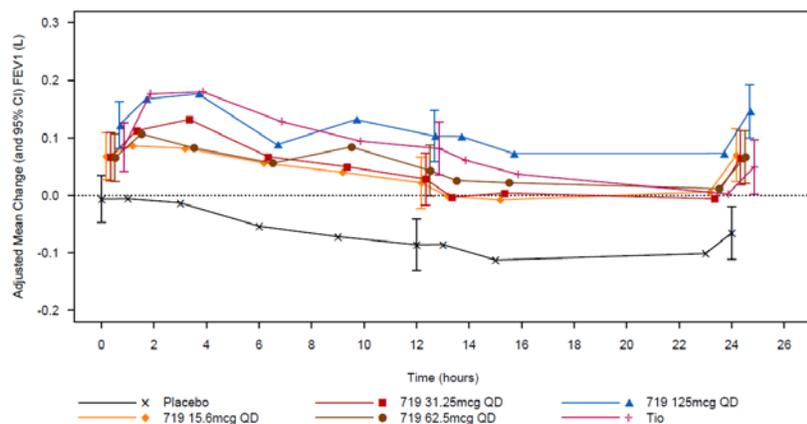
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 78 (Table 24)
 Note: modified ITT (mITT) population=all patients randomized who received at least one dose of study medication

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

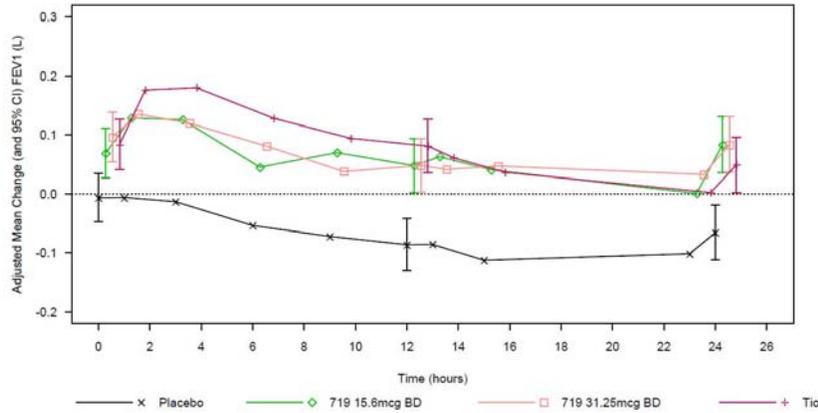
tiotropium. In Figure 5 the twice-daily regimens are compared to both placebo and tiotropium; all active arms demonstrate an effect over placebo, and the 31.25 mcg and 15.6 mcg twice-daily regimens approximate the curve for tiotropium, albeit with a somewhat lesser effect in the first 12 hours. In Figure 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



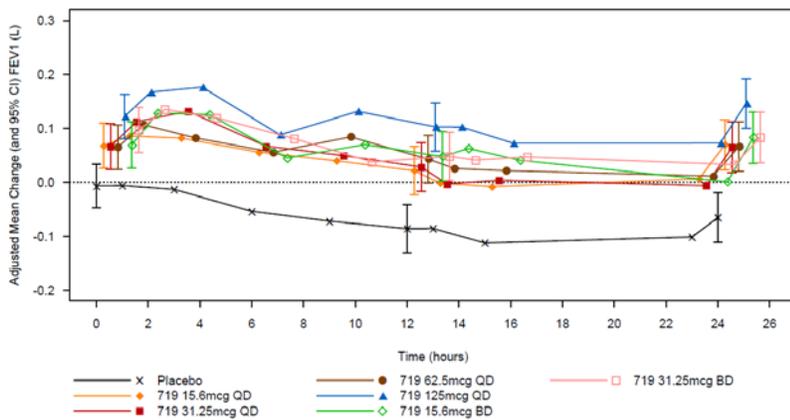
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 93 (Figure 16)

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



Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 95 (Figure 18)

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.

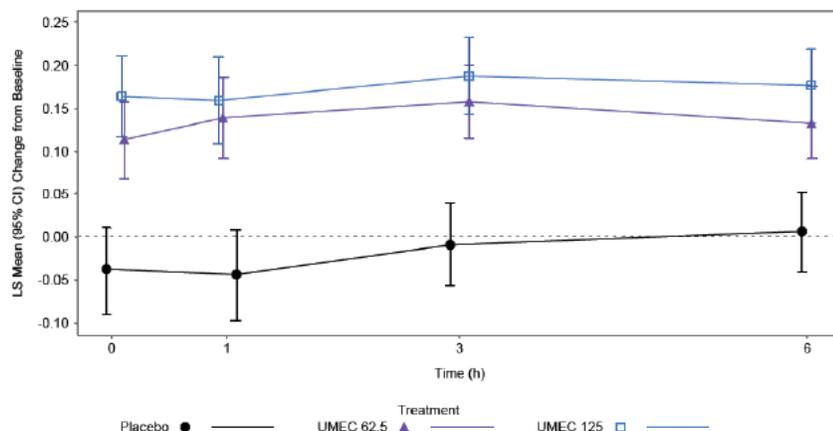
Table 7. Change in Trough FEV1 (L) on Day 85, Trial AC4115408, ITT Population

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.

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	101 101 101 101 100 101	Once-daily: VI 3 VI 6.25 VI 12.5 VI 25 VI 50 P	28 days	Trough FEV1
2008		COPD				
B2C109575	Dose-ranging	R, DB, PC, PG	102	Once-daily: VI 3	28 days	Trough FEV1

2008		Asthma	102 102 103 102 103	VI 6.25 VI 12.5 VI 25 VI 50 P		
HZA113310	Dose-ranging, dosing interval	R, DB, PC, CO	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
2010		Asthma				

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 (0.4672)	0.029 (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		
			Difference	95% CI	p-value
		LS Mean (SE)			
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.

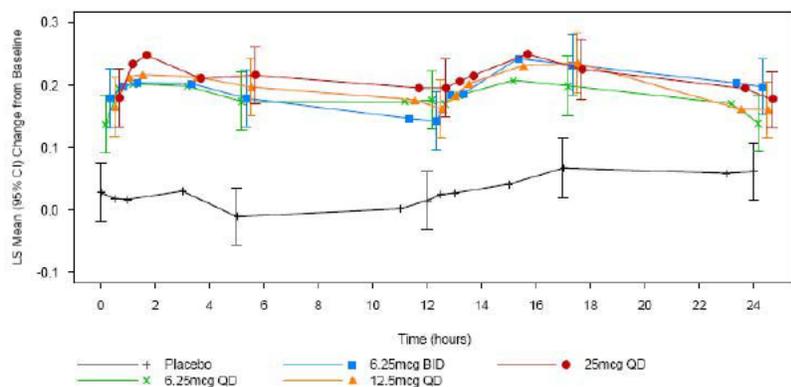
Table 12. Change in Trough FEV1 (L) at Day 7, Trial HZA113310, ITT Population

Treatment Arm	N	Change from BL	Treatment Difference from Placebo		
			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.

4.4.3 Pharmacokinetics

The preliminary assessment of the clinical pharmacology review is for Approval; however, final recommendations are pending at the time of this review.

The submission includes a clinical pharmacology program evaluating UMEC/VI, UMEC, and VI, predominantly in healthy subjects, but also including patients with COPD, hepatic impairment, and renal impairment.

The absolute bioavailability of umeclidinium and vilanterol are 13% and 26%, respectively; in both cases the systemic exposure is primarily due to absorption of the inhaled portion. T_{max} for both UMEC and VI is approximately 0.08-1 hour after oral inhalation administration. The half-life of both UMEC and VI after oral inhalation of UMEC/VI is approximately 11 hours. In COPD patients compared to healthy subjects, UMEC C_{max} and AUC_{0-24} were <50% lower, and VI C_{max} was 62% lower but VI AUC_{0-24} was 43% higher.

The effects of renal function and hepatic function on the pharmacokinetics of UMEC/VI, UMEC, and VI, were evaluated in several trials. 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.

The clinical development program includes a number of drug-drug interactions studies. The clinical pharmacology team 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.

Trials assessing cardiac conduction (“Thorough QT” studies) were also performed. No clinically significant QTc prolongation effects were detected.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

A summary of the trials conducted in support of UMEC and VI dose selection is provided in Section 4.4.2 of this review. The core phase 3 development program⁹ conducted in support of UMEC/VI includes two placebo-controlled efficacy 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	Design	N	Treatments	Duration	Primary Endpoint	Number of Sites
<i>Year completed</i>						<i>n (%) of patients from US</i>
Placebo-controlled efficacy and safety trials						
DB2113361	R, DB, PC, PG	403	UMEC/VI 125/25	24 weeks	Trough FEV1	153
2012		409	UMEC 125			316 (21)
		404	VI 25			
		277	P			
DB2113373	R, DB, PC, PG	414	UMEC/VI 62.5/25	24 weeks	Trough FEV1	163
2012		421	UMEC 62.5			428 (28)
		421	VI 25			
		280	P			
Active-comparator efficacy and safety trials						
DB2113360	R, DB, DD, AC, PG	216	UMEC/VI 125/25	24 weeks	Trough FEV1	91
2012		212	UMEC/VI 62.5/25			227 (27)
		209	VI 25			
		209	Tio 18			
DB2113374	R, DB, DD, AC, PG	217	UMEC/VI 125/25	24 weeks	Trough FEV1	95

⁹ An additional phase 3 trial, AC4115408, is described by the Applicant as providing additional support for UMEC dose selection, and so is discussed in Section 4.4.2.

2012		218 222 215	UMEC/VI 62.5/25 UMEC 125 Tio 18			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 2012	R, DB, PC, CO Incomplete block	128 130 41 41 64 151	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	42 139 (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

5.2 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 Section 4.4.2. 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 5.3 of this review; a discussion of the efficacy data generated by these trials is provided in Section 6.

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 7.1.1, and a discussion of the safety findings follows in the rest of Section 7. Any supportive efficacy and safety data generated from other trials are reviewed in the applicable efficacy or safety section.

5.3 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 7.1.1 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 $\leq 70\%$ 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) scan¹⁰ with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta₂-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

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).

- 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
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 \leq 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

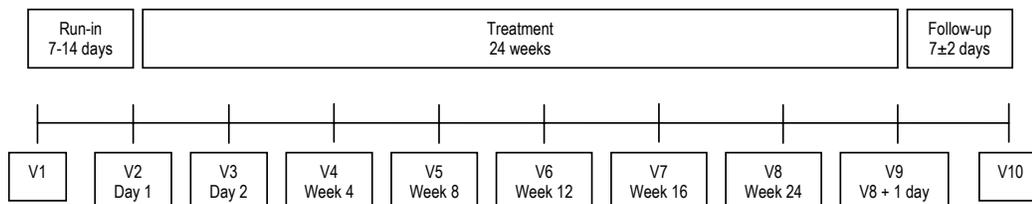
Withdrawal Criteria:

- 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 7.1.2 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								EW	Follow-up
	Visit 1 (Screening)	Visit 2 (Randomization)	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9		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	

Clinical Review
 Jennifer Rodriguez Pippins, MD, MPH
 NDA 203-975
 Anoro Ellipta (umeclidinium and vilanterol)

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	
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 FEV1¹¹ 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
- Proportion of patients achieving an increase in FEV1 of $\geq 12\%$ 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 24¹²
- 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

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.

