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*APPLICATION NUMBER:*

**205382Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type NDA  
Application Number(s) 205-382  
Priority or Standard Standard

Submit Date(s) April 30, 2013  
Received Date(s) April 30, 2013  
PDUFA Goal Date April 30, 2014  
Division / Office DPARP/OND

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Review Completion Date December 19, 2013

Established Name umeclidinium  
(Proposed) Trade Name Incruse Ellipta  
Therapeutic Class LAMA  
Applicant GlaxoSmithKline

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

Template Version: [March 6, 2009](#)

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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  
Jennifer Rodriguez Pippins, MD, MPH  
NDA 205-382  
TBD Ellipta (umeclidinium)

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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**

The recommended regulatory action from a clinical perspective for umeclidinium (UMEC) 62.5 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.

### **1.2 Risk Benefit Assessment**

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

Evidence of efficacy comes predominantly from two placebo-controlled efficacy and safety trials evaluating UMEC 62.5 mcg: one 12-week trial (AC4115408), and one 24-week trial (DB2113373). The 12-week trial evaluated two doses of umeclidinium, 62.5 mcg and 125 mcg, while the 24-week trial evaluated only UMEC 62.5. An additional 24-week placebo-controlled trial (DB2113361) evaluated UMEC 125 mcg. Results from Trial DB2113361 are reviewed in order to provide additional context; however, efficacy results for the higher UMEC dose cannot be extrapolated to the lower UMEC dose. Only the 62.5 mcg dose is being proposed by the Applicant. The 24-week trials, which were replicate in design, were designed primarily to provide factorial support for a related combination product, UMEC/VI. These three trials included patients with moderate to very severe COPD (GOLD stages II-IV), and the primary efficacy endpoint was trough FEV1 at the end of treatment (Day 85 for Trial AC4115408 and Day 169 for the 24-week trials).

Overall, the clinical development program provides replicate, statistically significant results for the primary endpoint for the comparison between both doses of umeclidinium and placebo. Results for the comparison between UMEC 62.5 mcg and placebo in the two efficacy trials are statistically significant, with an effect size ranging from 0.115 L in Trial DB2113373 to 0.127 L in Trial AC4115408. Similarly, results for the comparison between UMEC 125 mcg and placebo in two efficacy trials are statistically significant, with an effect size ranging from 0.152 L in the Trial AC4115408 to 0.160 L in Trial DB2113361. The point estimates observed for each nominal dose are consistent across trials, in spite of the difference in treatment duration. A small increase in the

magnitude of the treatment effect is noted for the higher UMEC dose (0.152 L for UMEC 125 mcg versus 0.127 L for UMEC 62.5 mcg) in Trial AC4115408, which included a head-to-head comparison of the two doses. Focusing on the results for UMEC 62.5 mcg, the dose proposed for approval, the magnitude of the treatment effect compared to placebo (0.115 L – 0.127 L) represents an outcome that is likely to be clinically meaningful. Moreover, the results of Trials DB2113361 and DB2113373 provide evidence of persistence of efficacy for up to 6 months.

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

It should also be noted that the clinical development program for the related combination product UMEC/VI provided replicate, statistically significant evidence of the contribution of both doses of UMEC to their respective fixed combinations.

The main safety database for the proposed product consists of 8 clinical trials in patients with COPD (the “All Clinical Trials” grouping), and includes 2,706 patients across all treatment arms. Across the four efficacy and one long-term safety trials, 1,412 patients were treated with either UMEC 62.5 mcg or 125 mcg. Across the “All Clinical Trials” grouping of trials, 524 patients were treated with either UMEC 62.5 mcg or 125 mcg for at least 24 weeks, and 133 treated with UMEC 125 mcg for at least 48 weeks. In addition, as part of the UMEC/VI combination product clinical development program, 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 were treated with UMEC/VI 125 mcg/25 mcg 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. Historically there have been concerns about the cardiovascular safety and stroke risk of inhaled anticholinergics; more recent controlled clinical data have been reassuring. 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 are demonstrated. 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. In the cardiovascular AESI analysis, imbalances favoring placebo are observed primarily in the efficacy trials; these include imbalances in serious events overall, as well as in the cardiac ischemia and cardiac arrhythmia subgroups of serious cardiovascular AESIs.

The review of MACE and cardiovascular AESI analyses for the UMEC/VI 125 mcg/25 mcg and 62.5 mcg/25 mcg products revealed similar imbalances in cardiovascular

events, particularly those pertaining to cardiac ischemia. However, in both the review of the combination product and in this review, several features of the observed data decrease concern regarding the numerical imbalances observed. The imbalances identified for events pertaining to cardiac ischemia in the cardiovascular AESI analysis are observed in the 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 efficacy trials, but also in the long-term safety trial which evaluated the higher UMEC and UMEC/VI doses 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 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 62.5 mcg in COPD provides replicate evidence of a bronchodilatory effect that is both statistically significant and likely to be clinically meaningful. Small numerical imbalances favoring placebo in serious cardiovascular adverse events including those pertaining to cardiac ischemia are noted; however, concern is mitigated by both the reassuring safety profile observed in the long-term safety trial, as well by the low number of overall events. The UMEC safety profile is therefore acceptable, and the overall benefit/risk profile for UMEC 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.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

The proposed product is a long-acting muscarinic antagonist (LAMA), or anticholinergic, inhalation dry powder administered by a dry powder inhaler. Inside the device there is a foil blister strip; each blister on the strip contains a white powder mix of the active pharmaceutical ingredient umeclidinium (62.5 mcg), as well as the excipients magnesium stearate and lactose monohydrate. A single umeclidinium (UMEC) dose is proposed: 62.5 mcg administered as one inhalation once daily. The proposed trade name is Incruse Ellipta.

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

*Incruse 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
			Budesonide/Formoterol fumarate
		Fluticasone	Breo Ellipta

		furoate/Vilanterol	
		Umeclidinium/Vilanterol	Anoro 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

While at the time of this review umeclidinium as a monotherapy is not marketed in the United States, a related combination product, Anoro Ellipta (umeclidinium and vilanterol inhalation powder) was approved on December 18, 2013. Anoro Ellipta is a fixed dose combination inhalation powder containing the same dose of umeclidinium, 62.5 mcg, proposed for the Incruse Ellipta product, along with vilanterol 25 mcg.

### 2.4 Important Safety Issues With Consideration to Related Drugs

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

The cardiovascular safety and stroke risk of inhaled anticholinergics have been discussed extensively both in the medical literature<sup>1-2</sup> and in open public forums.<sup>3</sup> In January 2010 FDA provided a Follow-Up<sup>4</sup> 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.<sup>5</sup> It should be noted that while UPLIFT provided convincing

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<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting.

<sup>4</sup> 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.

<sup>5</sup> Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.

evidence of the safety of Spiriva HandiHaler, concerns remained regarding the risk of mortality with an alternative formulation of tiotropium, Spiriva Respimat, which is not approved in the United States. To address these concerns the manufacturer of Spiriva Respimat undertook a large, prospective safety trial (TIOSPIR).

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

Since the approval of Tudorza Pressair, the large, prospective safety trial comparing Spiriva Respimat to Spiriva HandiHaler has been completed. The TIOSPIR trial evaluated over 17,000 patients and had a mean follow-up of 2.3 years. According to the published article<sup>6</sup>, Respimat was non-inferior to HandiHaler with respect to death, and the reported causes of death and the incidence of MACE were similar in patients who received Respimat versus HandiHaler. Overall, the results from TIOSPIR appear reassuring; however, these data have yet to be reviewed by the Agency.

## 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 and the related combination product UMEC/VI is provided in Table 2.

**Table 2. Regulatory History**

Product or Instrument	IND or NDA	Interaction/Date/Topic
UMEC	104,479 (IND)	<ul style="list-style-type: none"><li>• preIND May 26, 2009</li></ul>
UMEC/VI	106,616 (IND)	<ul style="list-style-type: none"><li>• EOP2 October 29, 2010: dose and dosing interval discussed</li><li>• preNDA January 18, 2012</li></ul>
	203-975 (NDA)	<ul style="list-style-type: none"><li>• Submitted December 18, 2013</li><li>• PDUFA date December 18, 2013</li></ul>

<sup>6</sup> Wise RA, Anzueto A, Cotton D, et al. *N Engl J Med*. 2013 Oct 17; 369(16):1491-501.

## 2.6 Other Relevant Background Information

The Applicant originally proposed two doses in the application (NDA 203-975) for the related combination product combining umeclidinium and vilanterol: UMEC/VI 125 mcg/25 and UMEC/VI 62.5 mcg/25 mcg. (b) (4)

. The UMEC application only included a single dose, 62.5 mcg, for consideration; (b) (4)

Dose selection is discussed further in Sections 4.4 and 6.1.8.

## 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) audit was not requested for this application, given that two relevant sites were already audited as part of the review process for the related combination product, UMEC/VI (NDA 203-975). Sites 087869 (Trial DB2113373) and 086085 (Trial DB2113361) were chosen on the basis of a center effect analysis conducted by the primary statistical reviewer for NDA 203-975. While no one site appeared likely to drive efficacy results, these two sites were chosen 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; 28 subjects from this site were involved in the UMEC development program. Impacted trials include one of key dose-ranging and dosing interval trials (AC4115321), and the long-term safety trial (DB2113359). The Applicant reports that sensitivity analyses of efficacy data were conducted for trial AC4115321 and results were generally consistent with those for the overall population. No sensitivity analyses were conducted for the long-term safety trial. These deviations are not likely to affect the overall conclusions of this review.

### **3.3 Financial Disclosures**

The Applicant provided financial interest information for clinical investigators involved in the UMEC clinical program as per regulation. Information was available for all investigators upon commencement of their participation, and the Applicant states that no investigator had a financial interest in GSK at that time point. Information was available for all except for one principal investigator at the end of their participation; in the one case where information was not obtained, this was due to the individual being deceased. The Applicant also notes that significant payments of other sorts were reported by three investigators. The Applicant concludes that the data generated by these three 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.

The drug product is a light grey and light green plastic inhaler with a dose counter. The inhaler contains a foil blister strip. Each blister on the 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).

#### **4.2 Clinical Microbiology**

Approval of this application is recommended from the product quality microbiology team (see NDA 205-382 review by Dr. Stephen E. Langille, June 6, 2013).

#### **4.3 Preclinical Pharmacology/Toxicology**

The r recommendation of the preclinical review is for Approval (see NDA 205-382 review by Dr. Matthew Whittaker, December 12, 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 25 and 16 times the maximum recommended human dose (MRHC) 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 22 and 18 times the MRHD on an AUC basis for male and female mice, respectively. The safety margin in rats was 18 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.

UMEC 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.

#### 4.4.2 Pharmacodynamics

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). These trials identified the 62.5 mcg and 125 mcg once-daily doses 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 interval	R, DB, PC, CO, incomplete block	163	Once-daily: UMEC 15.6 UMEC 31.25 UMEC 62.5 UMEC 125 Tio 18 (OL) P  Twice-daily: UMEC 15.6 UMEC 31.25 P	3 periods per subject, 7 days per period	Trough FEV1
2011						

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 26-27 (Table 1); Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4113589); Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073); Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321)

Note: N=number randomized

Key: CO=cross-over, DB=double-blind, PC=placebo-controlled, PG=parallel group, R=randomized, UMEC=umeclidinium, Tio=triotropium, P=placebo

### **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**

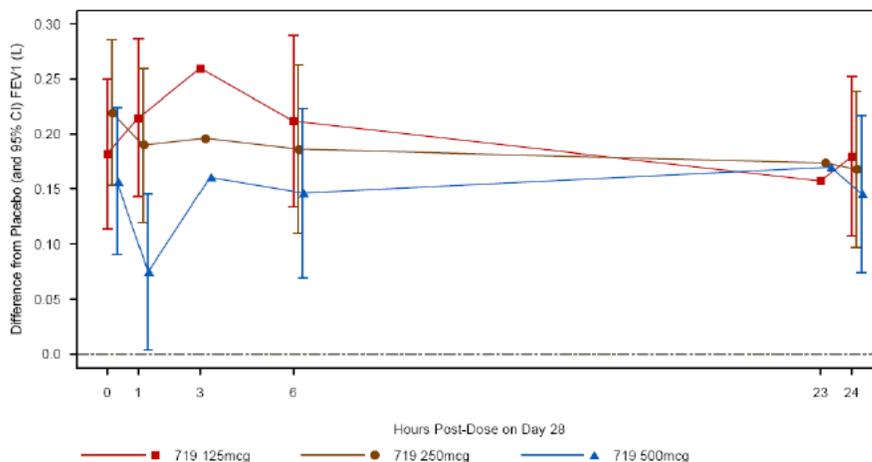
Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
				Difference	95% CI	p-value
		Mean (SD)	LS Mean (SE)			
UMEC 500	71	1.320 (0.4242)	0.163 (0.025)	0.150	0.080, 0.220	<0.001
UMEC 250	72	1.480 (0.5772)	0.181 (0.025)	0.168	0.099, 0.238	<0.001
UMEC 125	71	1.466 (0.4737)	0.171 (0.025)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

Source: Applicant's NDA 203-975 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 FEV<sub>1</sub>, 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 FEV<sub>1</sub> (L), 0-24 hours on Day 28, Trial AC4113589, ITT Population**



Source: Applicant's NDA 203-975 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 FEV<sub>1</sub>, are provided in Table 5.

**Table 5. Change in Trough FEV<sub>1</sub> (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
<b>Once-daily</b>						
UMEC	32	1.581	0.138	0.186	0.113,	<0.001

1000		(0.036)	(0.036)		0.259	
UMEC 500	38	1.535 (0.032)	0.092 (0.032)	0.140	0.074, 0.205	<0.001
UMEC 250	36	1.490 (0.033)	0.048 (0.033)	0.095	0.027, 0.162	0.006
UMEC 125	34	1.542 (0.034)	0.099 (0.034)	0.147	0.077, 0.216	<0.001
UMEC 62.5	35	1.524 (0.033)	0.081 (0.033)	0.128	0.060, 0.196	<0.001
Tio 18	35	1.500 (0.033)	0.058 (0.033)	0.105	0.037, 0.173	0.003
<b>Twice-daily</b>						
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	15 8	1.395 (0.017)	-0.047 (0.017)			

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073), pg. 64 (Table 12)

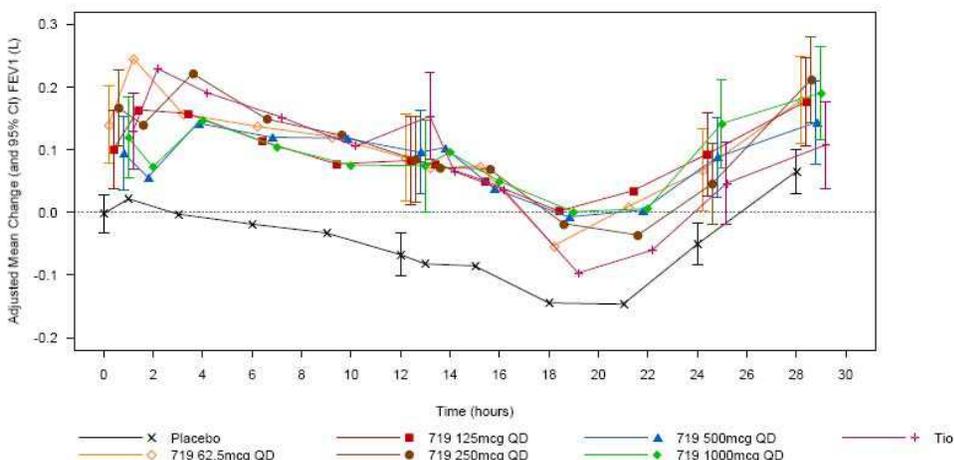
Note: modified ITT (mITT) population=all patients randomized who received at least one dose of study medication

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

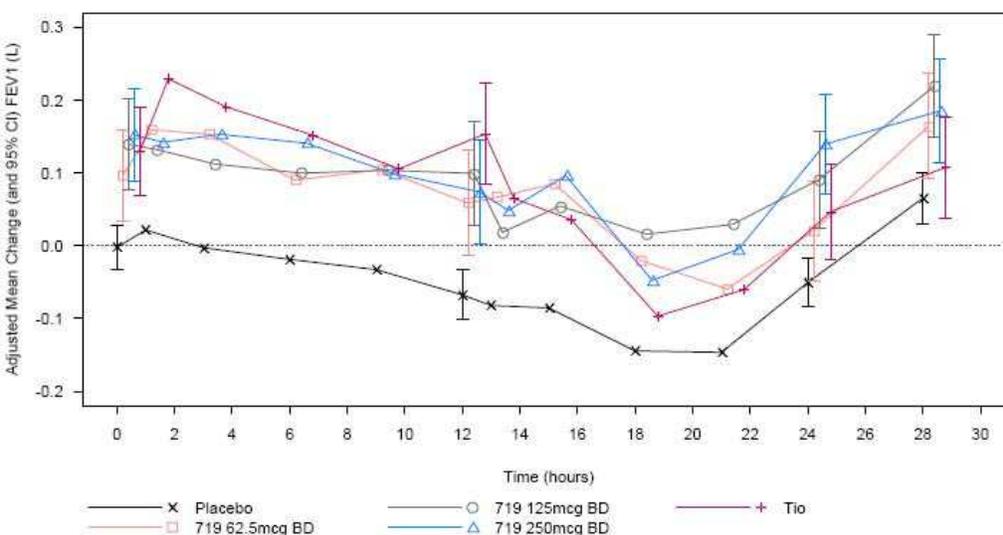
Figure 1 which presents *mean difference from placebo in change from baseline FEV1 over 24 hours*).

**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 NDA 203-975 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 NDA 203-975 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 FEV<sub>1</sub>, are provided in Table 6.

**Table 6. Change in Trough FEV<sub>1</sub> (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
<b>Once-daily</b>						
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
<b>Twice-daily</b>						
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)			

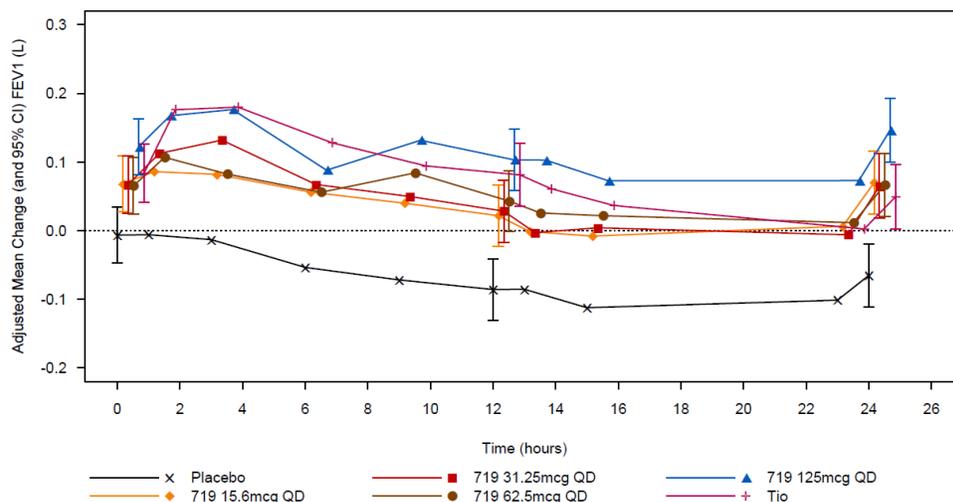
Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 78 (Table 24)  
 Note: modified ITT (mITT) population=all patients randomized who received at least one dose of study medication

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.

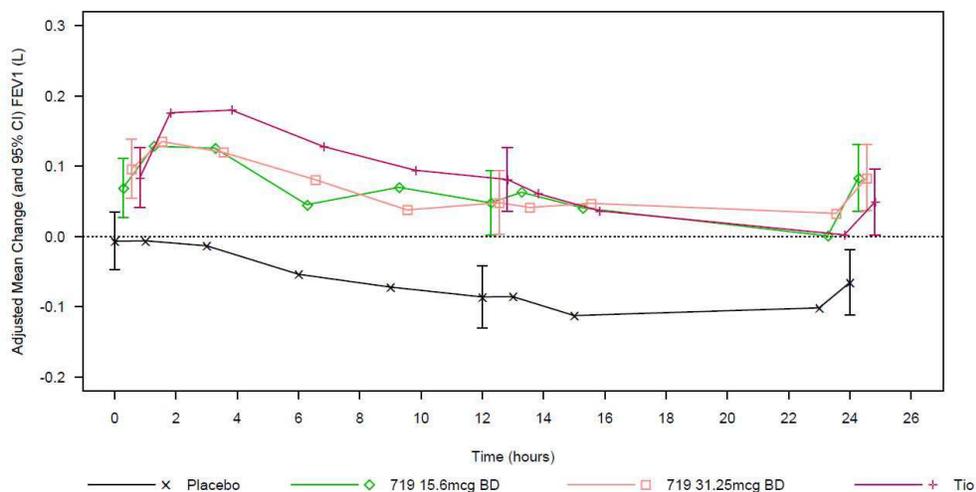
Results for 24-hour serial spirometry are shown below. In Figure 4, the once-daily regimens are compared to both placebo and tiotropium; all active arms demonstrate an effect over placebo, and the 125 mcg and 62.5 mcg curves straddle the curve for tiotropium. In Figure 5 the twice-daily regimens are 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**



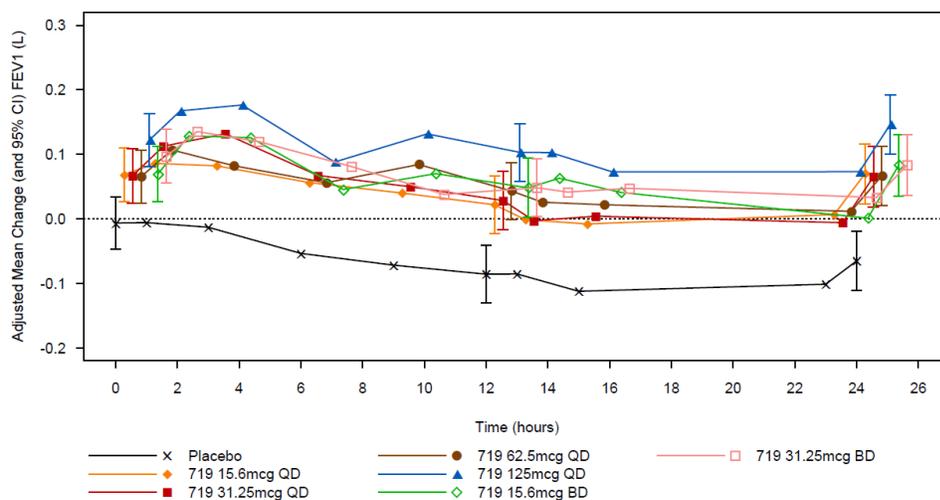
Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 93 (Figure 16)

**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 NDA 203-975 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 NDA 203-975 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). It should be noted that there are some differences between the figures presented above and those included in the approved label for Anoro Ellipta (e.g. the

figures present mean change from baseline, and both Day 1 and Day 7 are included), but the conclusions are the same.

**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 7.

**Table 7. 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)	–

Source:  
 Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4115321), pg. 78 (Table 24)  
 Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4113073), pg. 64 (Table 12)  
 Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (AC4113589), pg. 51 (Table 10)  
 \*modified ITT (mITT) population= all patients randomized who received at least one dose of study medication  
 #ITT population

Taking the results of these three 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.

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 reader is also referred to the clinical pharmacology review for the related combination product UMEC/VI (see NDA 203-975 by Dr. Jianmeng Chen and Dr. Ping Ji, August 16, 2013), as well as the approved labeling for the combination product.

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

The systemic exposure is primarily due to absorption of the inhaled portion.  $T_{max}$  for UMEC is approximately 5 to 15 minutes after oral inhalation administration. The half-life of UMEC after oral inhalation is approximately 11 hours. In COPD patients compared to healthy subjects, UMEC  $C_{max}$  was 50% lower and  $AUC_{0-24}$  was 29% higher.

The effects of renal function and hepatic function on the pharmacokinetics of UMEC were evaluated in several trials. 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, or in patients using concomitant CYP2D6 inhibitors or with genetic polymorphisms of CYP2D6 metabolism.

A trial assessing cardiac conduction (“Thorough QT” study) was 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 dose selection is provided in Section 4.4.2 of this review. The core phase 3 development program conducted in support of UMEC includes three placebo-controlled efficacy and safety trials, one with a 12-week treatment period (AC41154080) and two with 24-week treatment periods (DB2113361 and DB2113373), and a 52-week long-term safety trial (DB2113359). Additional supportive data is provided by a 24-week active comparator (tiotropium) trial (DB2113374) and two 12-week exercise trials (DB21214417 and DB2114418). A summary of these trials is provided in

Table 8.

**Table 8. Phase 3 Clinical Development Program**

Trial	Design	N	Treatments (once-daily)	Duration	Primary Endpoint	Number of Sites  <i>n (%) of patients from US</i>
<i>Year completed</i>						
<b>Placebo-controlled efficacy and safety trials</b>						
AC4115408	R, DB, PC, PG	69 69 68	UMEC 62.5 UMEC 125 P	12 weeks	Trough FEV1	27  48 (23)
2012						
DB2113361	R, DB, PC, PG	403 409 404 277	UMEC/VI 125/25 UMEC 125 VI 25 P	24 weeks	Trough FEV1	153  316 (21)
2012						
DB2113373	R, DB, PC, PG	414 421 421 280	UMEC/VI 62.5/25 UMEC 62.5 VI 25 P	24 weeks	Trough FEV1	163  428 (28)
2012						
<b>Active-comparator efficacy and safety trial</b>						
DB2113374	R, DB, DD, AC, PG	217 218 222 215	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 Tio 18	24 weeks	Trough FEV1	95  225 (26)
2012						
<b>Long-term Safety</b>						
DB2113359	R, DB, PC, PG	227 227 109	UMEC/VI 125/25 UMEC 125 P	52 weeks	Safety Assessments	53  156 (28)
2012						
<b>Exercise Endurance Trials</b>						
DB2114417	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)
2012						
DB2114418	R, DB, PC, CO Incomplete block	128 130 41 41	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 UMEC 62.5	12 weeks per period	Co-primary: EET post dose, Trough FEV1	42

2012		64 151	VI 25 P			139 (45)
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Source: Applicant's NDA 203-975 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 NDA 203-975 submission dated December 18, 2012, Section 5.3.5.1 (AC4115408), pg. 145 (Table 5.06); Applicant's NDA 203-975 submission dated December 18, 2012, Section 5.3.5.1 (DB2113361), pg. 376 (Table 5.06); Applicant's NDA 203-975 submission dated December 18, 2012, Section 5.3.5.1 (DB2113373), pg. 323 (Table 5.06); Applicant's NDA 203-975 submission dated December 18, 2012, Section 5.3.5.1 (DB2113374), pg. 274 (Table 5.06); Applicant's NDA 203-975 submission dated December 18, 2012, Section 5.3.5.1 (DB2113359), pg. 195 (Table 5.01), pg. 202 (Table 5.06); Applicant's NDA 203-975 submission dated December 18, 2012, Section 5.3.5.1 (DB2114417), pg. 246 (Table 5.08); Applicant's NDA 203-975 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, UMEC=umeclidinium, Tio=triotropium, P=placebo

## 5.2 Review Strategy

The focus of this review is on the clinical development program conducted in support of UMEC 62.5 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 discusses the three placebo-controlled efficacy and safety trials, which include one 12-week trial (AC4115408) and two 24-week trials (DB2113361 and DB2113373). Of the two 24-week trials, the focus is on Trial DB2113373, which evaluated the proposed UMEC 62.5 mcg dose. Trial DB2113361 evaluated the higher UMEC 125 mcg dose, and its results are reviewed in order to provide additional context; however, efficacy results for the higher UMEC 125 mcg dose cannot be extrapolated to the proposed 62.5 mcg dose. Additional support is provided by 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 design of Trial DB2113374, a 24-week active-controlled trial, is also described in Section 5.3 given its similarities to the other two 24-week trials; however, this trial is not discussed with respect to efficacy given the lack of a placebo comparator. Moreover, Trial DB2113374 evaluated only the higher UMEC monotherapy dose.

The review of safety focuses on safety data from two sources. The first source is safety data for the population pooled from the three placebo-controlled efficacy and safety trials, along with trial DB2113374 (the active-controlled 24-week trial). Together these four trials are referred to as the "efficacy trials." The second source is the 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 three placebo-controlled efficacy and safety trials, i.e., the one 12-week trial (AC4115408) and the two 24-week trials (DB2113361 and DB2113373), the one active-comparator trial (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.

#### **12-week Placebo-controlled Trial**

The administrative information for trial AC4115408 is presented below, followed by a summary of the protocol. There were no protocol amendments submitted for Trial AC4115408.

#### **Administrative Information**

AC4115408

- Study Title: “A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of GSK573719 Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease.”
- Study Dates: July 16, 2011 – February 13, 2012
- Study Sites: A total of 27 centers in the United States, Germany, and Japan
- Study Report Date: November 2012

#### **Objectives**

##### Primary:

- To evaluate the efficacy and safety of UMEC when administered once-daily via a novel DPI over 12 weeks in patients with COPD

##### Secondary:

- To evaluate the effects of UMEC on quality of life
- To evaluate the pharmacokinetics (PK) of UMEC in patients with COPD

#### **Design**

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

#### **Treatments**

Patients were randomized 1:1:1 to receive one of the following treatments:

- UMEC/VI 125 mcg once daily
- UMEC 62.5 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  $\geq 10$  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  $\geq 2$  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):  $\alpha$ -1 antitrypsin deficiency, active tuberculosis, active bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or computed tomography (CT) scan<sup>7</sup> with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta<sub>2</sub>-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

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<sup>7</sup> 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).

- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 9

**Table 9. 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
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 <sub>2</sub> -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 <sub>2</sub> -agonists, short-acting	12 hours
Inhaled short-acting beta <sub>2</sub> -agonists@	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting beta <sub>2</sub> -agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Protocol or Amendment), pg. 21 (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, or UMEC/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)
- No use of prohibited medications during run-in period

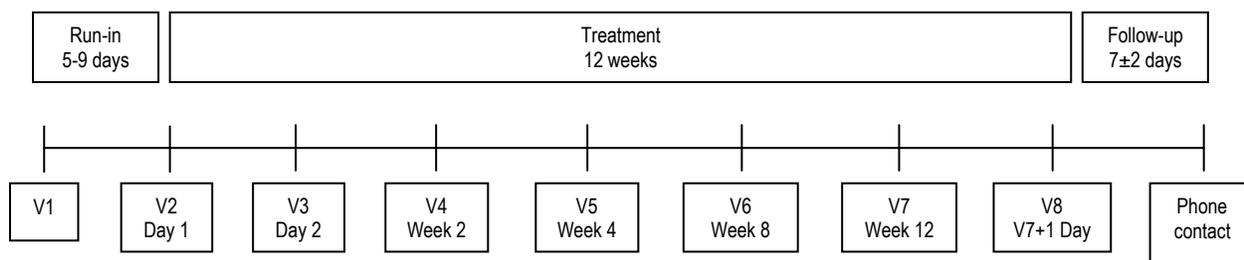
Withdrawal Criteria:

- 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 5 to 9-day run-in period, a 12-week treatment period, and a follow-up period (approximately 7 days), with a total of 8 clinic visits (and one phone contact) over the entire trial duration of approximately 14 weeks. A trial schematic is presented in Figure 7.

**Figure 7. Schematic, Trial AC4115408**



Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Protocol or Amendment), pg. 16 (Figure 1)

Spirometry:

As the Applicant is seeking an indication for the maintenance bronchodilator treatment of airflow obstruction, particular focus on the trial's 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 8. Six-hour serial spirometry was performed for all patients at Visits 2, 5, and 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. 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 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.

The full schedule of trial events is provided in Table 10.

**Table 10. Schedule of Trial Events, Trial AC4115408**

	Run-in	Treatment Period							EW	Follow-up
	Visit 1 (Screening) Day -9 to -5	Visit 2 (Randomization) Day 1	Visit 3 Day 2	Visit 4 Day 14 (±2)	Visit 5 Day 28 (±2)	Visit 6 Day 56 (-4 to +2)	Visit 7 Day 84 (-4 to +2)	Visit 8 Day 85 (V7+1)		Phone Contact 7±2 days after Visit 8 or EW
Informed Consent	X									
Demographics/ Medical and COPD history	X									
Physical Examination	X							X	X	
Smoking Status	X					X		X	X	
Smoking Cessation Counseling	X								X	
Chest X-ray <sup>1</sup>	X									
Verify Inclusion/Exclusion Criteria	X									
Verify Randomization Criteria		X								
Screening spirometry <sup>2</sup>	X									
mMRC	X									
Issue paper diary										
Review and/or		X	X	X	X	X	X	X	X	

collect paper diary										
Serial Spirometry <sup>3</sup>										X
Trough spirometry <sup>4</sup>			X	X	X	X	X	X		
BDI		X		X		X		X		
TDI		X				X		X		
SGRQ		X	X	X	X	X	X	X	X	X
AEs		X								
VS <sup>5</sup>				X		X		X		
12-lead ECG <sup>6</sup>	X	X	X	X	X	X	X	X		
COPD exacerbation assessment		X		X		X		X		
Clinical laboratory tests <sup>7</sup>		X	X	X	X	X	X	X		
Urine pregnancy tests	X	X				X		X	X	
PGx Sampling	X	X	X	X	X	X	X	X	X	
PK Sampling <sup>8</sup>	X	X				X		X		
Concurrent medications assessment	X	X	X	X	X	X	X	X	X	
Dispense/collect rescue medication	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 <sup>9</sup>				X	X	X	X	X	X	

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Protocol or Amendment), pg. 32-34 (Table 4)

<sup>1</sup> Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1

<sup>2</sup> Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing

<sup>3</sup> Performed as follows: 1, 3, and 6 hours; At Visit 2, pre-dose measurements will be obtained at -30 min and -5 min pre-dose. At Visits 5 and 7, when both serial and trough spirometry are to be conducted, the pre-dose serial measurements will consist of the trough measurements obtained at 23 and 24 hours after the previous day's morning dose

<sup>4</sup> Obtained at 23 and 24 hours after the previous day's morning dose

<sup>5</sup> On Visits 2, 5, and 7 performed pre-dose and 10 and 45 minutes post-dose; on Visits 3, 4, 6, and 8 performed at 23 hours after the previous day's dose

<sup>6</sup> Pre-dose and 10 and 45 minutes post-dose

<sup>7</sup> Hematology and chemistry

<sup>8</sup> Performed pre-dose, and 5 minutes and 15 minutes post-dose

<sup>9</sup> Assessed by reviewing device dose counter

## Endpoints

### Primary Endpoint:

- Trough FEV1<sup>8</sup> on Treatment Day 85

### Secondary Endpoint:

- Weighted mean FEV1 over 0 to 6 hours post-dose at Day 1, Weeks 4 and 12
- Serial FEV1 at 1, 3, 6, 23, and 24 hours post-dose at Day 1 and Week 12

### Other Endpoints:

- Trough FEV1 at Day 2, Weeks 2, 4, 8 and 12
- Serial FEV1 1, 3, and 6 hours post-dose at Week 4

<sup>8</sup> Trough FEV1 on Day 85 is defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 84.

- Trough FVC at Day 2, Weeks 2, 4, 8 and 12, and Day 85
- Weighted mean FVC over 0-6 hours post-dose at Day 1, Week 4 and 12
- Serial FVC at 1, 3, 6, 23 and 24 hours post-dose at Day 1 and Week 12
- Serial FVC at 1, 3, and 6 hours post-dose at Week 4
- Rescue albuterol/salbutamol use (percent of rescue-free days and puffs/day)
- Mean TDI foal score at Weeks 4, 8, and 12
- Proportion of responders to TDI
- Time to onset (defined as an increase of 100 mL above baseline in FEV1) during 0 to 6 hours post-dose of Day 1
- Proportion of subjects achieving an increase in FEV1 of  $\geq 12\%$  and  $\geq 200$  mL above baseline at any time during 0-6 hours post-dose on Day 1
- Proportion of patients with an increase of  $\geq 100$  mL above baseline in trough FEV1

Health-Related Quality of Life/Health Outcomes:

- St. George's Respiratory Questionnaire (SGRQ)

Pharmacokinetics:

- Plasma concentrations and derived PK parameters

**Statistical Considerations**

Sample Size:

A sample size of 56 evaluable patients in each treatment arm was estimated to have 90% power to detect an 130 mL difference between from placebo in trough FEV1, assuming a standard deviation of 210 mL and a two-sided 5% significance level.

The Applicant anticipated a 15% withdrawal rate; as a result, it was estimated that 66 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 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 85, was prespecified to be a mixed model repeated measures (MMRM) analysis, including trough FEV1 recorded at each of Days 2, 14, 28, 56, 84, and 85, and performed for the ITT Population.

Multiplicity:

In order to account for multiplicity, the protocol specified a step-down closed testing procedure for the primary endpoint, using the following hierarchy: UMEC 125 mcg vs. placebo, followed by UMEC 62.5 mcg vs. placebo.

Interim Analysis:

No interim analysis was planned.

**Protocol Amendments**

No protocol amendments were submitted for Trial AC4115408.

**24-week Placebo-controlled Trials**

The administrative information and protocol for the two 24-week 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 Powder 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  $\geq 10$  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  $\geq 2$  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):  $\alpha$ -1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or computed tomography (CT) scan<sup>9</sup> with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta<sub>2</sub>-agonist, lactose/milk protein or magnesium stearate
- History of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicated use of an inhaled anticholinergic
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- Lung volume reduction surgery within 12 months prior to Visit 1
- A significant abnormal ECG finding on the 12-lead ECG obtained at Visit 1
- A significant abnormal finding on the 24-hour Holter monitoring conducted at Visit 1 (applicable to a subset of patients)
- Significantly abnormal screening laboratory test results at Visit 1
- Unable to go without albuterol/salbutamol for the 4 hour period prior to spirometry testing at each trial visit
- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 11

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<sup>9</sup> 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).

**Table 11. 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 <sub>2</sub> -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 <sub>2</sub> -agonists, short-acting	12 hours
Inhaled short-acting beta <sub>2</sub> -agonists@	4 hours
Inhaled short-acting anticholinergics	4 hours
Inhaled short-acting anticholinergic/short-acting beta <sub>2</sub> -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 NDA 203-975 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

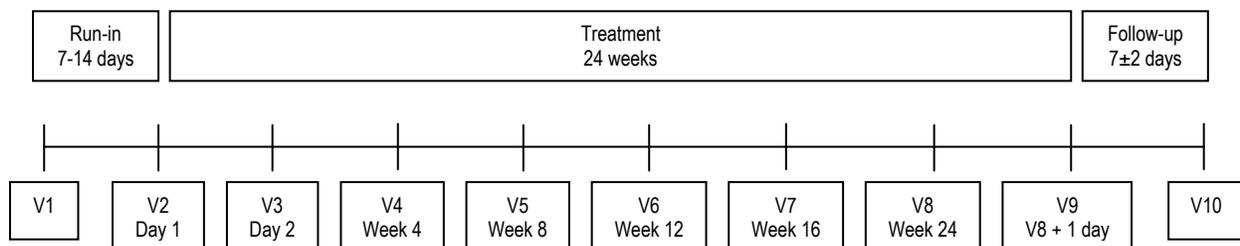
Withdrawal Criteria:

- 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 8.

**Figure 8. Schematic, Placebo-controlled Trials**



Source: Applicant's NDA 203-975 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 12.

**Table 12. Schedule of Trial Events, 24-week 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	
Smoking Cessation Counseling	X								X	X	
Chest X-ray <sup>1</sup>	X										
Verify Inclusion/Exclusion Criteria	X										
Verify Randomization		X									

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Criteria											
Screening spirometry <sup>2</sup>	X										
mMRC	X										
Issue eDiary	X										
Collect eDiary									X	X	
Review eDiary		X	X	X	X	X	X	X	X	X	
Issue paper diary	X	X		X	X	X	X	X			
Review and/or collect paper diary		X	X	X	X	X	X	X	X	X	
Post-treatment spirometry											X
Trough spirometry <sup>3</sup>			X	X	X	X	X	X	X		
6-hour serial spirometry <sup>4</sup>		X		X		X		X			
24-hour serial spirometry (subset) <sup>5</sup>		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 <sup>6</sup>	X	X				X		X		X	
Vital Signs <sup>7</sup>	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 <sup>8</sup>	X					X		X		X	
Plasma PK <sup>9</sup>		X			X			X			
Plasma PK 24 hours (subset) <sup>10</sup>		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 <sup>11</sup>				X	X	X	X	X		X	

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Protocol or Amendment), pg. 235-237(Table 6)

<sup>1</sup> Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1

<sup>2</sup> Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing

<sup>3</sup> Obtained at 23 and 24 hours after the previous day's morning dose

<sup>4</sup> Performed pre-dose and post-dose at 15 and 30 minutes and at 1, 3, and 6 hours

<sup>5</sup> Performed pre-dose and post dose at 15 and 30 minutes, and at 1, 3, 6, 12, 15, 21, 23, and 24 hours

<sup>6</sup> On Visits 2, 6, and 8 performed pre-dose and 10 and 45 minutes post-dose

<sup>7</sup> 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

<sup>8</sup> Hematology and chemistry

<sup>9</sup> Performed pre-dose and at 1 to 15 minutes post-dose

<sup>10</sup> 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

<sup>11</sup> Assessed by reviewing device dose counter

## **Endpoints**

### Primary Endpoint:

- Pre-dose trough FEV1<sup>10</sup> 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  $\geq 200$  mL above baseline at any time during 0-6 hours post-dose on Treatment Day 1
- Proportion of patients achieving an increase of  $\geq 100$  mL above baseline in trough FEV1
- Serial FEV1 over 0 to 6 hours post-dose (at each time point)
- Serial and trough FVC
- Weighted mean and serial FEV1 over 0 to 24 hours post-dose obtained in a subset of patients
- Rescue albuterol/salbutamol use (percentage of rescue-free days and puffs/day)
- Mean TDI focal score at Week 24<sup>11</sup>
- Mean TDI focal score at other time points
- Proportion of responders to TDI
- Mean SOBDA score
- Proportion of responders to SOBDA
- Time to first COPD exacerbation

### Health-Related Quality of Life/Health Outcomes:

- St. George's Respiratory Questionnaire (SGRQ)

### Population PK:

- Plasma concentrations and derived PK parameters for UMEC and VI

## **Statistical Considerations**

### Sample Size:

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

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<sup>10</sup> 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.

<sup>11</sup> 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."

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 submitted<sup>12</sup> and are summarized below. The changes provided by these amendments are reflected in the protocol description above.

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<sup>12</sup> 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.

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 Trial**

The administrative information and protocol for the active-controlled trial is presented below. This trial compared both doses of UMEC/VI to tiotropium; in addition, the trial included UMEC 125 mcg.

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**

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  $\geq 10$  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  $\geq 2$  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):  $\alpha$ -1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or CT scan<sup>13</sup> with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta<sub>2</sub>-agonist, lactose/milk protein or magnesium stearate

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<sup>13</sup> If no chest X-ray or CT scan was available from the 6 months prior to Visit 1, then a chest X-ray had to be obtained at Visit 1 (except for Germany, where such patients would be ineligible).

- History of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the Investigator, contraindicated use of an inhaled anticholinergic
- Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
- Lung volume reduction surgery within 12 months prior to Visit 1
- A significant abnormal ECG finding on the 12-lead ECG obtained at Visit 1
- Significantly abnormal screening laboratory test results at Visit 1
- Unable to go without albuterol/salbutamol for the 4 hour period prior to spirometry testing at each trial visit
- Use of the prohibited medications within certain washout intervals prior to Visit 1, as summarized in Table 11 (same guidelines as those for the placebo-controlled trials)
- Use of oxygen therapy for greater than 12 hours a day
- Daily, prescribed use of short-acting bronchodilators via nebulizer
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1
- A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1
- Previous use of UMEC, VI, UMEC/VI or fluticasone furoate/VI

Key Randomization Criteria:

- No evidence of a significantly abnormal 12-lead ECG pre-dose at Visit 2
- No COPD exacerbation or lower respiratory tract infection during run-in or at Visit 2
- For patients on ICS, regular use of a stable dose during the run-in period (dose  $\leq$  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

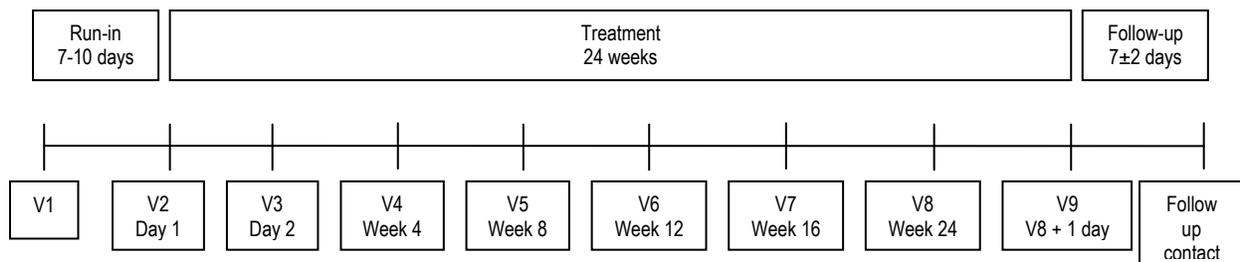
Withdrawal Criteria:

- 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 phone<sup>14</sup> over the entire trial duration of approximately 26 weeks. A trial schematic is presented in Figure 9.