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."

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.

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 submitted¹³ 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.

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

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.

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 scan¹⁴ with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta₂-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

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).

- 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 \leq 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

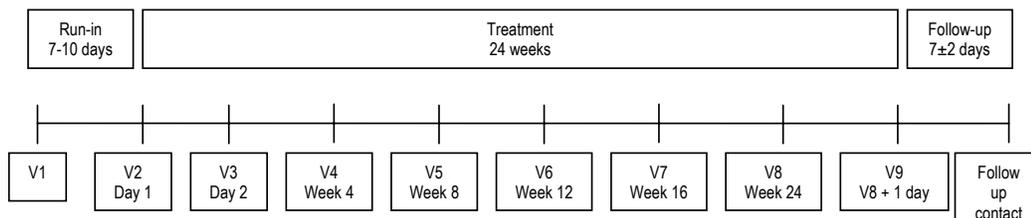
Withdrawal Criteria:

- 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 7.1.2 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 phone¹⁵ 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 5.3.5.1.4 (DB2113360, Protocol Amendment 1), pg. 17 (Figure 1)

Spirometry:

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

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 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								EW	Follow-up
	Visit 1 (Screening) Day -7 to -10	Visit 2 (Randomization) Day 1	Visit 3 Day 2	Visit 4 Day 28 (±2) Week 4	Visit 5 Day 56 (-4 to +2) Week 8	Visit 6 Day 84 (-4 to +2) Week 12	Visit 7 Day 112 (-4 to +2) Week 16	Visit 8 Day 168 (±4) Week 24	Visit 9 +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-blind medication				X	X	X	X	X			X
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 FEV1¹⁶ on Treatment Day 169

¹⁶ Trough FEV1 on Day 169 is defined as the mean of the FEV1 values obtained 23 and 24 hours after

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 $\geq 12\%$ 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
- 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

dosing on Treatment Day 168.

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 $\geq 35\%$ and $\leq 70\%$ 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 $\geq 120\%$ 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 scan¹⁷ with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta₂-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

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 \leq 1000 mcg/day of fluticasone propionate or equivalent)

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).

- Demonstrated ability to properly perform the Endurance Shuttle Walk Test (ESWT) at Visit 3 or 4
- ESWT exercise endurance time \leq 15 minutes, and with variability no greater than $>$ 2 minutes, at visit 3 or 4
- SpO₂ of \geq 85% during the ESWT at Visit 3, with no need for supplemental oxygen
- Ability to properly use inhaler after 3 demonstrations

Withdrawal Criteria:

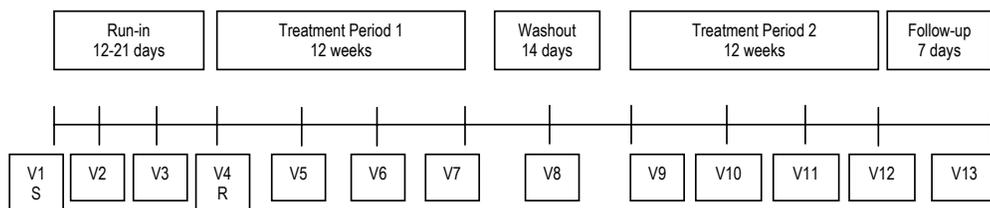
- Significant abnormal ECG finding
- Protocol-defined liver chemistry stopping criteria
- Positive pregnancy test

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				X	X	X	X		X	X	X	X		

& post dose														
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		
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	X
Exercise IC (subset, Trial DB2114417 only)			X	X	X	X	X		X	X	X	X		
Cardio-respiratory assessment (subset, Trial DB2114417 only)			X	X	X	X	X		X	X	X	X		
Dispense/collect rescue medication	X	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 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.

6 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.

Overall, these results provide replicate evidence of efficacy for the proposed product and indication.

6.1 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.

6.1.1 Methods

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

6.1.2 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/m²), 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%).

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 ₁ ≥80% predicted	0	0	0	0	0	0	0
II: 50% ≤ FEV ₁ < 80% predicted	240 (43)	409 (49)	362 (44)	191 (46)	280 (45)	498 (49)	195 (47)
III: 30% ≤ FEV ₁ < 50% predicted	265 (48)	331 (40)	375 (46)	172 (41)	286 (46)	425 (42)	169 (41)
IV: FEV ₁ < 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							

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.

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 comorbid 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	67 (12)	96 (11)	108 (13)	50 (12)	96 (15)	129 (12)	59 (14)

mediastinal disorders							
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" conditions are defined as those reported in $\geq 10\%$ 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 7.3.5. 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.

6.1.3 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 ^a	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^b							
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.

6.1.4 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

¹⁹ Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for

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, 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

Treatment," November 2007. Available at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf>. Accessed August 5, 2013.

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 (0.018)	0.186 (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.

6.1.5 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 Mean (SE)	Change from BL LS Mean (SE)	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
				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 Mean (SE)	Change from BL LS Mean (SE)	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
				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.

6.1.6 Other Endpoints

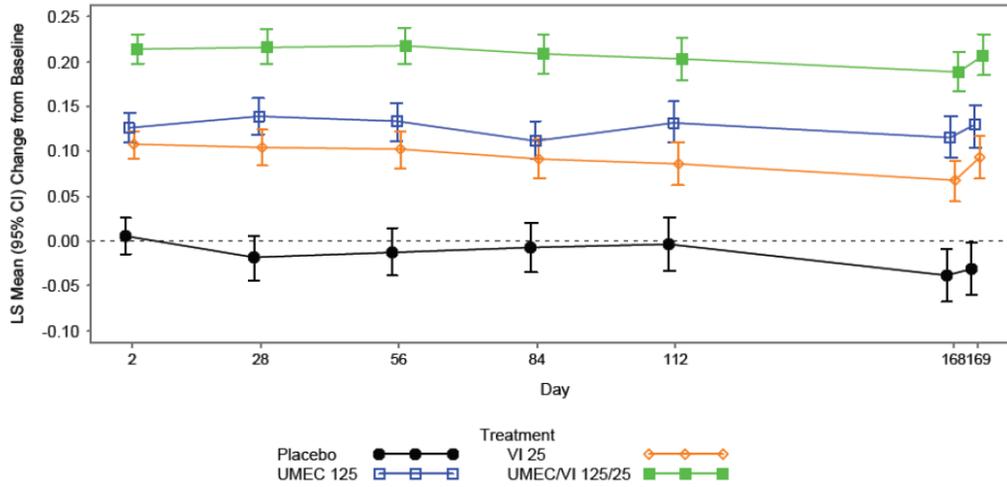
Additional Spirometric Assessments

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

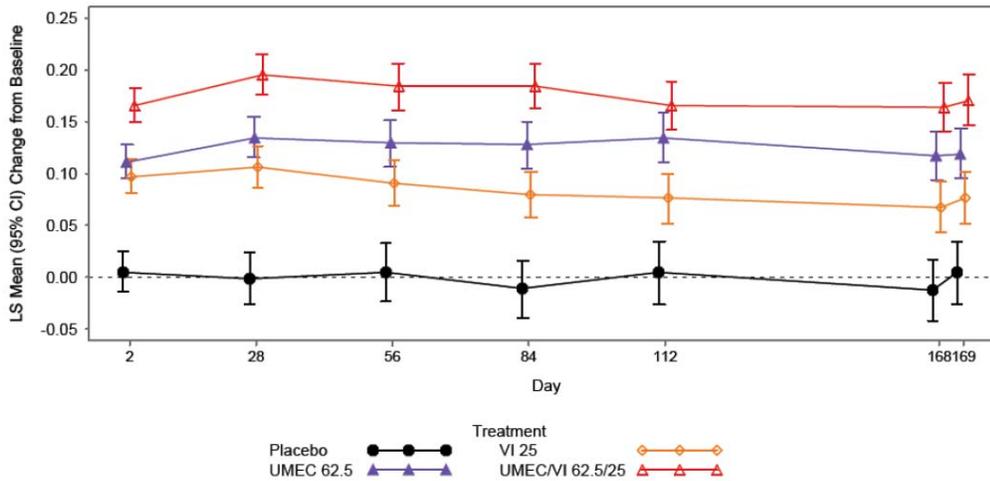
The primary analysis of trough FEV1 was conducted using data at Day 169. In addition, the primary efficacy trials analyzed trough FEV1 for other time points during the 24 week treatment period. Least squares mean change from baseline in trough FEV1 on Days 2, 28, 56, 84, 112, 168, and 169 for Trials 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



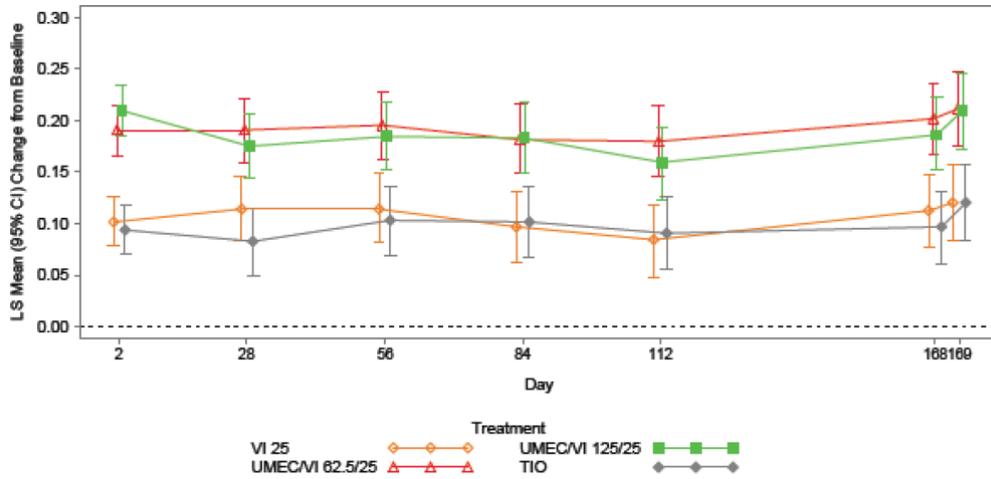
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 96 (Figure 4)

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



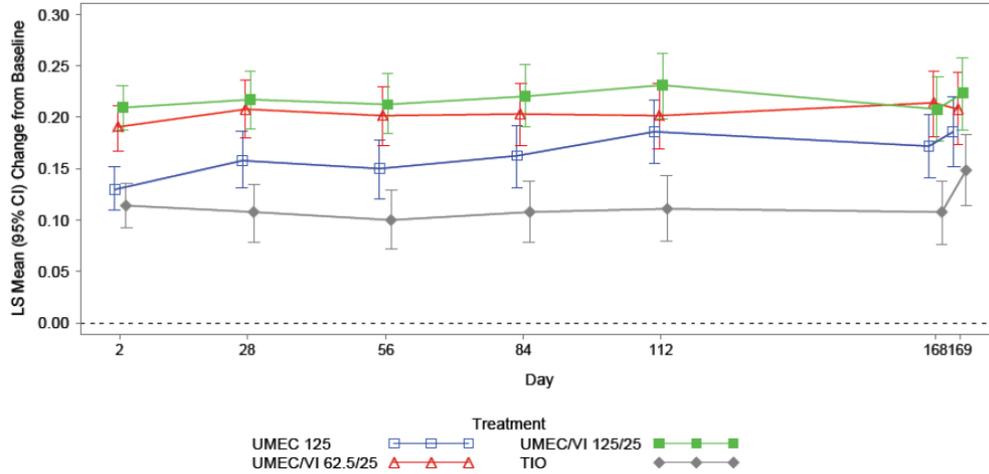
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 93 (Figure 4)

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)

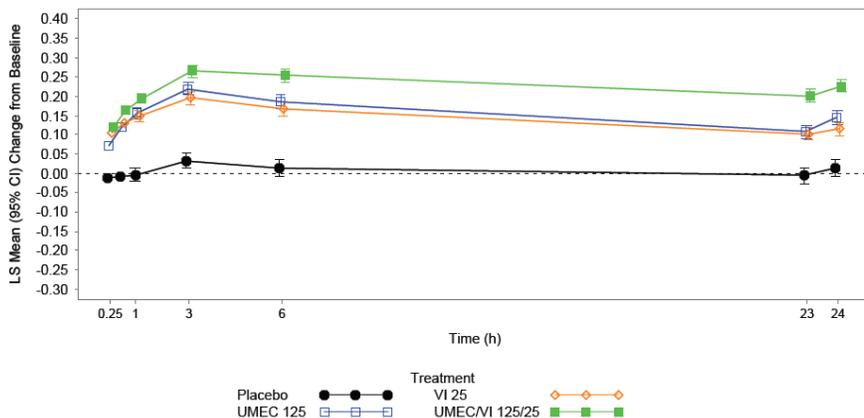
In each of the placebo-controlled trials there is separation between the curves for the combination product and placebo at all time points. In the two active-controlled trials, which each included both UMEC/VI doses, there is a high degree of overlap between the 125 mcg/25 mcg and 62.5 mcg/25 mcg doses 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

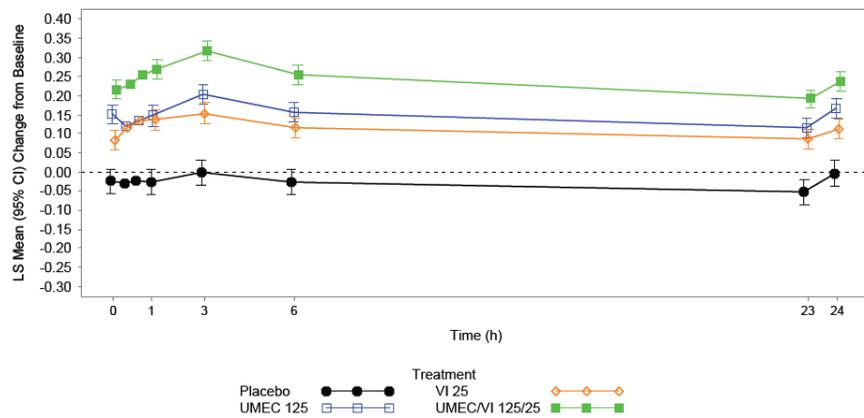
Each of the four primary efficacy trials evaluated serial FEV1 over the six hours immediately following dosing. The results for this parameter at the start of treatment (Day 1) and end of treatment (Day 168) are provided in Figures Figure 16, Figure 17, Figure 18, and Figure 19 for Trials DB2113361,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

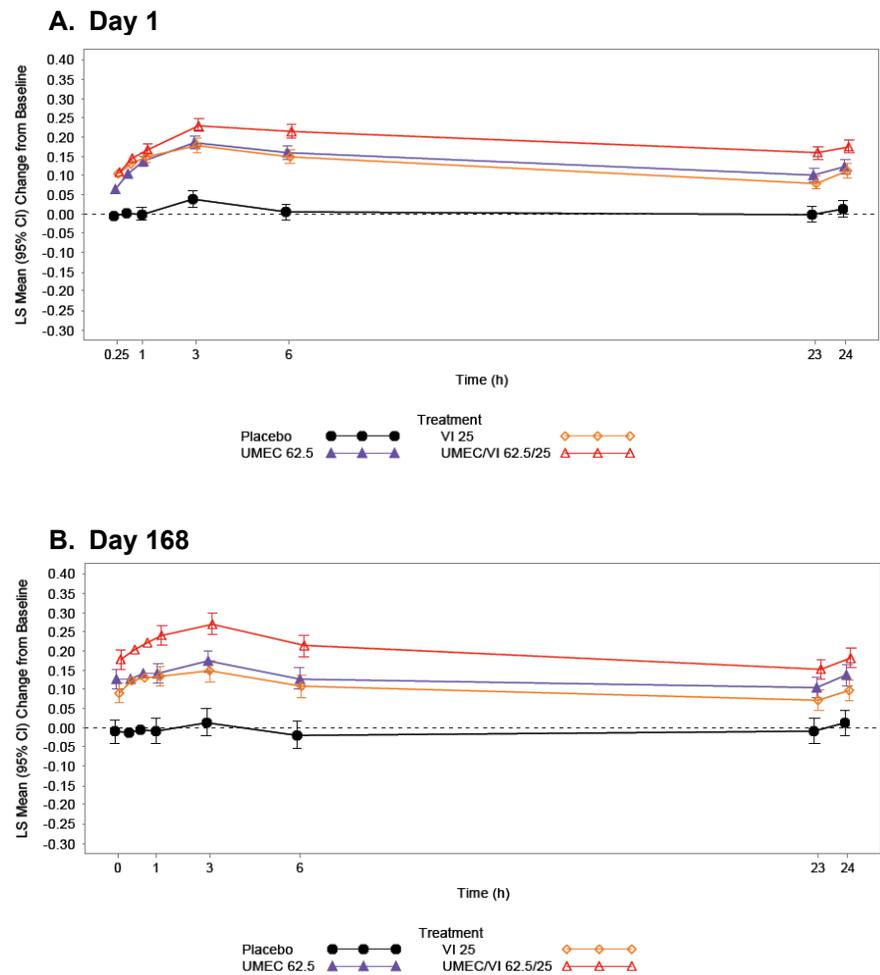


B. Day 168



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

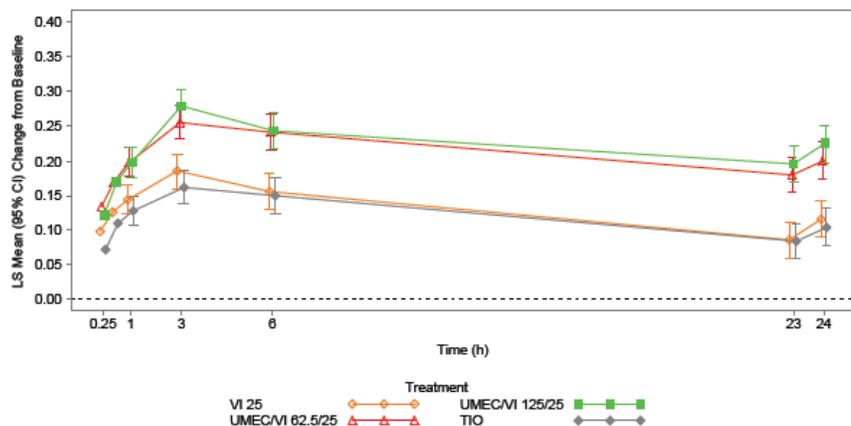
Figure 17. Least Squares Mean Change from Baseline in FEV1 (L), 0-6 hours, 23, and 24 hours on Day 1 and Day 168, Trial DB2113373, ITT Population



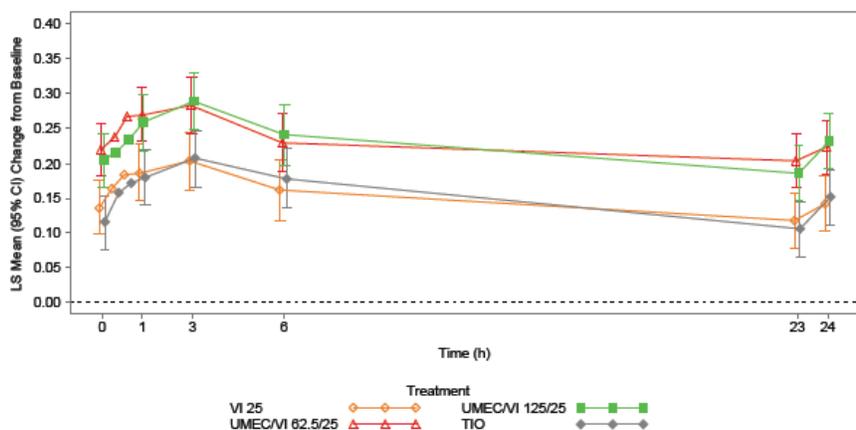
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 107,109 (Figure 10)

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



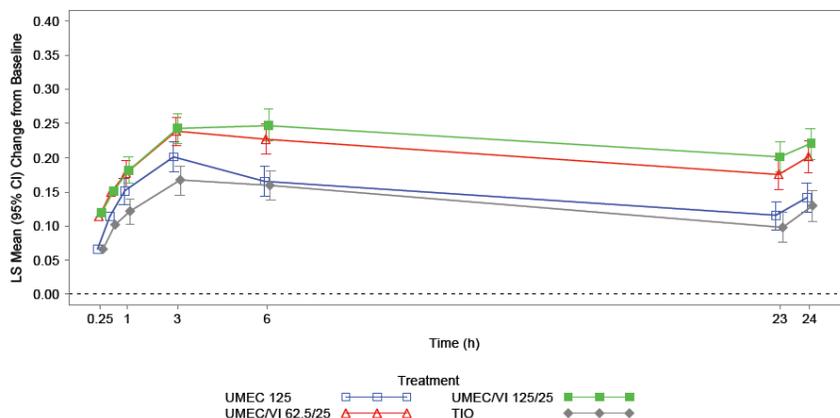
B. Day 168



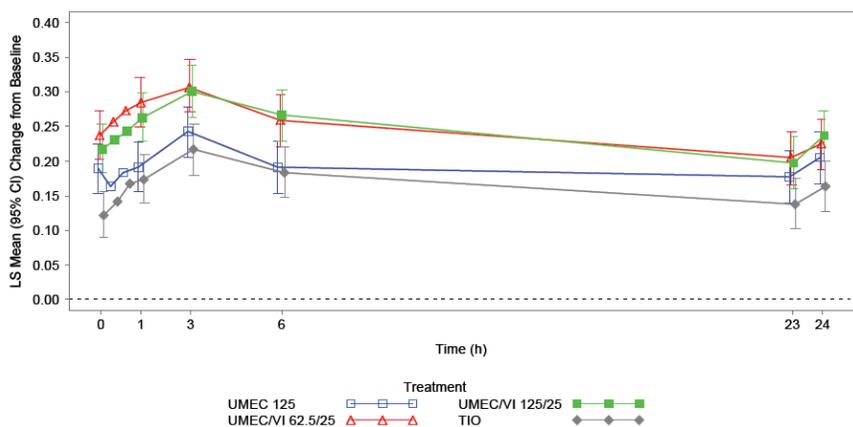
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Study Report Body), pg. 102 (Figure 10)
 Note: Figure is for the ITT population, excluding data from Investigator 040688 in Trial DB2113360