**Figure 9. Schematic, Active-comparator Trials**



Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1.4 (DB2113360, Protocol Amendment 1), pg. 17 (Figure 1)

Spirometry:

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

Both pre- and post-bronchodilator spirometry was conducted at screening for determination of eligibility and calculation of reversibility. Baseline spirometry was conducted at Visit 2 prior to randomization. Pre-dose trough spirometry was conducted at every on-treatment clinic visit after randomization. In addition, six-hour post-dose

<sup>14</sup> Except for patients in Germany, who had a follow-up clinic visit.

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 13.

**Table 13. Schedule of Trial Events, Active-comparator Trial**

	Run-in		Treatment Period							EW	Follow-up Contact
	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 Visit 8 +1 day		
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 <sup>1</sup>	X										
Physical Examination	X							X		X	
Screening spirometry <sup>2</sup>	X										
mMRC	X										
Trough spirometry <sup>3</sup>			X	X	X		X		X		
Serial spirometry <sup>4</sup>		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 <sup>5</sup>	X	X	X	X	X	X	X	X	X	X	
12-lead ECG <sup>6</sup>	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 <sup>7</sup>	X					X		X		X	

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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 <sup>8</sup>				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 NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113360, Protocol Amendment 1), pg. 37-39 (Table 5)

<sup>1</sup> Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1

<sup>2</sup> Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing

<sup>3</sup> Obtained at 23 and 24 hours after the previous day's morning dose

<sup>4</sup> Performed pre-dose and post-dose at 15 and 30 minutes and at 1, 3, and 6 hours

<sup>5</sup> 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

<sup>6</sup> On Visits 2, 6, and 8 performed pre-dose and 10 and 45 minutes post-dose

<sup>7</sup> Hematology and chemistry

<sup>8</sup> Assessed by reviewing device dose counter for novel DPI, and by reviewing remaining blister doses for tiotropium

## Endpoints

### Primary Endpoint:

- Pre-dose trough FEV1<sup>15</sup> on Treatment Day 169

### Secondary Endpoint:

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

### Other Endpoints:

- Mean SOBDA score
- Mean TDI focal score

<sup>15</sup> 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.

- 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  $\geq 200$  mL above baseline at any time during 0-6 hours post-dose on Treatment Day 1
- Proportion of patients achieving an increase of  $\geq 100$  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 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  $\geq 10$  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  $\geq 2$  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):  $\alpha$ -1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease

- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or CT scan<sup>16</sup> with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta<sub>2</sub>-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 11 (same guidelines as those for the placebo-controlled trials)
- Use of oxygen therapy for greater than 12 hours a day
- Daily, prescribed use of short-acting bronchodilators via nebulizer
- Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1
- A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1

Key Randomization Criteria:

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

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<sup>16</sup> 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).

Withdrawal Criteria:

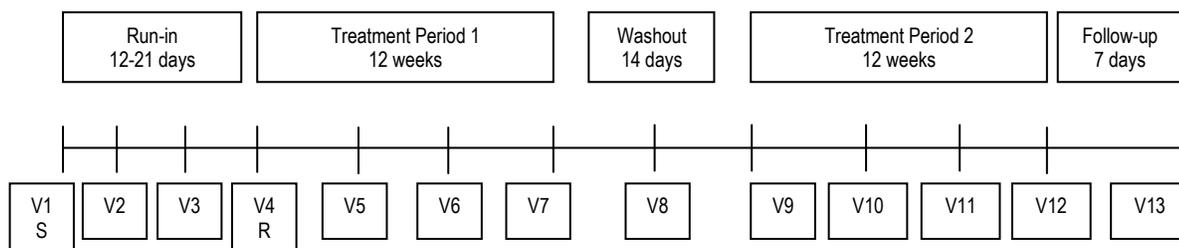
- Significant abnormal ECG finding
- Protocol-defined liver chemistry stopping criteria
- Positive pregnancy test

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 10.

**Figure 10. Schematic, Exercise Endurance Trials**



Source: Applicant's NDA 203-975 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 14.

**Table 14. 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 <sup>1</sup>	X													
Physical Examination	X											X	X	
Screening VS	X												X	
Screening ECG	X													
Screening spirometry <sup>2</sup>	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 <sup>3</sup> pre & post dose				X			X		X			X	X	
COPD exacerbation assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry pre and post-dose				X	X	X	X		X	X	X	X		
Lung volumes pre & post dose				X	X	X	X		X	X	X	X		
Diffusing capacity				X					X					
ISWT	X	X						X						
ESWT			X	X	X	X	X		X	X	X	X		
Pulse Oximetry		X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory <sup>4</sup>	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	

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Issue/collect double-blind diary				X			X		X			X	X	
Exercise dyspnea scale			X	X	X	X	X		X	X	X	X		
Inhaler use assessment				X	X	X								
Ease of use assessment						X								
Concomitant medications assessment	X	X	X	X	X	X	X	X	X	X	X	X	X	
Exercise IC (subset, Trial DB2114417 only)			X	X	X	X	X		X	X	X	X		
Cardio-respiratory 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	
Dispense trial medication				X					X					
Collect trial medications and assess compliance						X	X				X	X	X	

Source: Applicant's NDA 203-975 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

<sup>1</sup> Only if there is no chest X-ray or CT scan available within 6 months prior to Visit 1

<sup>2</sup> Performed as follows: pre-bronchodilator testing followed by post-albuterol/salbutamol testing, followed by post-ipratropium testing

<sup>3</sup> Pre-dose and 45 minutes post-dose

<sup>4</sup> 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 predominantly from the two placebo-controlled efficacy and safety trials evaluating UMEC 62.5 mcg: one 12-week trial (AC4115408), and one 24-week trial (DB2113373). The 12-week trial evaluated two doses of umeclidinium, 62.5 mcg and 125 mcg, while the 24-week trial evaluated only UMEC 62.5. An additional 24-week placebo-controlled trial (DB2113361) evaluated UMEC 125 mcg. Results from Trial DB2113361 are reviewed in order to provide additional context; however, efficacy results for the higher UMEC dose cannot be extrapolated to the lower UMEC dose. Only the 62.5 mcg dose is being proposed by the Applicant. The 24-week trials, which were replicate in design, were designed primarily to provide factorial support for a related combination product, UMEC/VI. These three trials included patients with moderate to very severe COPD (GOLD stages II-IV), and the primary efficacy endpoint was trough FEV1 at the end of treatment (Day 85 for Trial AC4115408 and Day 169 for the 24-week trials).

Results for the comparison between UMEC 62.5 mcg and placebo in two efficacy trials are statistically significant, with an effect size ranging from 0.115 L in Trial DB2113373 to 0.127 L in Trial AC4115408. Similarly, results for the comparison between UMEC 125 mcg and placebo in two efficacy trials are statistically significant, with an effect size ranging from 0.152 L in the Trial AC4115408 to 0.160 L in Trial DB2113361. The point estimates observed for each nominal dose are consistent across trials, in spite of the difference in treatment duration. A small increase in the magnitude of the treatment effect is noted for the higher UMEC dose (0.152 L for UMEC 125 mcg versus 0.127 L for UMEC 62.5 mcg) in Trial AC4115408, which included a head-to-head comparison of the two doses. Taken together, these trials provide replicate, statistically significant evidence of a treatment effect for both doses of the UMEC versus placebo. Focusing on the results for UMEC 62.5 mcg, the dose proposed for approval, the magnitude of the treatment effect compared to placebo (0.115 L – 0.127 L) represents an outcome that is likely to be clinically meaningful. Moreover, the results of Trials DB2113361 and DB2113373 provide evidence of persistence of efficacy for up to 6 months.

These results were robust to analyses conducted for various subgroups based on demographic factors (age, gender, 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, 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.

It should also be noted that the clinical development program for the related combination product UMEC/VI provided replicate, statistically significant evidence of the contribution of both doses of UMEC to their respective fixed combinations.

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

## 6.1 Indication

The Applicant proposes that UMEC 62.5 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 efficacy trials (AC4115408, DB2113361, DB2113373, and DB2113374).

### 6.1.2 Demographics

Demographic and baseline characteristics for the pooled ITT population from the efficacy trials (AC4115408, DB2113361, DB2113373, and DB2113374) are provided in Table 15.

**Table 15. Demographic and selected baseline characteristics for pooled ITT population, efficacy trials**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
<b>Age (years), n</b>	623	487	698
Mean	62.3	63.8	63.7
SD	8.77	9.22	8.40

Min, Max	40,86	40,93	40,86
<b>Sex, n</b>	623	487	698
Male, n (%)	412 (66)	342 (70)	460 (66)
<b>Race*, n</b>	623	487	698
White, n (%)	534 (86)	415 (85)	594 (85)
African American/ African heritage, n (%)	19 (3)	15 (3)	12 (2)
Asian, n (%)	57 (9)	42 (9)	83 (12)
American Indian or Alaska native, n (%)	1 (<1)	3 (<1)	0
Native Hawaiian or other Pacific Islander, n (%)	0	0	0
<b>Ethnicity, n</b>	623	487	698
Hispanic/Latino, n (%)	26 (4)	37 (8)	42 (6)
Not Hispanic/Latino, n (%)	597 (96)	450 (92)	656 (94)
<b>Height (cm), n</b>	623	487	698
Mean	168.7	168.9	169.1
SD	9.05	9.36	8.82
Min, Max	139,190	138,200	142,198
<b>Weight (kg), n</b>	623	487	698
Mean	76.78	76.34	75.63
SD	19.449	19.591	18.457
Min, Max	34.0,170.0	34.0, 169.0	33.8, 160.1
<b>BMI (kg/m<sup>2</sup>), n</b>	623	487	698
Mean	26.84	26.62	26.32
SD	5.959	5.891	5.696
Min, Max	12.3, 50.7	12.5, 53.9	14.4, 56.7
<b>Smoking status at Screening, n</b>	623	487	698
Current smoker, n (%)	329 (53)	244 (50)	353 (51)
Former smoker, n (%)	294 (47)	243 (50)	345 (49)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 98 (Table 28); pg. 102 (Table 32)

\*Applicant's table includes additional subcategories for race

Demographic and baseline characteristics were generally well balanced across treatment arms. A slightly higher percentage of males and persons reporting Hispanic/Latino ethnicity was observed for the UMEC 62.5 mcg arm compared to the other treatment groups. Patients of African American or African heritage accounted for 3% of the overall ITT population in the efficacy trials and 10% of patients at U.S. sites in the 24-week trials; the prevalence of COPD among non-Hispanic black adults in the United States in 2007-2009 (annual average) was 4.4%.<sup>17</sup>

<sup>17</sup> Akinbami LJ, Liu X. Chronic obstructive pulmonary disease among adults aged 18 and over in the United States, 1998-2009. NCHS Data Brief. 2011; 63:1-8.

Disease characteristics are presented for the pooled ITT population from the efficacy trials in Table 16.

**Table 16. COPD disease characteristics for pooled ITT population, efficacy trials**

	<b>Placebo N=623</b>	<b>UMEC 62.5 N=487</b>	<b>UMEC 125 N=698</b>
<b>GOLD stage, n</b>	622	486	696
I: FEV1 ≥80% predicted	0	0	0
II: 50%≤FEV1<80% predicted	273 (44)	216 (44)	314 (45)
III: 30%≤FEV1<50% predicted	291 (47)	202 (42)	311 (45)
IV: FEV1<30% predicted	58 (9)	68 (14)	71 (10)
<b>ICS use at Screening, n</b>	623	487	698
ICS user, n (%)	293 (47)	234 (48)	333 (48)
ICS non-user, n (%)	330 (53)	253 (52)	365 (52)
<b>Pre-bronchodilator FEV1 (L), n</b>	622	485	695
Mean	1.236	1.224	1.244
SD	0.4560	0.4969	0.4755
Median	1.170	1.150	1.170
Min, Max	0.38, 2.81	0.31, 2.80	0.35, 3.09
<b>Reversibility to Salbutamol, n</b>	621	483	694
Not reversible, n (%)	431 (69)	349 (72)	473 (68)
Reversible, n (%)	190 (31)	134 (28)	221 (32)
<b>Reversibility to Salbutamol and Ipratropium, n</b>	610	477	686
Not reversible, n (%)	291 (48)	226 (47)	298 (43)
Reversible, n (%)	319 (52)	251 (53)	388 (57)
<b>COPD Type*, n</b>	620	487	694
Chronic bronchitis, n (%)	429 (69)	324 (67)	438 (63)
Emphysema, n (%)	379 (61)	319 (66)	448 (65)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 101 (Table 31); pg. 105 (Table 37); pg. 106 (Table 38); pg. 107 (Table 39)

\*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. There was a slightly higher percentage of patients with GOLD Stage IV disease in the UMEC 62.5 mcg arm compared to the other treatment groups. ICS use at screening was nearly evenly split across the patient population. Pre-bronchodilator FEV1 was balanced across treatment groups (1.2L). Approximately one-third of the patient population demonstrated

reversibility to salbutamol, and approximately one-half demonstrated reversibility to both salbutamol and ipratropium. There was a slightly higher percentage of patients with reversibility to both salbutamol and ipratropium in the UMEC 125 mcg arm compared to the other treatment arms. Both chronic bronchitis and emphysema were represented in a substantial proportion of the population (61% or more); the percent of patients reporting each subtype was generally balanced across treatment arms.

The most common current and past comorbid conditions reported for the pooled ITT population from the efficacy trials are presented Table 17.

**Table 17. Common Comorbid conditions for pooled ITT population, efficacy trials**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
<b>Common Current Medical Conditions</b>			
Any condition	507 (81)	387 (79)	557 (80)
Cardiovascular risk factors	373 (60)	287 (59)	384 (55)
Musculoskeletal and connective tissue disorders	200 (32)	159 (33)	235 (34)
Cardiac disorders	115 (18)	114 (23)	129 (18)
Psychiatric disorders	91 (15)	69 (14)	106 (15)
Nervous system disorders	79 (13)	65 (13)	95 (14)
Endocrine disorders	73 (12)	54 (11)	87 (12)
Metabolism and nutrition disorders	77 (12)	69 (14)	76 (11)
Respiratory, thoracic, and mediastinal disorders	76 (12)	53 (11)	66 (9)
Vascular disorders	74 (12)	57 (12)	76 (11)
Skin and subcutaneous tissue disorders	75 (12)	48 (10)	46 (7)
<b>Common Past Medical Conditions</b>			
Any condition	304 (49)	255 (52)	401 (57)
Respiratory, thoracic, and mediastinal disorders	78 (13)	59 (12)	100 (14)
Cardiovascular risk factors	69 (11)	52 (11)	91 (13)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	56 (9)	49 (10)	70 (10)
Reproductive system and breast disorders	56 (9)	43 (9)	67 (10)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 71 (Table 32); pg. 72 (Table 33)

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. The percentage of patients currently reporting cardiovascular risk factors is slightly lower for the UMEC 125 mcg arm compared to the other treatment groups, while the percentage of patients currently reporting a cardiac disorder was slightly higher for the UMEC 62.5 mcg arm compared to the other treatment groups.