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)

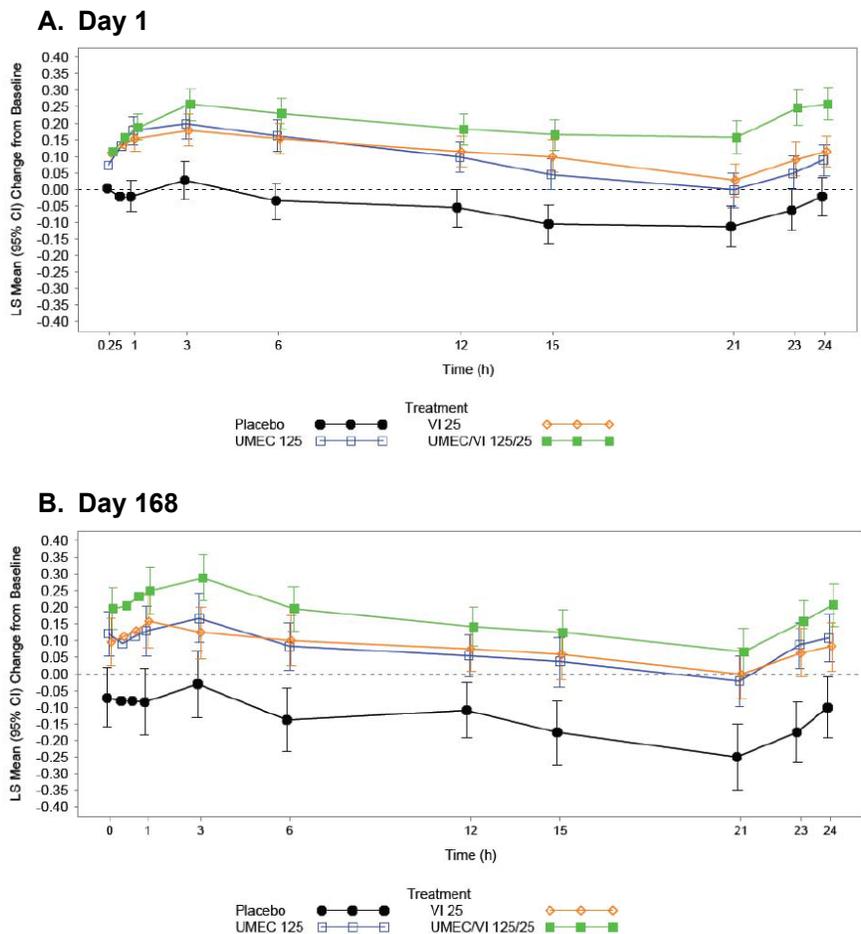
In each of the placebo-controlled trials there is separation between the curves for the combination products and placebo at all time points on both Day 1 and Day 168. There is also a separation between the combination products and monotherapies at most time points at both the start and end of treatment. 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)

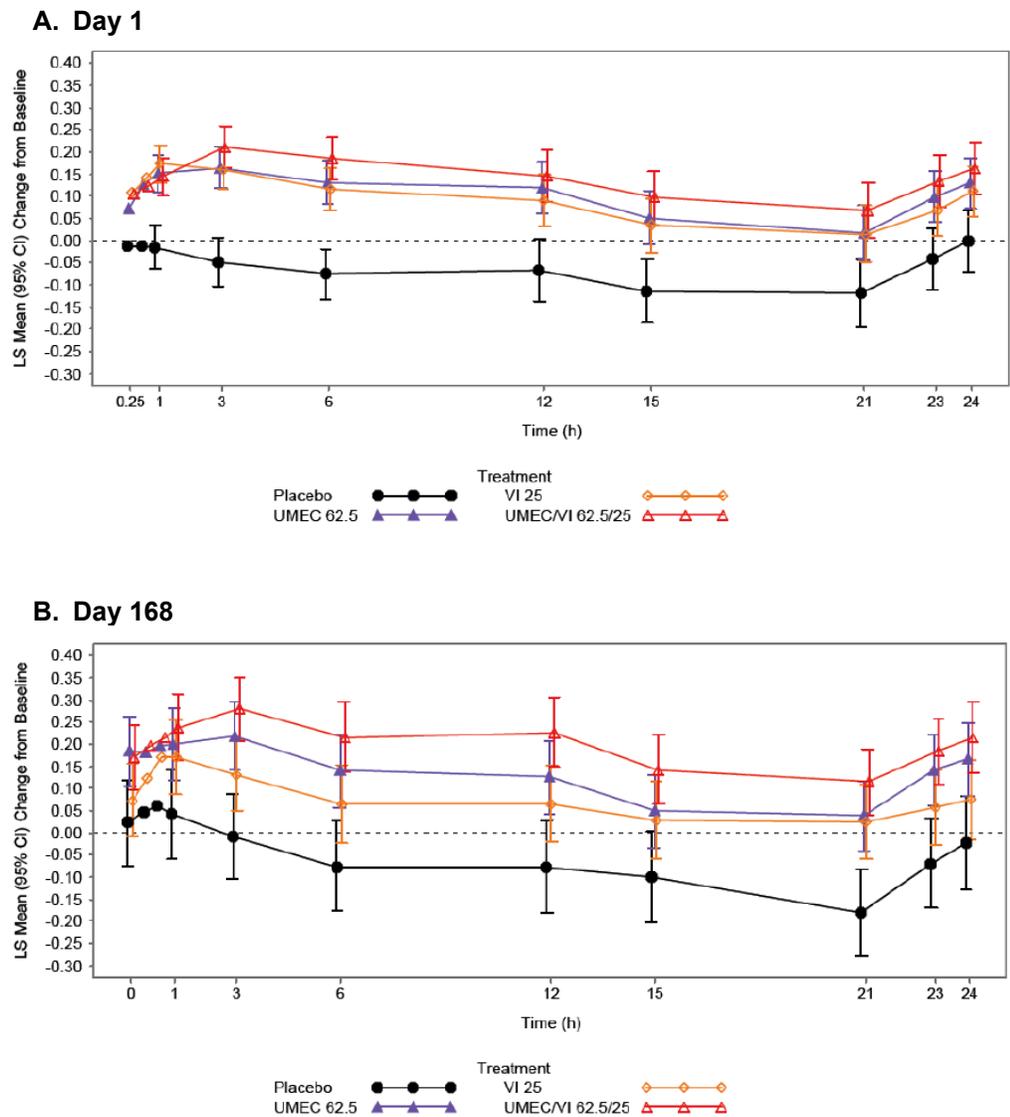
Serial FEV1 over 24 hours postdose was evaluated at selected sites for a subset of patients (approximately 200 from each trial, equivalent to 13% of the ITT population) in the two placebo-controlled trials. The results for this parameter at the start of treatment (Day 1) and end of treatment (Day 168)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



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



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 Mean (SE)	Change from BL LS Mean (SE)	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
				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 Mean (SE)	Change from BL LS Mean (SE)	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
				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

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 Anoro Ellipta (umeclidinium and vilanterol)

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		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 Mean (SE)	Change from BL LS Mean (SE)	Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
				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 Mean (SE)	Change from BL LS Mean (SE)	Treatment Difference from TIO			Treatment Difference from UMEC			Treatment Difference from VI		
				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. It should be noted that while the Applicant originally sought a labeling claim based on the results of the SOBDA analyses, they subsequently withdrew this claim from the proposed labeling.

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

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		Treatment Difference from Placebo			Treatment Difference from UMEC			Treatment Difference from VI		
		LS Mean (SE)	Change from BL (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

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.

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 (1.06)	-8.29 (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 n (%)	Non-responder n (%)	Comparison to TIO			Comparison to UMEC			Comparison to VI		
				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

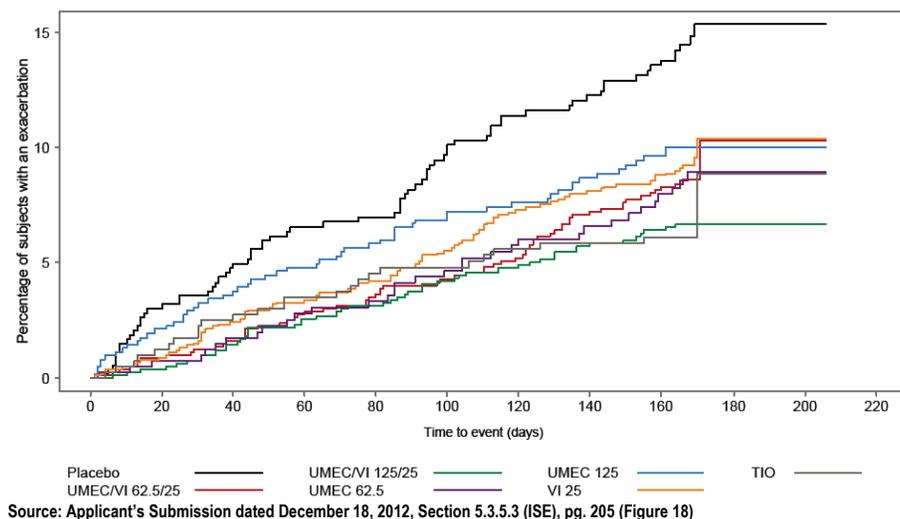
Arm	N	Pts Evt n (%)	Pts Cens n (%)	Prob Evt (%)	Comparison to P			Comparison to U*			Comparison to VI			Comparison to TIO		
					HZ	95% CI	p- value	HZ	95% CI	p- value	HZ	95% CI	p- value	HZ	95% CI	p- value
U/VI 125/ 25	826	50 (6)	776 (94)	6.7	0.4	0.2, 0.5	<0.001	0.7	0.5, 1.0	0.048	0.6	0.4, 0.9	0.007	1.1	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 Evt=patients with event; Pts Cens=patients censored; Prob Evt=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.

6.1.7 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 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
≤ 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									

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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		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	266	1.421	0.176	0.204	0.154,	<0.001	0.041	-	0.084	0.104	0.062,	<0.001	0.069	0.016,	0.011

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125/ 25		(0.016)	(0.016)		0.254			0.006, 0.088			0.145			0.123	
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		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	131	1.356	0.112	0.112	0.038,	0.003									

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25		(0.023)	(0.023)		0.186										
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		Treatment Difference from Placebo			Treatment Difference from U			Treatment Difference from VI			Treatment Difference from TIO		
		LS Mean (SE)	Δ 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 62.5/25	225	1.420 (0.018)	0.175 (0.018)	0.215	0.158, 0.272	<0.001	0.062	0.004, 0.119	0.036	0.069	0.021, 0.116	0.005	0.104	0.043, 0.164	<0.001
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	523	1.313	0.068	0.079	0.042	<0.001									

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25		(0.012)	(0.012)		0.117										
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		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		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
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		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

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 4.4 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.





(b) (4)

6.1.9 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 6.1.4 and 6.1.5.

6.1.10 Additional Efficacy Issues/Analyses

As described in Section 5.3, 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 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 6.1.4 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 LS Mean (SE)	Treatment Difference from Placebo			Treatment Difference from UMEC*			Treatment Difference from VI		
			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	-10.0	-55.5,	0.665						

		(19.7)		35.4							
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 ESWT²². 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.

7 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

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

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.

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 to 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 as the low number of overall events. The UMEC/VI safety profile is therefore adequate to support approval.

7.1 Methods

7.1.1 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 5.3; 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 conducted 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 $\geq 35\%$ and $\leq 80\%$ 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 scan²³ with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta₂-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

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.

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
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

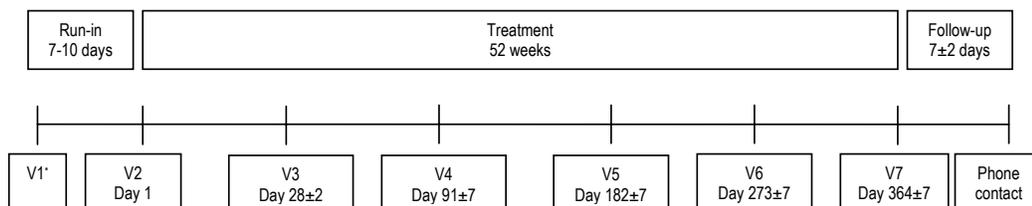
Withdrawal Criteria:

- 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 7.1.2 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	Visit 1A (Re-Screen)	Treatment Period							EW	Follow-up
	Visit 1 (Screening)		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	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 \pm 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	X	X				X		X	X		

Counseling										
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 medication 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.

7.1.2 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
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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

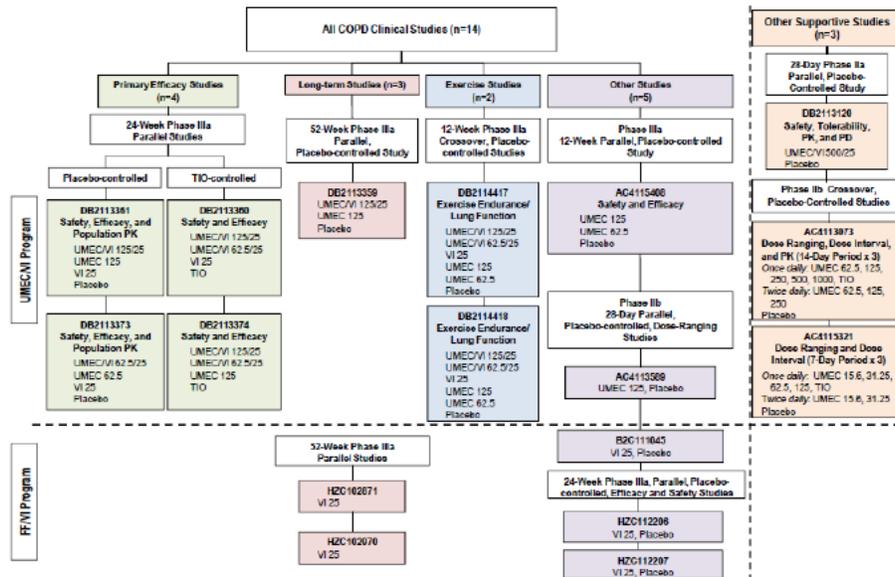
Source: Applicant's Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 128-129

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.

7.1.3 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, DB2113373, DB2113360, DB2113374

Long-Term Safety Trial	DB21133459
Other Trials	DB2114417, DB2114418, AC4115408, AC4113589, B2C111045, DB2113120, AC4113073, AC4115321
FF/VI Trials	HZC102871, HZC102970, HZC112206, HZC112207

7.2 Adequacy of Safety Assessments

7.2.1 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	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N=1637	N=1124	N=1330	N=576	N=1087	N=2501	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 6.1.2 (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 American/ 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/m²)			
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 FEV1 (L), n	108	225	225
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 comorbid conditions of the ITT population from the primary efficacy trials are discussed in Section 6.1.2 (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 7.3.5. 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 6.1.3 (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)
Withdraw 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 7.3.5.

7.2.2 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.

7.2.3 Special Animal and/or In Vitro Testing

The development program included an *in vitro* evaluation of hemolytic potential in rat, dog, and human peripheral blood (WD2008/01499; see nonclinical review by Dr. Jane Sohn, NDA 203-975, June 25, 2013).

7.2.4 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.

7.2.5 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. Details of these studies are discussed in the Clinical Pharmacology Summary Document; the clinical conclusions drawn from these studies are discussed in Section 7.5.5 of this review.

7.2.6 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 7.3.5.

7.3 Major Safety Results

7.3.1 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

Deleted: ¶

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.

7.3.2 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 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
	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)
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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	0	0	2 (<1)	2 (<1)	0	1 (<1)	0

disease							
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 7.3.5 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 7.3.5 of this review.

7.3.3 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	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
	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	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
	N=555	N=842	N=832	N=418	N=629	N=1034	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 7.3.5 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 7.3.5 of this review. Overall, most PTs in either the primary efficacy or long-term safety trials were reported for only 3 patients or fewer.

7.3.4 Significant Adverse Events

Adverse events leading to dropout are discussed in Section 7.3.3. 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 7.3.5.

7.3.5 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 <ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> • CNS Hemorrhages and 	Stroke Special Interest AE Subgroup <ul style="list-style-type: none"> • CNS Hemorrhages and

	Cerebrovascular Conditions SMQ (excluding fatalities)	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 Events	Number of 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 the 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
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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 40 (7)	N=842 70 (8)	N=832 55 (7)	N=418 41 (10)	N=629 52 (8)	N=1034 95 (9)	N=423 27 (6)
Long-term Safety	N=109 25 (23)	--	N=226 34 (15)	--	N=227 49 (22)	--	--
Exercise	N=321 8 (2)	N=282 7 (2)	N=272 10 (4)	N=89 2 (2)	N=91 1 (1)	N=140 6 (4)	--
All COPD	N=1637 129 (8)	N=1124 77 (7)	N=1330 99 (7)	N=576 45 (8)	N=1087 107 (10)	N=2501 243 (10)	N=423 27 (6)
Exposure-adjusted frequency	Number of Subjects with Events per 1000 Subject-Years						
Primary Efficacy	SY=208 192.7	SY=346 202.4	SY=336 163.6	SY=168 244.2	SY=249 208.9	SY=411 231.0	SY=173 156.0
Long-term Safety	SY=80 311.0	--	SY=177 192.6	--	SY=167 293.1	--	--
Exercise	SY=68 117.0	SY=62 112.7	SY=60 166.9	SY=20 100.8	SY=19 51.7	SY=30 199.5	--
All COPD	SY=535 241.2	SY=408 188.7	SY=573 172.9	SY=202 222.4	SY=454 235.5	SY=1271 191.2	SY=173 156.0

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 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	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
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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 7.4.4), 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 7.4.3. 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 AEs by subgroup, for the primary efficacy and long term safety trials, are presented in Table 78 and Table 79, respectively.

Table 78. Serious Cardiovascular AEs, 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 AEs 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 frequency	Number of Subjects with Events per 1000 Subject-Years						
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 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
	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.

7.4 Supportive Safety Results

7.4.1 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
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	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)
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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.

7.4.2 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

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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 7.3.5; 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 7.3.5 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 7.3.5 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)

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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.

7.4.3 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 7.3.5 of this review.

7.4.4 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 7.3.5).

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	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO

	N=555	N=842	N=832	N=418	N=629	N=1034	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 \geq 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 \geq 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 significant abnormality	25 (23)	54 (24)	58 (26)
ST depression	13 (12)	21 (9)	16 (7)
Frequent VPD \geq 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)
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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 n (%)	UMEC/VI 125/25 N=226 n (%)	UMEC 125 N=227 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 seconds	2 (3)	2 (4)	1 (2)	0	1 (2)	0
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	UMEC/VI 125/25	UMEC 125
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	N=109	N=226	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 (see IRT review, NDA 203-975, May 9, 2013). 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).

7.4.5 Special Safety Studies/Clinical Trials

See 7.4.4 for a description of DB2114635 and HZA102936 ("Thorough QT" studies).

7.4.6 Immunogenicity

As a combination of two small molecules, UMEC/VI is not anticipated to induce an immune response, and immunogenicity was not assessed.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

As noted in Section 7.2.2, the dose dependency for adverse events is discussed throughout this safety review.

7.5.2 Time Dependency for Adverse Events

No specific analysis of time dependency was conducted for adverse events.

7.5.3 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)
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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 7.4.1).

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 7.4.1).

7.5.4 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 was 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 was 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.

7.5.5 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.

7.6 Additional Safety Evaluations

7.6.1 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 (see nonclinical review by Dr. Jane Sohn, NDA 203-975, June 25, 2013).

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred in the UMEC/VI COPD clinical development program.

7.6.3 Pediatrics and Assessment of Effects on Growth

The Applicant requests a waiver for conducting pediatric studies, based on the rationale that COPD is a disease exclusive to the adult population. The Clinical Review finds the justification for the waiver to be acceptable.

7.6.4 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.

7.7 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.

8 Postmarket Experience

UMEC/VI is not available for marketing in any country.

9 Appendices

9.1 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.

9.2 Labeling Recommendations

A discussion of final labeling recommendations is deferred until after the Advisory Committee process is complete. Preliminary recommendations include the following:

- Presentation of UMEC dose-ranging data
 - Inclusion of both Day 1 and Day 7 data is recommended
 - (b) (4)
 - (b) (4)
 - (b) (4)
- Description of cardiac safety data
 - Currently proposed label includes a class Warning and Precautions statement regarding the cardiovascular effects of LABAs and LAMAs, and (b) (4)
 - Inclusion of additional information describing the increased incidence of cardiac ischemia/nonfatal myocardial infarction is recommended

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.

(b) (4)



9.3 Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee meeting will be held after the finalization of this review; therefore, the conclusions in this review are preliminary pending that discussion. The anticipated focus of the meeting, which is scheduled for September 10, 2013, will be the adequacy of the data to support the efficacy and safety of the proposed product. The cardiovascular safety of UMEC/VI will be a topic of interest.