### 6.1.3 Subject Disposition

The disposition of the patients participating in the efficacy trials (AC4115408, DB2113361, DB2113373, and DB2113374) who were assigned to placebo, UMEC 62.5, or UMEC 125 is provided in Table 18. The “efficacy trials” grouping integrates data at the 12-week time point, corresponding to the duration of trial AC4115408. In addition, integrated disposition data at the 24-week time point, corresponding to the duration of the longer trials (DB2113361, DB2113373, and DB2113374) is provided in Table 19.

**Table 18. Subject Disposition for the Efficacy Trials, 12-week Integration**

	Placebo	UMEC 62.5	UMEC 125
<b>Randomized</b>	<b>Number of Patients</b>		
All Efficacy Trials	625	490	700
AC4115408	68	69	69
DB2113361	277	--	409
DB2113373	280	421	--
DB2113374	--	--	222
<b>Intent-To-Treat</b>	<b>Number of Patients (% of Randomized)</b>		
All Efficacy Trials	623 (>99)	487 (>99)	698 (>99)
AC4115408	68 (100)	69 (100)	69 (100)
DB2113361	275 (>99)	--	407 (>99)
DB2113373	280 (100)	418 (>99)	--
DB2113374	--	--	222 (100)
<b>Disposition</b>	<b>Number of Patients (% of ITT)</b>		
<b>Completion Status</b>			
Completed*	437 (70)	386 (79)	533 (76)
Withdrawn	186 (30)	101 (21)	165 (24)

Primary Reason/ Subreason for Withdrawal#			
Adverse event	26 (4)	35 (7)	44 (6)
Lack of Efficacy	89 (14)	25 (5)	64 (9)
Exacerbation	66 (11)	23 (5)	48 (7)
Protocol deviation	8 (1)	7 (1)	4 (<1)
Met protocol-defined stopping criteria	31 (5)	13 (3)	27 (4)
ECG abnormality	22 (4)	7 (1)	19 (3)
Holter abnormality	9 (1)	4 (<1)	8 (1)
Lab abnormality	0	2 (<1)	0
Study closed/terminated	0	0	0
Lost to follow-up	1 (<1)	0	3 (<1)
Withdrew consent	31 (5)	21 (4)	23 (3)
Patient relocated	3 (<1)	2 (<1)	1 (<1)
Frequency of visits	5 (<1)	2 (<1)	0
Burden of procedures	7 (1)	4 (<1)	4 (<1)
Other	9 (1)	10 (2)	15 (2)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.1 (AC4115408), pg. 58 (Table 8); Section 5.3.5.1 (DB2113361), pg. 75 (Table 10); Section 5.3.5.1 (DB2113373), pg. 74 (Table 10); Section 5.3.5.1 (DB2113374), pg. 64 (Table 11); Section 5.3.5.3 (ISS), pg. 53 (Table 14)

\*A patient was considered to have completed the treatment period if they completed the last clinic visit 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

**Table 19. Subject Disposition for Efficacy Trials, 24-week Integration**

	Placebo	UMEC 62.5	UMEC 125
<b>Randomized</b>	<b>Number of Patients</b>		
All Efficacy Trials in 24-week Integration	557	421	631
DB2113361	277	--	409
DB2113373	280	421	--
DB2113374	--	--	222
<b>Intent-To-Treat</b>	<b>Number of Patients (% of Randomized)</b>		
All Efficacy Trials	555 (>99)	418 (>99)	629 (>99)
DB2113361	275 (>99)	--	407 (>99)
DB2113373	280 (100)	418 (>99)	--
DB2113374	--	--	222 (100)
<b>Disposition</b>	<b>Number of Patients (% of ITT)</b>		
<b>Completion Status</b>			

Completed*	387 (70)	324 (78)	477 (76)
Withdrawn	168 (30)	94 (22)	152 (24)
<b>Primary Reason/ Subreason for Withdrawal#</b>			
Adverse event	26 (5)	34 (8)	41 (7)
Lack of Efficacy	81 (15)	20 (5)	60 (10)
Exacerbation	60 (11)	18 (4)	46 (7)
Protocol deviation	8 (1)	7 (2)	4 (<1)
Met protocol-defined stopping criteria	25 (5)	13 (3)	22 (3)
ECG abnormality	16 (3)	7 (2)	14 (2)
Holter abnormality	9 (2)	4 (<1)	8 (1)
Lab abnormality	0	2 (<1)	0
Study closed/terminated	0	0	0
Lost to follow-up	1 (<1)	0	2 (<1)
Withdrew consent	27 (5)	20 (5)	23 (4)
Patient relocated	3 (<1)	2 (<1)	1 (<1)
Frequency of visits	5 (<1)	1 (<1)	0
Burden of procedures	4 (<1)	4 (<1)	4 (<1)
Other	8 (1)	10 (2)	15 (2)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.1 (DB2113361), pg. 75 (Table 10); Section 5.3.5.1 (DB2113373), pg. 74 (Table 10); Section 5.3.5.1 (DB2113374), pg. 64 (Table 11); Section 5.3.5.3 (ISE), pg. 96 (Table 26)

\*A patient was considered to have completed the treatment period if they completed the last clinic visit 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.

### Withdrawals

Focusing first on the data for the efficacy trials integrated at 12 weeks, the percentage of patients who withdrew from the efficacy trials was higher for the placebo arm (30%) compared to the active treatment arms (21-24%). The most commonly reported primary reason for withdrawal was "lack of efficacy," which was also higher for the placebo arm (14%) compared to the active treatment arms (5-9%), as was the most commonly reported sub-reason "exacerbation" (11% versus 5-7% 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 (7%) and 125 mcg (6%) treatment arms compared to placebo (4%). The other primary reasons and sub-reasons reported for withdrawal were generally balanced across treatment arms. Similar patterns are observed for the efficacy trials integrated at 24 weeks.

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint for each of the three main efficacy trials was pre-dose trough FEV1, measured on Day 85 (Week 12) for Trial AC4115408, and on Day 169 (Week 24) for Trials DB2113361 and DB2113373. Spirometry is an appropriate choice of endpoint for a purported bronchodilator. The UMEC 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,"<sup>18</sup> 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 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's bronchodilatory action.

Results for the analysis of the primary endpoint are provided in Table 20 for the 12-week placebo controlled trial (AC4115408), and in Table 21 for the two 24-week placebo-controlled trials (DB2113361 and DB2113373).

**Table 20. Trough FEV1 (L) at Day 85, Trial AC4115408, ITT Population**

Treatment Arm	N	BL		Treatment Difference from Placebo		
		LS Mean (SE)	Change from BL LS Mean (SE)	Difference	95% CI	p-value
UMEC 125	69	1.388 (0.027)	0.145 (0.027)	0.152	0.076, 0.229	<0.001
UMEC 62.5	69	1.363 (0.026)	0.120 (0.026)	0.127	0.052, 0.202	<0.001
Placebo	68	1.235 (0.028)	-0.007 (0.028)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 70 (Table 22)

<sup>18</sup> 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.

**Table 21. Trough FEV1 (L) at Day 169, 24-Week Placebo-controlled Trials, ITT Population**

Treatment Arm	N	BL		Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	1.405 (0.012)	0.129 (0.012)	0.160	0.122, 0.198	<0.001
Placebo	275	1.245 (0.015)	-0.031 (0.015)			
<b>DB2113373</b>						
UMEC 62.5	418	1.354 (0.013)	0.119 (0.013)	0.115	0.076, 0.155	<0.001
Placebo	280	1.239 (0.016)	0.004 (0.016)			

Source: Applicant's NDA 203-975 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

Results for the comparison between UMEC 62.5 mcg and placebo in the two efficacy trials are statistically significant, with an effect size ranging from 0.115 L in the Trial DB2113373 to 0.127 L in Trial AC4115408. Similarly, results for the comparison between UMEC 125 mcg and placebo in two efficacy trials are statistically significant, with an effect size ranging from 0.152 L in Trial AC4115408 to 0.160 L in Trial DB2113361. The point estimates observed for each nominal dose are consistent across trials, in spite of the difference in treatment duration. A small increase in the magnitude of the treatment effect is noted for the higher UMEC dose (0.152 L for UMEC 125 mcg versus 0.127 L for UMEC 62.5 mcg) in Trial AC4115408, which included a head-to-head comparison of the two doses. Taken together, these three trials provide replicate, statistically significant evidence of a treatment effect for both doses of the UMEC versus placebo. Focusing on the results for UMEC 62.5 mcg, the dose proposed for approval, the magnitude of the treatment effect compared to placebo (0.115 L – 0.127 L) represents an outcome that is likely to be clinically meaningful.

It should also be noted that the UMEC/VI clinical development program provided replicate, statistically significant evidence of the contribution of both doses of UMEC to their respective fixed combinations (see NDA 203-975 clinical review by Dr. Jennifer Rodriguez Pippins, August 15, 2013).

Additional evidence of efficacy is drawn from the two 12-week exercise endurance trials (DB2114417 and DB2114418, shown in Table 22), which included trough FEV1 as a co-primary endpoint.

**Table 22. Trough FEV1 (L) at Week 12, Exercise Endurance Trials, ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>DB2114417</b>						
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
Placebo	170	1.404 (0.015)	-0.032 (0.015)			
<b>DB2114418</b>						
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
Placebo	151	1.277 (0.016)	-0.043 (0.016)			

Source: Applicant's NDA 203-975 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 exercise endurance trials, while different in design, provide additional support as they also included a placebo arm; however, the comparison between UMEC and placebo was not included in the testing hierarchy, and nominal p-values are provided. An effect is demonstrated for the comparison of each of the UMEC doses to placebo; however, unlike the main efficacy trials, the magnitude of the effect size observed in the exercise endurance trials varies widely (87 ml to 144 ml for UMEC 62.5 mcg, and 140 to 255 ml for UMEC 125 mcg).

Results for secondary and additional endpoints for UMEC are supportive of the findings for the primary endpoint, and are discussed below.

### 6.1.5 Analysis of Secondary Endpoints(s)

Weighted mean FEV1 over 0 to 6 hours post-dose was prespecified as a secondary endpoint in each of the three efficacy trials. Day 84 (for the 12-week trial) and Day 168 (for the 24-week trials) results for this secondary endpoint are provided in Table 23 and Table 24, respectively.

**Table 23. Change in 0 to 6 hours Weighted Mean FEV1 (L) at Day 84, Trial AC4115408, Trials, 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	1.432 (0.026)	0.188 (0.026)	0.191	0.117, 0.265	<0.001
UMEC 62.5	69	1.407 (0.025)	0.163 (0.025)	0.166	0.094, 0.239	<0.001
Placebo	68	1.241 (0.027)	-0.003 (0.027)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 73 (Table 24)

**Table 24. Change in 0 to 6 hours Weighted Mean FEV1 (L) at Day 168, 24-Week Placebo-controlled Trials, ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	1.435 (0.012)	0.160 (0.012)	0.178	(0.141, 0.216)	<0.001
Placebo	275	1.257 (0.015)	-0.018 (0.015)			
<b>DB2113373</b>						
UMEC 62.5	418	1.387 (0.013)	1.151 (0.013)	0.150	(0.110, 0.190)	<0.001
Placebo	280	1.237 (0.016)	0.001 (0.016)			

Source: Applicant's NDA 203-975 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

Across the three efficacy trials there is replicate evidence of a statistically significant result for the comparison between UMEC and placebo; this is true for both the 62.5 mcg and 125 mcg doses. These results are supportive of the findings for the primary endpoint.

In addition to weighted mean FEV1 over 0 to 6 hours post-dose, Trial AC4115408 also included serial FEV1 as a prespecified secondary endpoint. These results are presented in Section 6.1.6, along with results from Trials DB2113361 and DB2113373, which included serial FEV1 as an additional endpoint.

### 6.1.6 Other Endpoints

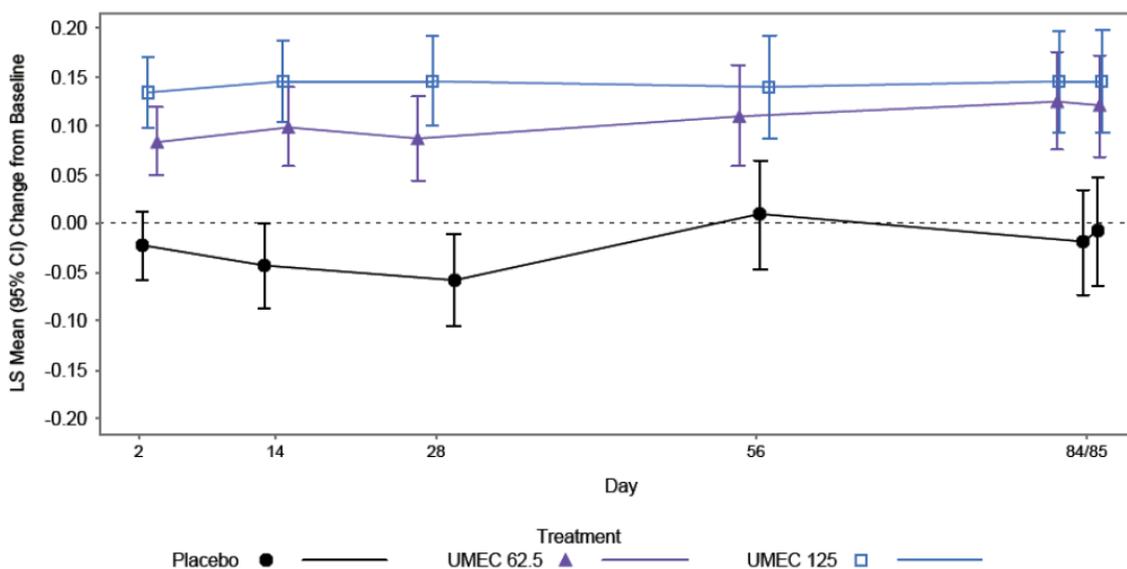
#### **Additional Spirometric Assessments**

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

#### ***Trough FEV1, additional time points***

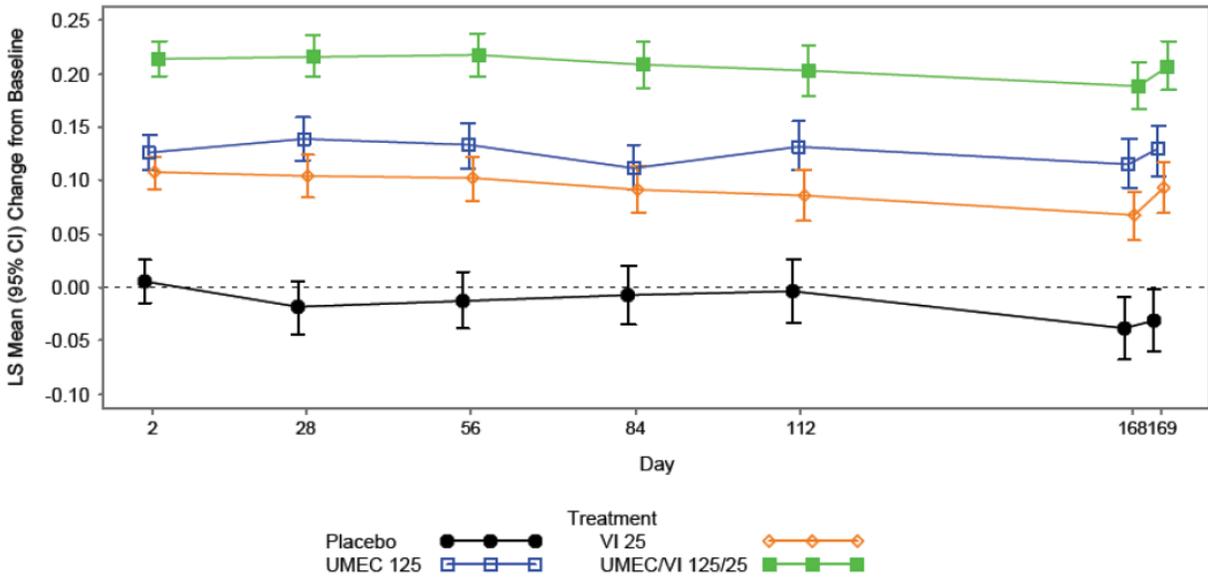
The primary analysis of trough FEV1 was conducted using data at Day 85 (for Trial AC4115408) or Day 169 (Trials DB2113361 and DB2113373). In addition, the three efficacy trials analyzed trough FEV1 for other time points during the 12 or 24 week treatment period. Least squares mean change from baseline in trough FEV1 on Days 2, 14, 28, 56, 84 and 85 for Trial AC4115408 is presented in Figure 11. Least squares mean change from baseline in trough FEV1 on Days 2, 28, 56, 84, 112, 168, and 169 for Trials DB2113361 and DB2113373 are presented in Figure 12 and Figure 13, respectively.