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/s/

JENNIFER R PIPPINS
08/15/2013

SUSAN L LIMB
08/15/2013

MEDICAL OFFICER REVIEW			
Division Of Pulmonary and Allergy Drug Products (HFD-570)			
APPLICATION:	NDA 203-975	TRADE NAME:	Anoro Ellipta
APPLICANT/SPONSOR:	GlaxoSmithKline	USAN NAME:	umeclidinium/vilanterol
MEDICAL OFFICER:	Jennifer Rodriguez Pippins, MD, MPH		
TEAM LEADER:	Susan Limb, MD	CATEGORY:	LAMA/LABA
DATE:	February 1, 2013	ROUTE:	Oral inhalation
SUBMISSIONS REVIEWED IN THIS DOCUMENT			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
12/18/2012	12/18/2012	NDA 203-975 SD# 1 eCTD# 0	Original NDA
<u>REVIEW SUMMARY:</u>			

MEDICAL OFFICER REVIEW

Division Of Pulmonary and Allergy Drug Products (HFD-570)

GlaxoSmithKline (GSK) has submitted a 505(b)(1) New Drug Application (NDA) for umeclidinium/vilanterol (UMEC/VI), a combination product comprised of two new molecular entities. 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 emphysema.” Two doses are proposed for approval: UMEC/VI 62.5 mcg/25 mcg once daily, and 125 mcg/25 mcg once daily.

A related GSK product, with the proposed tradename Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder, is currently under review as NDA 204-275. The proposed indication is the treatment of airway obstruction and the reduction of exacerbations in patients with COPD. To date, NDAs have been not been submitted for the umeclidinium and vilanterol monotherapies.

Dose-ranging was conducted for each of the monocomponents separately. All four key UMEC dose-ranging trials were conducted in a COPD population, while two of the three key VI dose-ranging trials were conducted in an asthma population. The dose of vilanterol proposed for the UMEC/VI combination product, 25 mcg, is the same as that proposed for the FF/VI product currently under review (NDA 204-275). The NDA review for UMEC/VI will therefore rely on the evaluation of VI dose-ranging that is being conducted as part of the NDA 204-275 review. The adequacy of the dose-ranging for UMEC will be a review issue.

The phase 3 clinical program for UMEC/VI is comprised primarily of two 24-week placebo-controlled trials, two 24-week active control trials, two 12-week exercise endurance trials, and one 52-week long-term safety trial.

For each of the proposed doses (125 mcg/25 mcg and 62.5 mcg/25 mcg), a statistically significant result is demonstrated for the comparison to placebo for the primary efficacy endpoint of trough FEV1 on Day 169. The effect sizes are 238 ml and 167 ml for the higher and lower proposed doses, respectively. It is noted that there is only a single trial comparing each dosing level to placebo. The clinical program provides replicate evidence of a statistically significant treatment effect for each of the monocomponents compared to placebo. The clinical development program also provides replicate evidence for the contribution of the UMEC monocomponent to both the 125 mcg/25 mcg and the 62.5 mcg/25 mcg products. With regard to the other monocomponent, the clinical program does not provide replicate evidence for the contribution of VI to the 125 mcg/25 mcg combination; this will be a review issue. (b) (4)

The primary safety database for this NDA is comprised of 14 main COPD trials, which range in duration from 28 days to 52 weeks, along with three additional supportive trials, which range in duration from 7 days to 28 days. In addition, the safety database includes data from 8 trials evaluating VI (with or without FF) in asthma patients. Across the phase 3 placebo-controlled and active comparator trials, 281 and 326 patients were exposed for >24 weeks to UMEC/VI 125 mcg/25 mcg and 62.5 mcg/25 mcg, respectively, while 37 patients were exposed to 125 mcg/ 25 mcg for >364 days in the 52-week long-term safety trial. The overall safety database is adequate. On initial review, the overall pattern of AEs, SAEs, and deaths appears typical for LAMA and LABA products.

On its face, the clinical section is organized in a manner to allow substantive review to begin. From a clinical perspective, the NDA is fileable.

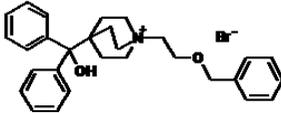
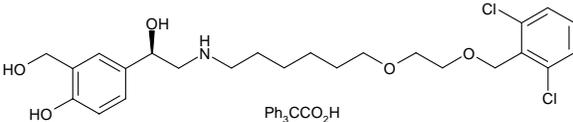
RECOMMENDED REGULATORY ACTION:

FILEABLE

NOT FILEABLE

1. GENERAL INFORMATION

1.1 Active Drug

Generic name:	umeclidinium/vilanterol
Chemical name:	umeclidinium: 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide vilanterol: triphenylacetic acid-4-((1 <i>R</i>)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl)-2-(hydroxymethyl)phenol (1:1)
Proposed Trade name:	Anoro Ellipta
Pharmacologic category:	LAMA (umeclidinium)/LABA (vilanterol)
Route of administration:	Oral inhalation
Proposed doses:	umeclidinium/vilanterol: 62.5 mcg / 25 mcg once daily 125 mcg/25 mcg once daily
Molecular Formula:	umeclidinium: $C_{29}H_{34}NO_2^+Br^-$ vilanterol: $C_{24}H_{33}Cl_2NO_5 \cdot C_{20}H_{16}O_2$
Molecular Weight:	umeclidinium: 508.5 vilanterol: 774.8
Molecular Structure:	umeclidinium:  vilanterol: 

1.2 Background

GlaxoSmithKline (GSK) has submitted a 505(b)(1) New Drug Application (NDA) for umeclidinium/vilanterol (UMEC/VI), a combination product comprised of two new molecular entities. 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 emphysema.” Two doses are proposed for approval: UMEC/VI 62.5 mcg/25 mcg once daily, and 125 mcg/25 mcg once daily. The submission is electronic.

1.3 Regulatory History

A summary of the regulatory history is provided in Table 1.

Table 1. Regulatory History

Product or Instrument	IND	Interaction/Date/Topic
VI	74,696	<ul style="list-style-type: none"> preIND January 31, 2007 Teleconference March 24, 2010, to discuss dose and dosing interval in COPD
UMEC	104,479	<ul style="list-style-type: none"> preIND May 26, 2009
UMEC/VI	106,616	<ul style="list-style-type: none"> EOP2 October 29, 2010, dose and dosing interval discussed preNDA January 18, 2012
FF/VI	77,955	<ul style="list-style-type: none"> EOP2 March 31, 2009 (asthma), June 17,2009 (COPD), June 8, 2010 (asthma)
SOBDA*		<ul style="list-style-type: none"> Meetings on August 29, 2006, June 16, 2008, May 10, 2010, July 27, 2010 Written feedback provided by Agency on June 30, 2010

*SOBDA=Shortness of Breath with Daily Activities Questionnaire

Reviewer’s Comment:

A related GSK product, with the proposed tradename Breo Ellipta (fluticasone furoate/vilanterol) Inhalation Powder, is currently under review as NDA 204-275. The proposed indication is the treatment of airway obstruction and reduction of exacerbations in patients with COPD. To date, NDAs have been not been submitted for the umeclidinium and vilanterol monotherapies.

2. CLINICAL DEVELOPMENT PROGRAM: Dose-Ranging

Dose-ranging was conducted for each of the monocomponents separately. There were four key UMEC dose-ranging trials and three key VI dose-ranging trials. All four key UMEC dose-ranging trials were conducted in a COPD population, while two of the three key VI dose-ranging trials were conducted in an asthma population. A summary of the principle dose-ranging trials is provided in Table 2.

Table 2. Clinical Development Program: Dose-Ranging

Trial	Objective	Design	Population	Treatment	Duration	Primary Endpoint
-------	-----------	--------	------------	-----------	----------	------------------

UMEC						
AC4113589	Dose-ranging	R, DB, PC, PG	COPD	UMEC 125, 250, 500 P	28 days	Trough FEV1
AC4113073	Dose-ranging Dosing interval PK	R, DB, PC, XO Incomplete block	COPD	Once-daily: UMEC 62.5, 125, 250, 500, 1000 Tio 18 P Twice-daily: UMEC 62.5, 125, 250 P	14 days per period	Trough FEV1
AC4115321	Dose-ranging Dosing interval	R, DB, PC, XO Incomplete block	COPD	Once-daily: UMEC 15.6, 31.25, 62.5, 125 Tio 18 P Twice-daily: UMEC 15.6, 31.25 P	7 days per period	Trough FEV1
AC4115408	Efficacy, safety	R, DB, PC, PG	COPD	UMEC 62.5, 125 P	12 weeks	Trough FEV1
VI						
B2C111045	Dose-ranging	R, DB, PC, PG	COPD	VI 3, 6.25, 12.5, 25, 50 P	28 days	Trough FEV1
HZA113310	Dose-ranging Dosing interval	R, DB, PC, XO	Asthma	Once-daily: VI 6.25, 12.5, 25 Twice-daily: VI 6.25 P	7 days per period	Trough FEV1
B2C109575	Dose-ranging	R, DB, PC, PG	Asthma	VI 3, 6.25, 12.5, 25, 50 P	28 days	Trough FEV1

Reviewer's Comment:

The dose of vilanterol proposed for the UMEC/VI combination product, 25 mcg, is the same as that proposed for the FF/VI product currently under review (NDA 204-275). Both combination products are proposed for use in COPD. The NDA review for UMEC/VI will therefore rely on the evaluation of VI dose-ranging that is being conducted as part of the NDA 204-275 review. The adequacy of the dose-ranging for UMEC will be a review issue.

3. CLINICAL DEVELOPMENT PROGRAM: Phase 3 Trials

The phase 3 clinical program for UMEC/VI is comprised primarily of two 24-week placebo-controlled trials, two 24-week active control trials, two 12-week exercise endurance trials, and one 52-week long-term safety trial. A summary of the Phase 3 program is provided in Table 3.

Table 3. Clinical Development Program: Phase 3 Trials

Trial	Objective	Design	Population	Treatment	Duration	Primary Endpoint
Placebo-controlled Trials						
DB2113361	Efficacy, safety Population PK	R, DB, PC	COPD	UMEC/VI 125/25 UMEC 125 VI 25 P	24 weeks	Trough FEV1
DB2113373	Efficacy, safety Population PK	R, DB, PC	COPD	UMEC/VI 62.5/25 UMEC 62.5 VI 25 P	24 weeks	Trough FEV1
Active Comparator Trials (tiotropium)						
DB2113360	Efficacy, safety	R, DB, DD, AC	COPD	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 Tio 18	24 weeks	Trough FEV1
DB2113374	Efficacy, safety	R, DB, DD, AC	COPD	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 Tio 18	24 weeks	Trough FEV1
Exercise Endurance Trials						
DB2114417	Exercise Endurance Lung function	R, DB, PC, XO Incomplete block	COPD	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 P	12 weeks per period	Co-primary: EET postdose Trough FEV1
DB2114418	Exercise Endurance Lung function	R, CB, PC, XO Incomplete block	COPD	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5 VI 25 P	12 weeks per period	Co-primary: EET postdose Trough FEV1
Long-term safety						
DB2113359	Long-term safety	R, DB, PC	COPD	UMEC/VI 125/25 UMEC 125 P	52 weeks	AEs Exacerbations Rescue meds Trough FEV FVC

4. OVERVIEW OF EFFICACY

This section provides a brief summary of key efficacy findings from the phase 3 program.