**Figure 11. Least Squares Mean Change from Baseline in Trough FEV1 (L) at selected time points, Trial AC4115408, ITT Population**



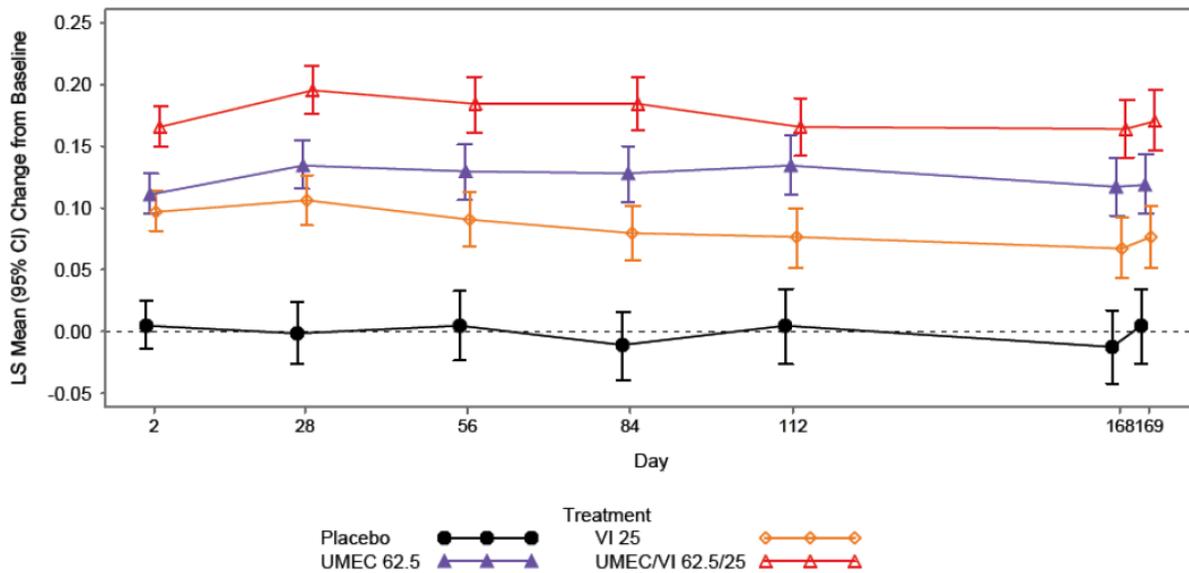
Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 71 (Figure 4)

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



Source: Applicant's NDA 203-975 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 NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 93 (Figure 4)

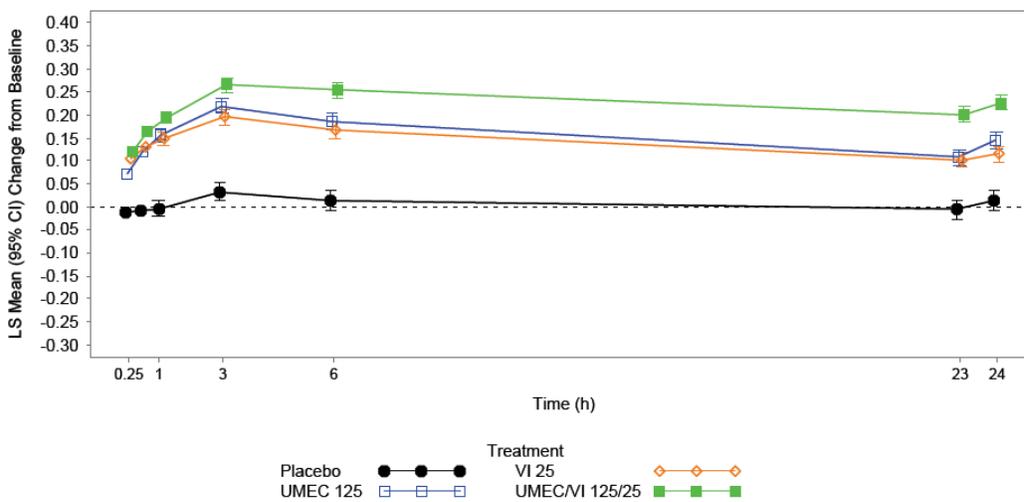
Focusing on the results for the monotherapy, in each of the three efficacy trials there is separation between the curves for UMEC and placebo at all time points. This is true for both the 62.5 mcg and 125 mcg doses. These results are supportive of the findings for the primary endpoint.

**Serial FEV1, 0 to 6 hours postdose**

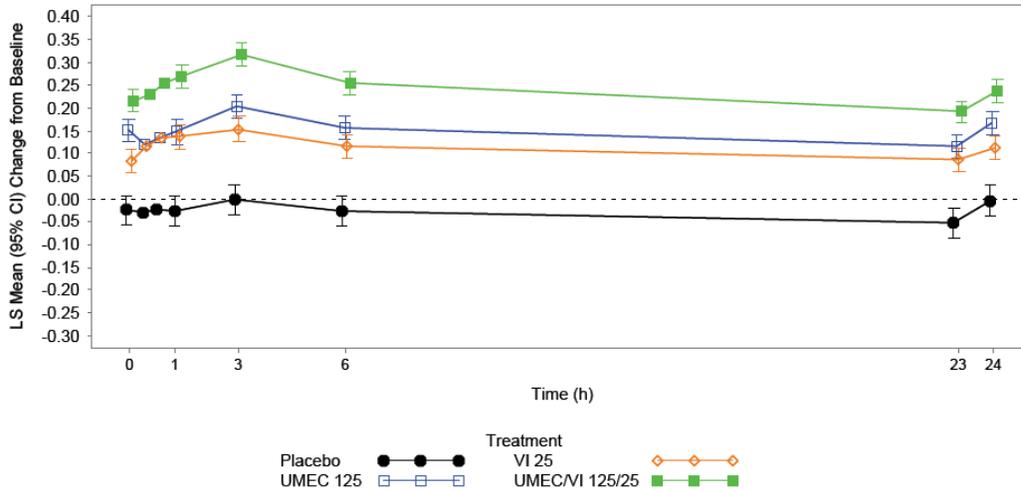
Each of the three efficacy trials evaluated FEV1 over the six hours immediately following dosing. The results for serial FEV1, 0-6 hours postdose, at the start of treatment (Day 1) and end of treatment (Day 168) are provided in Figure 14 and Figure 15 for Trials DB2113361 and DB2113373, respectively. Serial FEV1, 0-24 hours postdose, for Trial AC4115048 and a subset of patients in Trials DDB2113361 and DB2113374, is discussed below.

**Figure 14. 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**



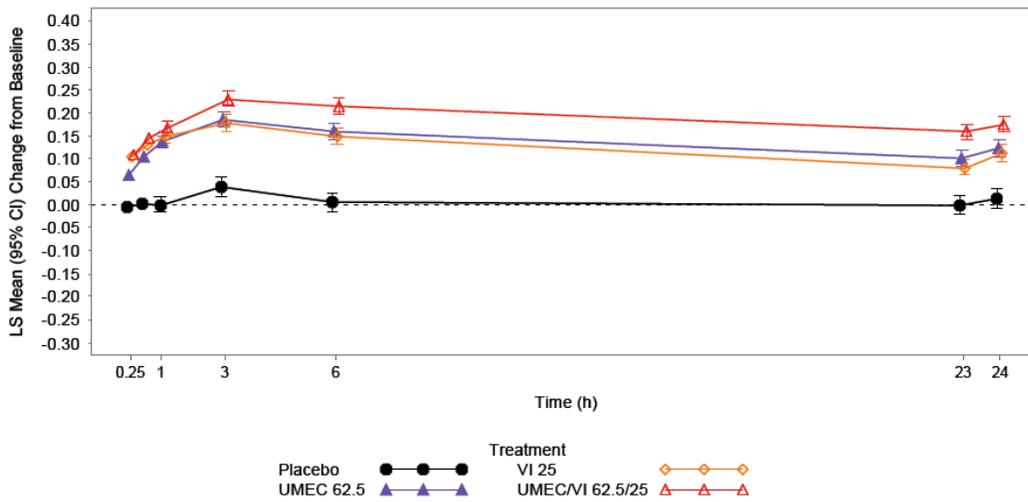
**B. Day 168**



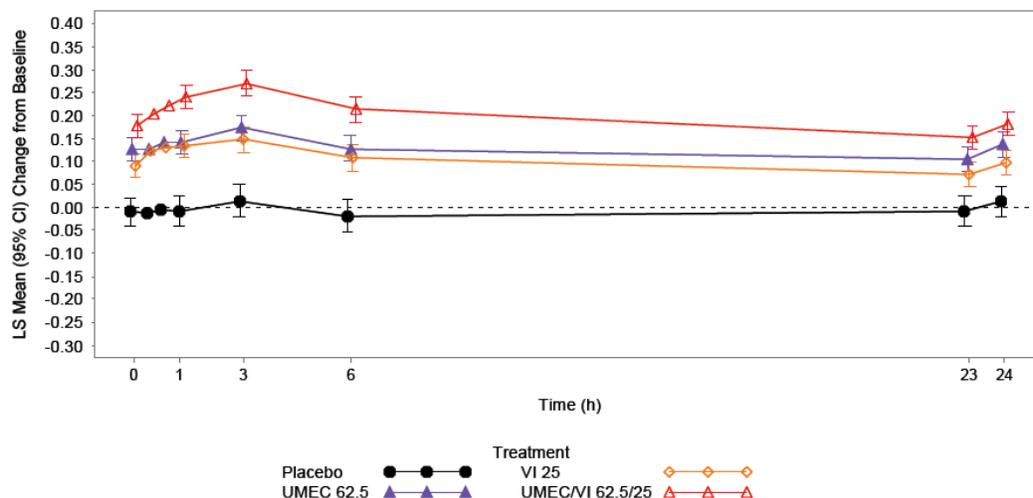
Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 111, 113 (Figure 10)

**Figure 15. Least Squares Mean Change from Baseline in FEV1 (L), 0-6 hours, 23, and 24 hours on Day 1 and Day 168, Trial DB2113373, ITT Population**

**A. Day 1**



## B. Day 168



Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 107,109 (Figure 10)

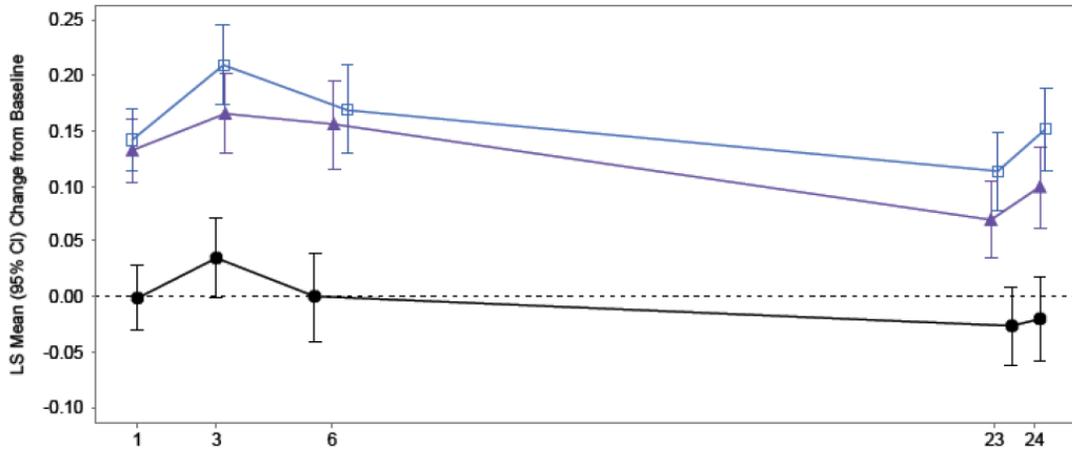
Focusing on the results for the monotherapy, in each of the 24-week trials there is separation between the curves for UMEC and placebo at all time points on both Day 1 and Day 168. This is true for both the 62.5 mcg and 125 mcg doses. These results are supportive of the findings for the primary endpoint.

### **Serial FEV1, 0 to 24 hours postdose**

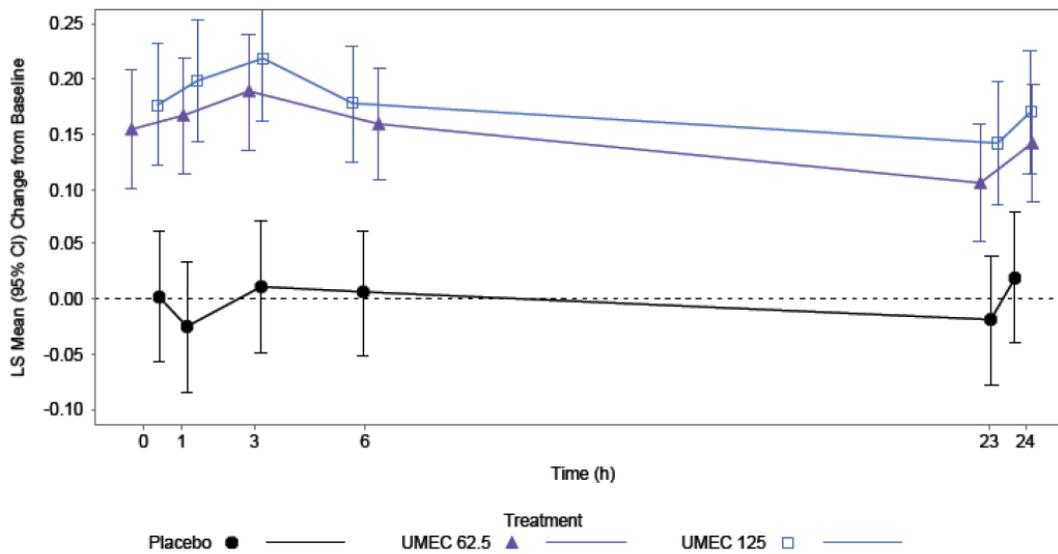
Serial FEV1 over 24 hours postdose was evaluated for all patients in the 12-week trial, and at selected sites for a subset of patients in the two placebo-controlled 24-week trials (approximately 200 from each trial, equivalent to 13% of the ITT population from the two trials). The results for this parameter at the start of treatment (Day 1) and end of treatment (Day 84 or Day 168) are provided in Figure 16, Figure 17, and Figure 18 for Trials AC4115408, DB2113361, and DB211373, respectively.

**Figure 16. Least Squares Mean Change from Baseline in FEV1 (L), 0-24 hours on Day 1 and Day 84, Trial AC4115408, ITT Population**

**A. Day 1**

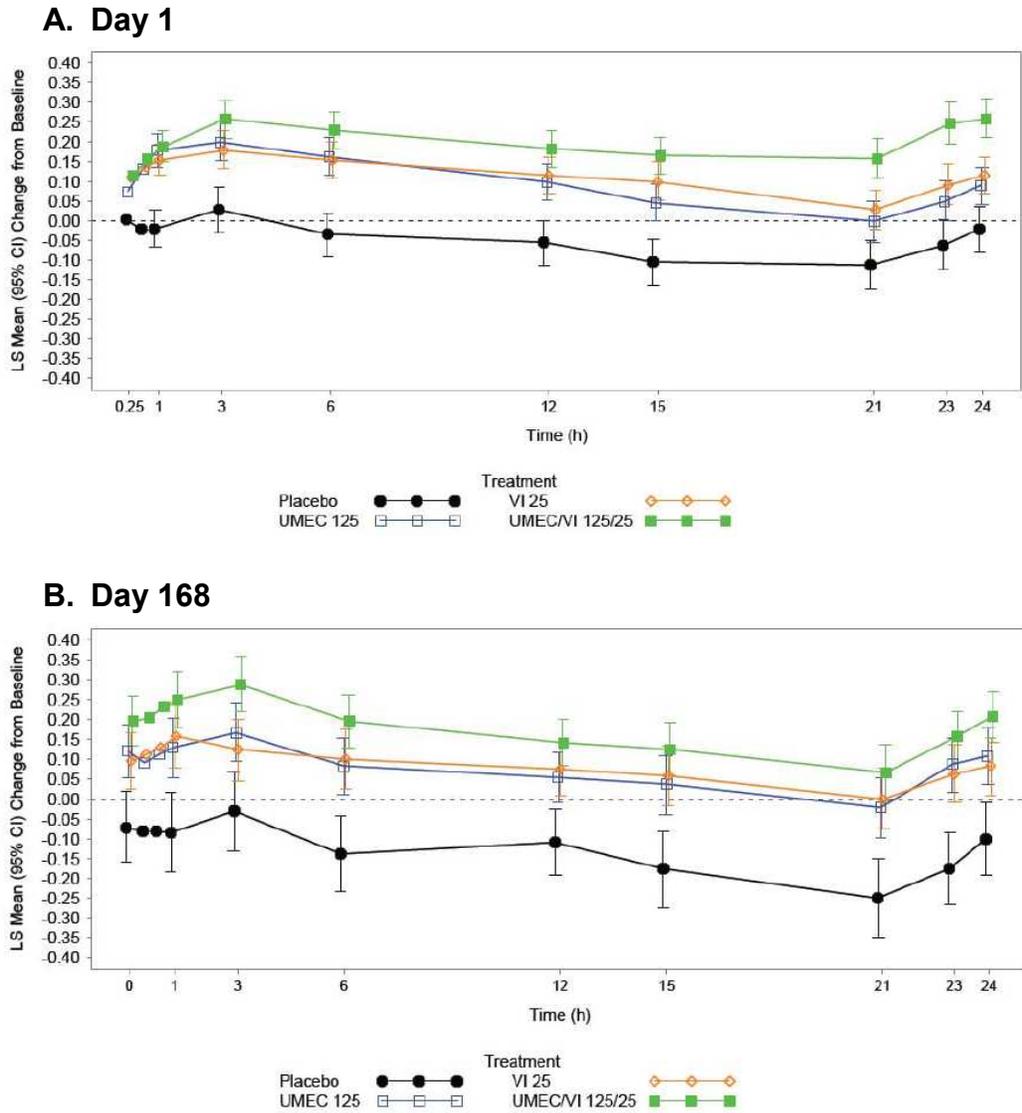


**B. Day 84**



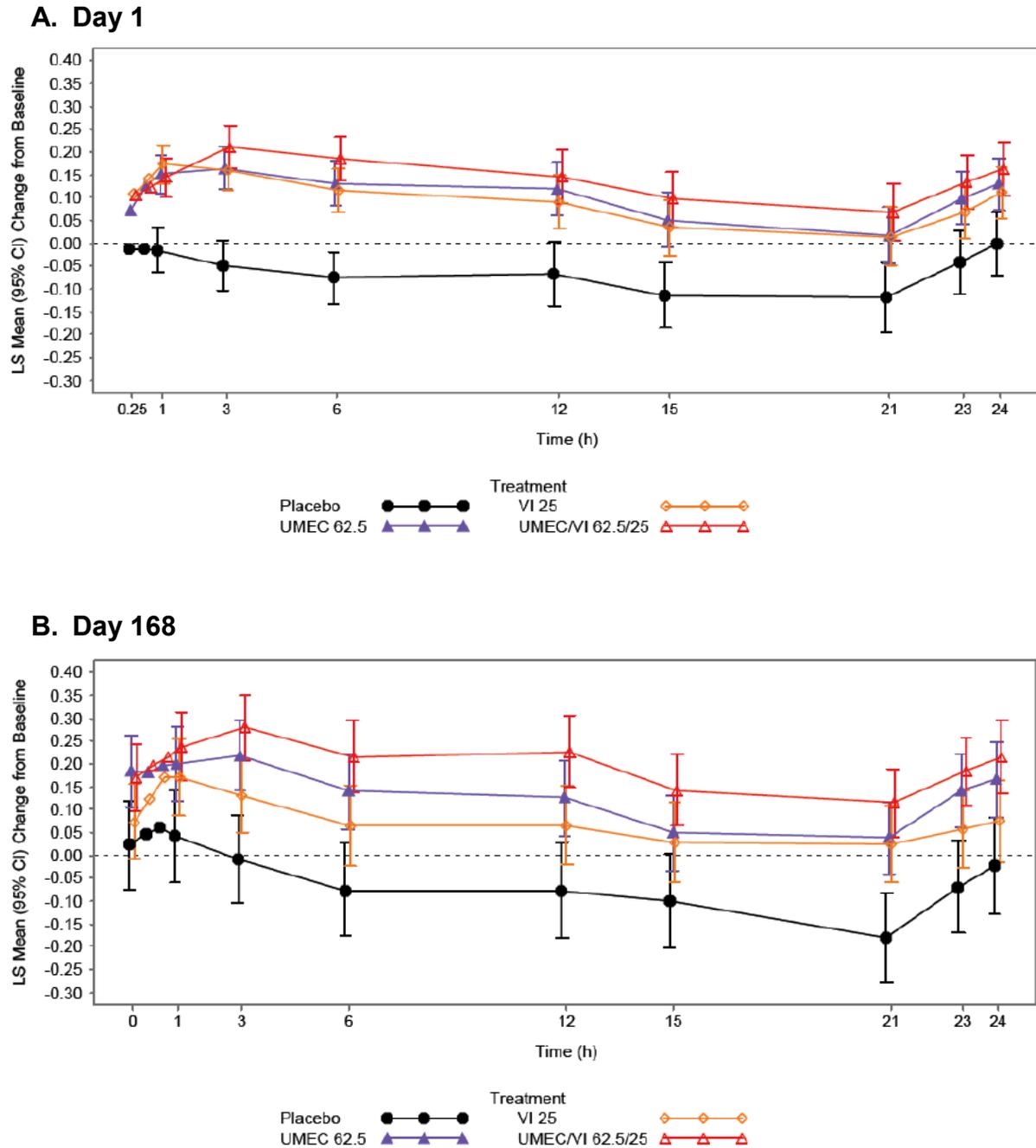
Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 76 (Figure 6)

**Figure 17. Least Squares Mean Change from Baseline in FEV1 (L), 0-24 hours on Day 1 and Day 168, Trial DB2113361, Subpopulation**



Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 130-131 (Figure 15)

**Figure 18. Least Squares Mean Change from Baseline in FEV1 (L), 0-24 hours on Day 1 and Day 168, Trial DB2113373, Subpopulation**



Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113373, Study Report Body), pg. 125-126 (Figure 15)

Focusing on the results for the monotherapy, in each of the three efficacy trials there is separation between the curves for UMEC and placebo on both Day 1 and either Day 84 or Day 168 at all time points. This is true for both the 62.5 mcg and 125 mcg doses. 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 24-week placebo-controlled trials (Table 25). Peak FEV1 was not assessed in Trial AC4115408.

**Table 25. Change in Peak FEV1 (L) at Day 168, 24-Week Placebo-controlled Trials, ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		Mean (SE)	LS Mean (SE)	LS Mean	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	1.515 (0.012)	0.241 (0.012)	0.180	0.141, 0.219	<0.001
Placebo	275	1.336 (0.016)	0.061 (0.016)			
<b>DB2113373</b>						
UMEC 62.5	418	1.460 (0.014)	0.226 (0.014)	0.130	0.088, 0.172	<0.001
Placebo	280	1.331 (0.017)	0.096 (0.017)			

Source: Applicant's NDA 203-975 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

For the additional endpoint of peak FEV1, the comparison of each dose of UMEC to placebo is statistically significant in the single trial evaluating that dose. These results are supportive of the findings for the primary endpoint.

**Time to Onset**

Time to onset on Day 1, defined as the first time during the 0 to 6 hour postdose period at which a scheduled postdose FEV1 was  $\geq$  100 mL above baseline, was evaluated in each of the three efficacy trials. Result for the 12-week and 24-week trials are provided in Table 26 and Table 27, respectively.

**Table 26. Time to Onset on Day 1, Trial AC4115408, ITT Population**

Treatment Arm	N	Median Time to Onset (minutes)*	Comparison to Placebo		
			Hazard Ratio	95% CI	p-value
UMEC 125	69	63	4.34	2.65, 7.10	<0.001
UMEC 62.5	69	65	3.65	2.22, 5.99	<0.001
Placebo	68	NA			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 Trial AC4115408, Study Report Body), pg. 436 (Table 6.44)  
 \*Kaplan-Meier estimate; a patient was classified as censored if he or she had at least one post-dose FEV1 on Day 1, but did not achieve an increase of  $\geq 100$  mL from baseline at any scheduled FEV1 assessment during 0-6 h post-dose.

**Table 27. Time to Onset on Day 1, 24-Week Placebo-controlled Trials, ITT Population**

Treatment Arm	N	Median Time to Onset (minutes)*	Comparison to Placebo		
			Hazard Ratio	95% CI	p-value
<b>DB2113361</b>					
UMEC 125	407	34	3.84	3.09, 4.79	<0.001
Placebo	275	NA			
<b>DB2113373</b>					
UMEC 62.5	418	56	3.14	2.52, 3.90	<0.001
Placebo	280	NA			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (DB2113361, Study Report Body), pg. 114 (Table 33); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 110 (Table 33)

\*Kaplan-Meier estimate; if greater than 50% of data were censored, then the median was NA.

There is replicate, statistically significant evidence for a difference between UMEC and placebo with respect to time to onset. The data would support a labeling claim of a time to onset of 65 minutes for the UMEC 62.5 mcg dose.

### **Rescue Medication Use**

Change in rescue medication use over the treatment period was evaluated in each of the three efficacy trials. Results for this endpoint from the 12-week trial and 24-week trials are provided in Table 28 and Table 29, respectively.

**Table 28. Change in Mean Number of Puffs of Rescue Medication per Day at Week 12, 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	2.3 (0.2)	-0.6 (0.2)	-0.6	-1.2, 0.0	0.069
UMEC 62.5	69	2.2 (0.2)	-0.7 (0.2)	-0.7	-1.3, -0.1	0.025
Placebo	68	2.9 (0.2)	-0.0 (0.2)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 87 (Table 29)

**Table 29. Change in Mean Number of Puffs of Rescue Medication per Day at Week 24, Trials DB2113361 and DB2113373, ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	2.8 (0.1)	-1.5 (0.1)	-0.8	-1.3, -0.4	<0.001
Placebo	275	3.7 (0.2)	-0.7 (0.2)			
<b>DB2113373</b>						
UMEC 62.5	418	3.8 (0.2)	-1.7 (0.2)	-0.3	-0.8, 0.2	0.276
Placebo	280	4.1 (0.2)	-1.4 (0.2)			

Source: Applicant's NDA 203-975 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

Across the three efficacy trials there are two comparisons between each UMEC dose and placebo for the endpoint of change in mean rescue medication use. For each of the UMEC doses the result for this endpoint meets the threshold for statistical significance in only one of the two comparisons. (b) (4)

**SGRQ**

Disease-specific health related quality of life was assessed in the UMEC 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,<sup>19</sup> and there is regulatory precedent for inclusion of SGRQ data in labeling.<sup>20</sup>

Change in SGRQ total score was evaluated in each of the three 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 12-week and 24-week trials are provided in Table 30 and Table 31, respectively. In addition, the Applicant conducted a responder analysis, the results of which are presented in Table 32 and Table 33 for the 12-week and 24-week trials, respectively.

**Table 30. Change in SGRQ Total Score at Day 84, 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	39.46 (1.53)	-6.12 (1.53)	-10.87	-15.25, -6.49	<0.001
UMEC 62.5	69	42.43 (1.47)	-3.14 (1.47)	-7.90	-12.20, -3.60	<0.001
Placebo	68	50.33 (1.60)	4.75 (1.60)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 92 (Table 33)

**Table 31. Change in SGRQ Total Score at Day 168, 24-Week Placebo-controlled Trials, ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	43.38 (0.66)	-4.14 (0.66)	-0.31	-2.46, 1.85	0.778
Placebo	275	43.69 (0.88)	-3.83 (0.88)			

<sup>19</sup> 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.

<sup>20</sup> 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.

DB2113374						
UMEC 62.5	418	41.93 (0.75)	-7.25 (0.75)	-4.69	-7.07, -2.31	<0.001
Placebo	280	46.62 (0.95)	-2.56 (0.95)			

Source: Applicant's NDA 203-975 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

**Table 32. SGRQ Responder Analysis at Day 84, Trial AC4115408, ITT Population**

Treatment Arm	N	Responder	Non-responder	Comparison to Placebo		
		n (%)	n (%)	OR	95% CI	p-value
UMEC 125	69	30 (52)	28 (48)	3.20	1.40, 7.34	0.006
UMEC 62.5	69	28 (44)	35 (56)	2.44	1.08, 5.50	0.032
Placebo	68	14 (26)	40 (74)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.1 (AC4115408, Study Report Body), pg. 94 (Table 34) (DB2113373, Study Report Body), pg. 139 (Table 51)  
 Key: OR=odds ratio  
 Note: Response defined as a SGRQ total score of 4 units below baseline or lower

**Table 33. SGRQ Responder Analysis at Day 168, 24-Week Placebo-controlled Trials, ITT Population**

Treatment Arm	N	Responder	Non-responder	Comparison to Placebo		
		n (%)	n (%)	OR	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	144 (40)	217 (60)	1.2	0.8, 1.7	0.345
Placebo	275	80 (37)	139 (63)			
<b>DB2113373</b>						
UMEC 62.5	418	172 (44)	216 (56)	1.6	1.2, 2.3	0.003
Placebo	280	86 (34)	168 (66)			

Source: Applicant's NDA 203-975 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: Response defined as a SGRQ total score of 4 units below baseline or lower

Results for the SGRQ are mixed. Focusing first on the endpoint of change in SGRQ total score, while there are replicate, statistically significant results for the UMEC 62.5 mcg dose, only a single trial provides statistically significant results for the higher UMEC 125 mcg dose. It should also be noted that while the treatment effect for the UMEC 62.5 mcg dose meets the threshold for a clinically meaningful improvement (-4.0) in two trials, the large treatment effect observed in Trial AC4115408 is due primarily to worsening in the placebo group, which experiences a 4.75 unit mean increase in SGRQ score.