Results for the Primary Endpoint, comparison to placebo

Results for mean change in trough FEV1 at Day 169, for the active treatment arms vs. placebo, are provided in Table 4.

Table 4. Trough FEV1 (L) at Day 169, comparison to placebo

DB2113361				
	Placebo	UMEC/VI	UMEC	VI
	N=275	125/25 N=403	125 N=407	25 N=404
n*	269	401	404	402
n#	182	323	312	299
LS mean (SE)	1.245 (0.0153)	1.484 (0.0119)	1.405 (0.0119)	1.370 (0.0121)
LS mean change (SE)	-0.031 (0.0153)	0.207 (0.0119)	0.129 (0.0119)	0.093 (0.0121)
Comparison to placebo	--	0.238	0.160	0.124
95% CI		(0.200, 0.276)	(0.122, 0.198)	(0.086, 0.162)
p-value		<0.001	<0.001	<0.001
DB2113373				
	Placebo	UMEC/VI	UMEC	VI
	N=280	62.5/25 N=413	62.5 N=418	25 N=421
n*	278	411	416	419
n#	201	330	322	317
LS mean (SE)	1.239 (0.0158)	1.406 (0.0126)	1.354 (0.0126)	1.311 (0.0127)
LS mean change (SE)	0.004 (0.0158)	0.171 (0.0126)	0.119 (0.0126)	0.076 (0.0127)
Comparison to placebo	--	0.167	0.115	0.072
95% CI		(0.128, 0.207)	(0.076, 0.155)	(0.032, 0.112)
p-value		<0.001	<0.001	<0.001

*Number of subjects with analyzable data for 1 or more time points

#Number of subjects with analyzable data at the current time point

Reviewer's Comment:

For each of the proposed doses (125mcg/25 mcg and 62.5mcg/25 mcg), a statistically significant result is demonstrated for the comparison to placebo for the primary efficacy endpoint of trough FEV1 on Day 169. The effect sizes are 238 ml and 167 ml for the higher and lower proposed doses, respectively. It is noted that there is only a single trial comparing each dosing level to placebo. The clinical program provides replicate evidence of a statistically significant treatment effect for each of the monocomponents compared to placebo.

Results for the Primary Endpoint, contribution of each monocomponent

The clinical program included a comparison of the proposed combinations to their constituent monocomponents. The contribution of the UMEC monocomponent was evaluated by comparing UMEC/VI to VI (Table 5); the contribution of the VI monocomponent was evaluated by comparing UMEC/VI to UMEC (Table 6).

Table 5. Trough FEV1 (L), contribution of UMEC

	Time Point	Treatment Difference	95% CI	p-value
Contribution of UMEC 125: Comparison of UMEC 125/25 to VI 25				
DB2113361	Day 169	0.114	0.081,0.148	<0.001
DB2113360	Day 169	0.088	0.036,0.140	<0.001
DB2114417	Week 12	0.070	0.019,0.120	0.007
DB2114418	Week 12	0.150	0.098,0.201	<0.001
Contribution of UMEC 62.5: Comparison of UMEC 62.5/25 to VI 25				
DB2113373	Day 169	0.095	0.060,0.130	<0.001
DB2113360	Day 169	0.090	0.039,0.142	<0.001
DB2114417	Week 12	0.111	0.062,0.161	<0.001
DB2114418	Week 12	0.132	0.081,0.183	<0.001

Reviewer's Comment:

The clinical development program provides replicate evidence for the contribution of the UMEC monocomponent to both the 125 mcg/25 mcg and the 62.5 mcg/25 mcg products.

Table 6. Trough FEV1 (L), contribution of VI

	Time Point	Treatment Difference	95% CI	p-value
Contribution of VI 25: Comparison of UMEC 125/25 to UMEC 125				
DB2113361	Day 169	0.079	0.046,0.112	<0.001
DB2113374	Day 169	0.037	-0.012,0.087	0.142
DB2114417	Week 12	0.029	-0.028,0.086	0.320
DB2114418	Week 12	0.006	-0.055,0.067	0.849
Contribution of VI 25: Comparison of UMEC 62.5/25 to UMEC 62.5				
DB2113373	Day 169	0.052	0.017,0.087	0.004
DB2114417	Week 12	0.124	0.067,0.181	<0.001
DB2114418	Week 12	0.099	0.041,0.157	<0.001

Reviewer's Comment:

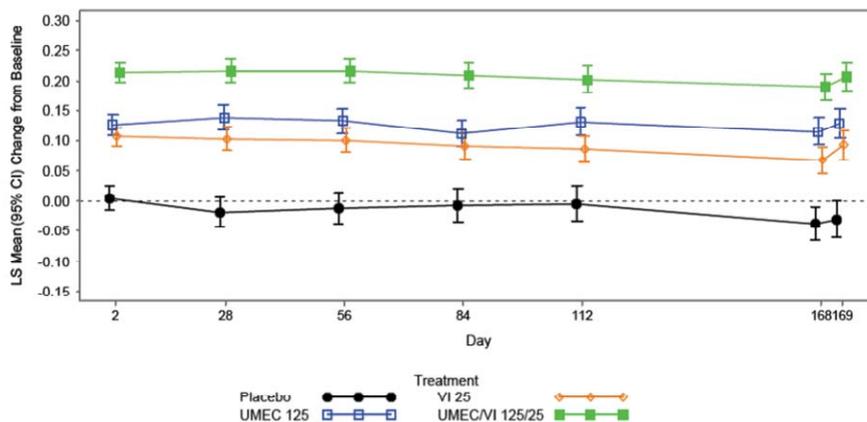
The clinical program does not provide replicate evidence for the contribution of the VI monocomponent to the 125 mcg/25 mcg combination. This will be a review issue.

Additional spirometric assessments: trough FEV1 over 24-week treatment period

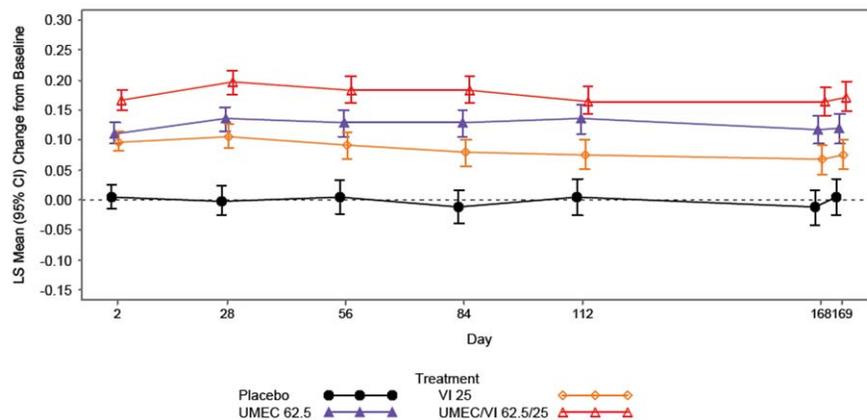
Mean change in trough FEV1, for the combination vs. placebo, over the duration of the 24 week trials is presented in Figure 1.

Figure 1. Change from baseline in trough FEV1 over the 24-week treatment period

A. Trial DB2113361



B. Trial DB2113373



Reviewer's Comment:

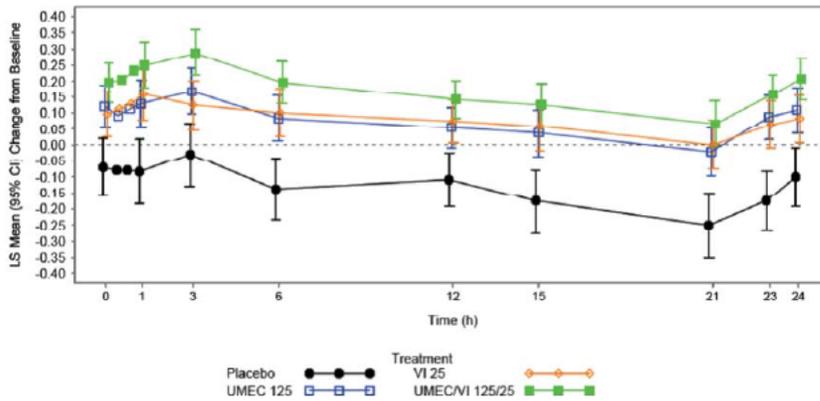
At first glance, the treatment effect for (b) (4) (comparison to placebo) appears to persist across the duration of the 24 week treatment period.

Additional spirometric assessments: serial FEV1 over 24 hours

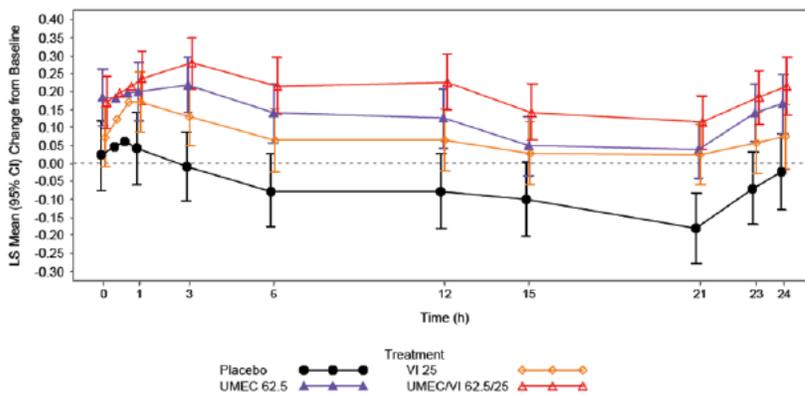
A subset of approximately 200 patients from each of the placebo-controlled trials underwent comprehensive 24-hour serial spirometry. The 24-hour serial FEV1 profile on day 168 is provided in Figure 2.

Figure 2. Change from baseline in FEV1 (L) over time (0 to 24 hours) on Day 168, subset of patients in placebo-controlled trials

A. Trial DB2113361



B. Trial DB2113373



Reviewer's Comment:

At first glance, the treatment effect for both proposed doses (comparison to placebo) appears to persist across the 24 hours dosing interval on Day 168.

Results for Additional Efficacy Analyses

The phase 3 program a number of additional efficacy analyses. For the purposes of this filing and planning review, a brief summary of the results from three such analyses, SOBDA, SGRQ, and the comparison to tiotropium, are presented. (b) (4)

SOBDA

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

Results for the analysis of change in mean SOBDA score at Week 24 in the placebo-controlled trials are provided in Table 7.

Table 7. Mean SOBDA at Week 24, comparison to placebo

DB2113361				
	Placebo	UMEC/VI	UMEC	VI
	N=275	125/25 N=403	125 N=407	25 N=404
n*	227	364	374	360
n#	118	234	215	212
LS mean (SE)	1.89 (0.038)	1.74 (0.029)	1.81 (0.029)	1.86 (0.029)
LS mean change (SE)	-0.07 (0.038)	-0.22 (0.029)	-0.15 (0.029)	-0.10 (0.029)
Comparison to placebo	--	-0.15	-0.08	-0.03
95% CI		(-0.24, -0.06)	(-0.17, 0.02)	(-0.13, 0.06)
p-value		0.002	0.106	0.515
DB2113373				
	Placebo	UMEC/VI	UMEC	VI
	N=280	62.5/25 N=413	62.5 N=418	25 N=421
n*	248	376	370	375
n#	125	230	209	202
LS mean (SE)	1.94 (0.037)	1.77 (0.029)	1.84 (0.029)	1.79 (0.030)
LS mean change (SE)	-0.06 (0.037)	-0.23 (0.029)	-0.16 (0.029)	-0.21 (0.030)
Comparison to placebo	--	-0.17	-0.10	-0.14
95% CI		(-0.26, -0.08)	(-0.19, 0.00)	(-0.24, -0.05)
p-value		<0.001	0.043	0.002

*Number of subjects with analyzable data for 1 or more time points

#Number of subjects with analyzable data at the current time point

Reviewer's Comment:

(b) (4)
 It notes treatment effects of -0.15 and -0.17, and states that the minimally clinically important difference for the SOBDA is -0.1 to -0.2.

As noted above, the SOBDA is a novel 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. ^(b)
⁽⁴⁾ The reliability of this instrument to support a claim will be a review issue.

SGRQ

The St. George's Respiratory Questionnaire (SGRQ) is a measure of health-related quality of life. There is regulatory precedent for the use of SGRQ to support a product claim in COPD.

Results for the analysis of change in mean SGRQ score at Week 24 in the placebo-controlled trials are provided in Table 8.

Table 7. Mean SGRQ at Week 24, comparison to placebo

DB2113361				
	Placebo	UMEC/VI	UMEC	VI
	N=275	125/25 N=403	125 N=407	25 N=404
n*	219	356	361	353
n#	165	297	294	274
LS mean (SE)	43.69 (0.875)	40.10 (0.665)	43.38 (0.664)	42.82 (0.681)
LS mean change (SE)	-3.83 (0.875)	-7.43 (0.665)	-4.14 (0.664)	-4.71 (0.681)
Comparison to placebo	--	-3.60	-0.31	-0.87
95% CI		(-5.76, -1.44)	(-2.46, 1.85)	(-3.05, 1.30)
p-value		0.001	0.778	0.432
DB2113373				
	Placebo	UMEC/VI	UMEC	VI
	N=280	62.5/25 N=413	62.5 N=418	25 N=421
n*	254	381	388	381
n#	192	317	312	304
LS mean (SE)	46.62 (0.950)	41.11 (0.749)	41.93 (0.753)	41.43 (0.760)
LS mean change (SE)	-2.56 (0.950)	-8.07 (0.749)	-7.25 (0.753)	-7.75 (0.760)
Comparison to placebo	--	-5.51	-4.69	-5.19
95% CI		(-7.88, -3.13)	(-7.07, -2.31)	(-7.58, -2.80)
p-value		<0.001	<0.001	<0.001

*Number of subjects with analyzable data for 1 or more time points

#Number of subjects with analyzable data at the current time point

Reviewer's Comment:

(b) (4)
They may be more appropriate for the medical literature as they pertain to the practice of medicine.

(b) (4)

Reviewer's Comment

The adequacy of the data to (b) (4) will be a review issue.

5. OVERVIEW OF SAFETY

The primary safety database for this NDA is comprised of 14 main COPD trials, which range in duration from 28 days to 52 weeks, along with three additional supportive trials, which range in duration from 7 days to 28 days. In addition, the safety database includes data from 8 trials evaluating VI (with or without FF) in asthma patients.

Pre-specified AEs of interest include the following:

- Cardiovascular:
 - Adjudicated cardiovascular deaths (MACE analysis)
 - QT, arrhythmias, sudden death, ischemia, heart failure, stroke, hypertension
- Anticholinergic: urinary retention, ocular effects, other anticholinergic effects
- Metabolic: changes in glucose and potassium
- Neurologic: tremor
- COPD-related: pneumonia
- Asthma composite: asthma-related hospitalizations, intubations, deaths

A summary of exposure from the phase 3 placebo-controlled and active comparator trials (24 week duration) and the long-term safety trial (52 week duration) is provided in Tables 9 and 10.

Table 9. Exposure in the Phase 3 placebo-controlled and active comparator 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
Range							
≥ 1 day	555	842	832	418	629	1034	423
> 12 weeks	452	749	729	364	538	897	374
> 24 weeks	169	326	281	154	154	343	116

Table 10. Exposure in the long-term safety trial

	Placebo N=109	UMEC/VI 62.5/25 N=0	UMEC/VI 125/25 N=226	UMEC 62.5 N=0	UMEC 125 N=227	VI 25 N=0	TIO N=0
Range							
1-91 days	18	--	19	--	30	--	--
92-182 days	13		31		31		
183-273 days	7		25		20		
274-364 days	52		114		111		
> 364 days	19		37		35		

Reviewer's Comment

While the number of patients exposed to the combination product for 1 year is only 37, the overall safety database for both the combination and monotherapies is adequate.

An overview of adverse events reported in the 24-week placebo-controlled and active comparator trial, and in the 52-week long-term safety trial, is provided in Tables 11 and 12.

Table 11. Overall Summary of Adverse Events, 24-week placebo-controlled and active comparator trials

	Number (%) of subjects						
	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
Any on-treatment AE	264 (48)	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)
Any AE leading to	26 (5)	50 (6)	47 (6)	31 (7)	41 (7)	59 (6)	20 (5)

discontinuation of drug or study withdrawal*							
Any on-treatment SAE	26 (5)	50 (6)	43 (5)	27 (6)	37 (6)	59 (6)	22 (5)
Any post-treatment SAE	2 (<1)	5 (<1)	6 (<1)	5 (1)	2 (<1)	7 (<1)	0
Any fatal AE*	2 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)

*Both on-treatment and post-treatment

Table 11. Overall Summary of Adverse Events, 52-week long-term safety trial

	Number (%) of subjects						
	Placebo N=109	UMEC/VI 62.5/25 N=0	UMEC/VI 125/25 N=226	UMEC 62.5 N=0	UMEC 125 N=227	VI 25 N=0	TIO N=0
Any on-treatment AE	57 (52)	--	120 (53)	--	132 (58)	--	--
Any post-treatment AE	2 (2)		5 (2)		5 (2)		
Any AE leading to discontinuation of drug or study withdrawal*	13 (12)	--	17 (8)	--	21 (9)	--	--
Any on-treatment SAE	7 (6)	--	14 (6)	--	17 (7)	--	--
Any post-treatment SAE	1 (<1)	--	0	--	3 (1)	--	--
Any on-treatment fatal AE	0	--	0	--	2 (<1)	--	--
Any post-treatment fatal AE	1 (<1)		0		2 (<1)		

*Both on-treatment and post-treatment

Reviewer’s Comment:

In the 24-week placebo-controlled and active comparator trials the frequency of any on-treatment AE is slightly higher for both combination products (53%) compared to placebo (48%), but the frequency of AEs leading to drug discontinuation or study withdrawal, SAEs, and fatal AEs is comparable between the placebo and combination arms. In the 52-week long-term safety trial the frequency of any AE, SAE, and fatal AE is comparable between the UMEC/VI 125 mcg/25 mcg and placebo arms, while the frequency of AEs leading to drug discontinuation or study withdrawal is higher for the placebo group. On initial review, the overall pattern of AEs, SAEs, and deaths appears typical for LAMA and LABA products.

6. ITEMS REQUIRED FOR FILING

See attached Clinical Filing Checklist (Appendix A).

7. BRIEF REVIEW OF PROPOSED LABELING

Preliminary review of the proposed label raises the following issues:

- Section 14 Clinical Studies, (b) (4)

(b) (4)

Reviewer's Comment:

(b) (4)

- Section 14 Clinical Studies, (b) (4)

(b) (4)

Reviewer's Comment:

The results for change in SGRQ at 24 weeks are statistically significant for (b) (4) the 62.5 mcg/25 mcg dose has a treatment effect equal to or greater than the generally recognized MCID for this measure (-4.00). Replicate evidence for the 62.5 mcg/25 mcg dose is not provided.

- Section 14 Clinical Studies, active comparator (b) (4) claim

The proposed label includes a section 14.2 summarizing data from the two active comparator trials.

Reviewer's Comment:

(b) (4)

8. DSI REVIEW/AUDIT

Given that this is an NME, a DSI review is requested. A center effect analysis was conducted by the primary statistical reviewer for the two placebo-controlled trials. This analysis took into account the magnitude of the treatment effect for the primary endpoint, the number of patients, and the percent dropout per site. While no one site appears likely to drive efficacy results, based on the analysis the preliminary clinical recommendation is for audit of the following two sites:

- 1) Site 086085, Trial DB2113361 (ex-US)

N=19, 26% dropout, large effect size

- 2) Site 087869, Trial DB2113373 (US)

N=35, 37% dropout, large effect size

9. PEDIATRIC DEVELOPMENT PLAN

GSK requests a waiver of pediatric trials, from birth to 17 years of age, providing the rationale that COPD is an adult-specific disease.

Reviewer's Comment:

The Applicant's request appears to be reasonable.

10. RECOMMENDATION

The application is fileable.

11. COMMENTS FOR THE SPONSOR

- 1. We note that your rationale [redacted] (b) (4) 62.5 mcg/25 mcg dose [redacted] (b) (4) The adequacy of the data to support approval [redacted] (b) (4) will be a review issue.
- 2. We note your proposal [redacted] (b) (4) As noted during our May 10, 2010, meeting, [redacted] (b) (4) will be a review issue and the ability of [redacted] (b) (4) We note that the [redacted]

evaluation of (b) (4) presents many challenges, and the successful development of a patient reported outcome instrument to measure (b) (4) is without precedent.

3. (b) (4)
While the results are of clinical interest, we question whether these results are necessary to support a regulatory action and believe these results may be more appropriately described in the literature as they pertain to the practice of medicine.
4. The adequacy of the data to support the contribution of the VI (b) (4)
(b) (4) combination product will be a review issue.

Appendix A. Clinical Filing Checklist

NDA/BLA Number: 203-975

Applicant: GSK

Stamp Date: December 18, 2012

Drug Name:
umeclidinium/vilanterol

NDA/BLA Type: 505(b)(1)

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			

	Content Parameter	Yes	No	NA	Comment
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			medDRA 15.0
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			The application notes several deviations from GCP

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___Yes___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

1. [Redacted] (b) (4)
2. [Redacted] (b) (4)
3. [Redacted] (b) (4)
While the results are of clinical interest, we question whether these results are necessary to support a regulatory action and believe these results may be more appropriately described in the literature as they pertain to the practice of medicine.
4. The adequacy of the data to support the contribution of the VI [Redacted] (b) (4)
[Redacted] combination product will be a review issue.

Reviewing Medical Officer Date

Clinical Team Leader Date

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

/s/

JENNIFER R PIPPINS
02/01/2013

SUSAN L LIMB
02/01/2013