Similar to the results for change in SGRQ total score, the responder analysis demonstrates replicate, statistically significant results for the lower UMEC 62.5 mcg dose, but not for the higher 125 mcg dose.

The statistical review for this application includes a discussion of the impact of missing data on efficacy results, including the results for SGRQ (see NDA 205-382 review by Dr. Greg Levin). If an alternative approach is used to address missing data (Jump to Reference multiple imputation approach), the magnitude of the treatment effect for UMEC 62.5 mcg compared to placebo on change in SGRQ total score falls below the MCID threshold. It should also be noted that the clinical review of the UMEC/VI program concluded that the [REDACTED] (b) (4) clinical review by Dr. Jennifer Rodriguez Pippins, August 15, 2013). (b) (4)

**COPD Exacerbations**

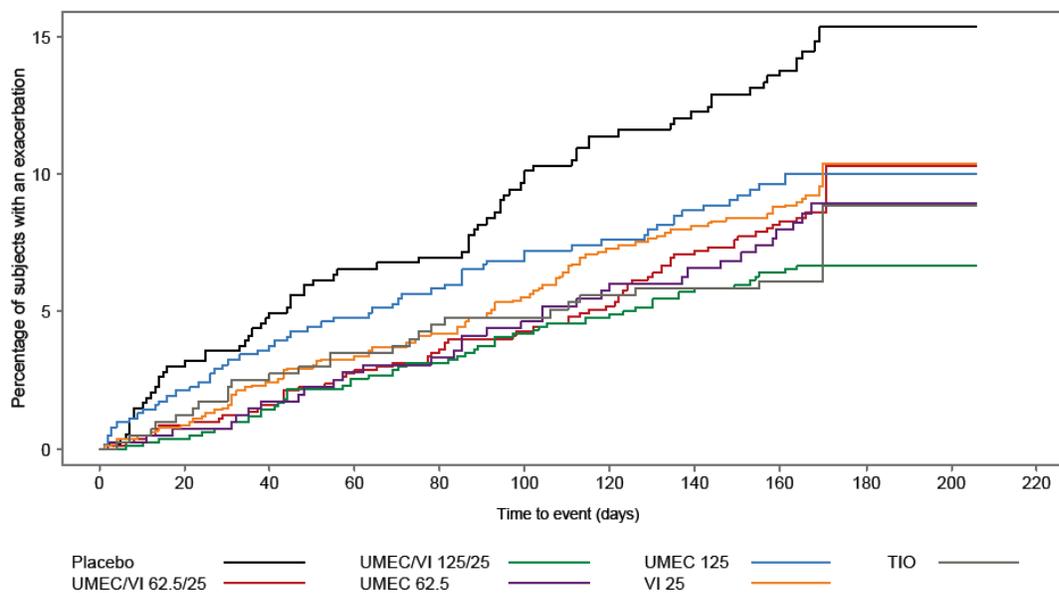
While the 24-week efficacy trials were not designed specifically for this purpose, the impact of UMEC on COPD exacerbations was explored as an additional endpoint. As described in Section 5.3, the protocols for these trials defined a COPD exacerbation as an acute worsening of symptoms of COPD requiring 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 24-week efficacy trial population (including active-controlled Trial DB2113374) are provided in Table 34 and Figure 19 (also includes Trial DB2113360). Time to first COPD exacerbation was not evaluated by the Applicant in Trial AC4115408, due to the trial’s shorter duration and smaller size.

**Table 34. Analysis of Time to First On-Treatment COPD Exacerbation, Integrated 24-Week Efficacy Trials (DB2113361, DB2113373, DB2113374), ITT Population**

Treatment Arm	N	Patient with Event n (%)	Patients Censored n (%)	Probability of Event (%)	Comparison to Placebo		
					Hazard Ratio	95% CI	p-value
UMEC 125	629	58 (9)	571 (91)	10.0	0.5	0.4, 0.8	0.002
UMEC 62.5	418	33 (8)	385 (92)	8.9	0.6	0.4, 0.9	0.011
Placebo	555	73 (13)	482 (87)	15.3			

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.3 (ISE), pg. 203 (Table 84)

**Figure 19. Kaplan-Meier Plot of Time to First On-Treatment COPD Exacerbation, Integrated 24-Week Efficacy Trials (DB2113361, DB2113373, DB2113360, DB2113374), ITT Population**



Source: Applicant's NDA 203-975 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 UMEC treatment arms (8-9%) compared to placebo (13%). Hazard ratios for the comparison to placebo were statistically significant for both doses of UMEC; the same was also true for both doses of the UMEC/VI combination products compared to placebo (data not shown). The Kaplan-Meier plot of time to first on-treatment COPD exacerbation demonstrates a separation between all the active treatment arms and placebo.

While these results suggest a possible favorable impact of UMEC 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, salbutamol 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 24-week efficacy trials (including the active-controlled trial DB2113374).

### **Demographics**

This review presents subgroup analyses based on the demographic factors of age (Table 35) and gender (Table 36), and geography (Table 37). A subgroup analysis by race is not included in this review, given the predominance of whites in the study population. The Applicant's subgroup analyses were conducted for the integrated ITT population drawn from the three 24-week trials, including the active controlled trial (DB2113374).

For each of the subgroup analyses conducted, results across demographic categories are consistent with the analysis for the overall ITT population: both the 62.5 mcg and 125 mcg doses are associated with a statistically significant treatment effect. Variability in the magnitude of effect size across demographic subgroups (98-195 mL for the 62.5 mcg dose, and 126-174 mL for the 125 mcg dose) is noted.

### **Age**

**Table 35. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by Age**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
				Difference	95% CI	p-value
		LS Mean (SE)	LS Mean (SE)			
<b>≤ 64 years</b>						
UMEC 125	332	1.489 (0.015)	0.153 (0.015)	0.158	0.115, 0.201	<0.001
UMEC 62.5	216	1.455 (0.019)	0.119 (0.019)	0.124	0.076, 0.171	<0.001
Placebo	331	1.331 (0.015)	-0.005 (0.015)			
<b>65-74 years</b>						
UMEC 125	229	1.274 (0.016)	0.139 (0.016)	0.156	0.108, 0.204	<0.001
UMEC 62.5	148	1.247 (0.020)	0.113 (0.020)	0.130	0.077, 0.182	<0.001
Placebo	166	1.118 (0.019)	-0.017 (0.019)			
<b>75-84 years</b>						
UMEC 125	61	1.137 (0.031)	0.127 (0.031)	0.131	0.037, 0.225	0.007

UMEC 62.5	49	1.201 (0.036)	0.191 (0.036)	0.195	0.098, 0.291	<0.001
Placebo	49	1.007 (0.035)	-0.003 (0.035)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 797-817 (Table 3.71)

Key: BL=baseline

Note: N= ITT Population, number of patients with analyzable data for one or more time points

### Gender

**Table 36. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by Gender**

Treatment Arm	N	BL		Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>Male</b>						
UMEC 125	415	1.381 (0.013)	0.150 (0.013)	0.148	0.111, 0.185	<0.001
UMEC 62.5	296	1.380 (0.015)	0.149 (0.015)	0.147	0.107, 0.187	<0.001
Placebo	367	1.233 (0.014)	0.002 (0.014)			
<b>Female</b>						
UMEC 125	208	1.367 (0.018)	0.136 (0.018)	0.164	0.112, 0.216	<0.001
UMEC 62.5	120	1.301 (0.023)	0.070 (0.023)	0.098	0.039, 0.157	0.001
Placebo	180	1.203 (0.020)	-0.028 (0.020)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 783-796 (Table 3.70)

Key: BL=baseline

Note: N= ITT Population, number of patients with analyzable data for one or more time points

### Geographic Region

**Table 37. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by Geographic Region**

Treatment Arm	N	BL		Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>US</b>						

UMEC 125	143	1.367 (0.022)	0.136 (0.022)	0.174	0.112, 0.236	<0.001
UMEC 62.5	118	1.345 (0.024)	0.114 (0.024)	0.152	0.088, 0.215	<0.001
Placebo	134	1.193 (0.023)	-0.038 (0.023)			
<b>European Union</b>						
UMEC 125	307	1.375 (0.015)	0.144 (0.015)	0.153	0.111, 0.195	<0.001
UMEC 62.5	124	1.349 (0.023)	0.118 (0.023)	0.127	0.072, 0.182	<0.001
Placebo	262	1.223 (0.016)	-0.008 (0.016)			
<b>Other</b>						
UMEC 125	173	1.381 (0.020)	0.150 (0.020)	0.126	0.068, 0.184	<0.001
UMEC 62.5	174	1.376 (0.020)	0.145 (0.020)	0.121	0.064, 0.177	<0.001
Placebo	151	1.255 (0.022)	0.024 (0.022)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 846-866 (Table 3.73)

Key: BL=baseline

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 38), concomitant ICS use (Table 39), and salbutamol reversibility (Table 40), as well as smoking status (Table 41). 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 62.5 mcg and the 125 mcg doses are associated with a statistically significant treatment effect for the comparison to placebo. Variability in the magnitude of effect size across the subgroups (89-174 mL for the 62.5 mcg dose, and 130-185 mL for the 125 mcg dose) is again noted.

### ***COPD Severity***

**Table 38. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by COPD Severity**

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

GOLD Stage II						
UMEC 125	280	1.407 (0.016)	0.177 (0.016)	0.179	0.134, 0.223	<0.001
UMEC 62.5	190	1.402 (0.019)	0.172 (0.019)	0.174	0.126, 0.222	<0.001
Placebo	236	1.229 (0.017)	-0.002 (0.017)			
GOLD Stages III and IV						
UMEC 125	341	1.353 (0.014)	0.123 (0.014)	0.135	0.094, 0.175	<0.001
UMEC 62.5	225	1.308 (0.018)	0.77 (0.018)	0.089	0.044, 0.135	<0.001
Placebo	310	1.219 (0.015)	-0.012 (0.015)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 895-908 (Table 3.76)

Key: BL=baseline

Note: N= ITT Population, number of patients with analyzable data for one or more time points

### Concomitant ICS Use

**Table 39. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by Concomitant ICS Use**

Treatment Arm	N	BL		Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
ICS user						
UMEC 125	314	1.391 (0.015)	0.160 (0.015)	0.162	0.119, 0.205	<0.001
UMEC 62.5	218	1.332 (0.018)	0.101 (0.018)	0.103	0.057, 0.149	<0.001
Placebo	271	1.229 (0.016)	-0.002 (0.016)			
ICS non-user						
UMEC 125	309	1.363 (0.015)	0.132 (0.015)	0.146	0.104, 0.188	<0.001
UMEC 62.5	198	1.382 (0.018)	0.151 (0.018)	0.165	0.118, 0.212	<0.001
Placebo	276	1.217 (0.016)	-0.014 (0.016)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 881-894 (Table 3.75)

Key: BL=baseline

Note: N= ITT Population, number of patients with analyzable data for one or more time points

**Salbutamol Reversibility**

**Table 40. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by Salbutamol Reversibility**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>Not Reversible</b>						
UMEC 125	414	1.353 (0.013)	0.121 (0.013)	0.136	0.100, 0.172	<0.001
UMEC 62.5	292	1.344 (0.015)	0.112 (0.015)	0.127	0.087, 0.167	<0.001
Placebo	380	1.217 (0.013)	-0.015 (0.013)			
<b>Reversible</b>						
UMEC 125	206	1.425 (0.018)	0.193 (0.018)	0.185	0.133, 0.238	<0.001
UMEC 62.5	121	1.389 (0.023)	0.158 (0.023)	0.150	0.091, 0.209	<0.001
Placebo	165	1.239 (0.020)	0.008 (0.020)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 923-936 (Table 3.78)

Key: BL=baseline

Note: N= ITT Population, number of patients with analyzable data for one or more time points

**Smoking Status**

**Table 41. Trough FEV1 (L) at Day 169, Integrated 24-Week Trials (DB2113361, DB2113373, DB2113374), ITT Population, by Smoking Status**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>Former Smoker</b>						
UMEC 125	314	1.361 (0.015)	0.130 (0.015)	0.130	0.086, 0.174	<0.001
UMEC 62.5	209	1.357 (0.018)	0.126 (0.018)	0.125	0.078, 0.173	<0.001
Placebo	259	1.231 (0.017)	0.000 (0.017)			
<b>Current Smoker</b>						

UMEC 125	309	1.391 (0.014)	0.160 (0.014)	0.173	0.132, 0.215	<0.001
UMEC 62.5	207	1.356 (0.018)	0.125 (0.018)	0.138	0.092, 0.184	<0.001
Placebo	288	1.218 (0.015)	-0.013 (0.015)			

Source: Applicant's NDA 205-382 submission dated April 30, 2013, Section 5.3.5.3 (ISE), pg. 909-922 (Table 3.77)

Key: BL=baseline

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. The three efficacy trials provide replicate, statistically significant, evidence for a treatment effect for each of the two UMEC doses compared to placebo. The application puts forward only the 62.5 mcg dose for approval; this is the same as the UMEC dose included in the approved UMEC/VI combination product. (b) (4)



the efficacy results for the 62.5 mcg UMEC dose stand on their own merit; they are of a magnitude that is likely to be clinically meaningful.

### 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 placebo-controlled 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 of two of the following treatments: UMEC/VI 125 mcg/25 mcg once daily, UMEC/VI 62.5 mcg/25 mcg once daily, UMEC 125 mcg once daily, VI 25 mcg once daily, and placebo. Each treatment was delivered via DPI for a duration of 12 weeks. The trials prespecified two co-primary endpoints: exercise endurance time (ETT) post-dose at Week 12, and trough FEV1 at Week 12. Results for trough FEV1 are presented in Section 6.1.4 of this review.

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 for UMEC/VI (both doses) in only in a single trial (DB2114418; data not shown). Results for 3-hour postdose ETT for UMEC 62.5 mcg compared to placebo were not statistically significant in either trial, and statistically significant for UMEC 125 mcg compared to placebo in a single trial. It should be noted that the Agency regards exercise endurance as a multi-factorial entity that is 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 main safety database for the proposed product consists of 8 clinical trials in patients with COPD (the “All Clinical Trials” grouping), and includes 2,706 patients across all treatment arms. Across the four efficacy and one long-term safety trials, 1,412 patients were treated with either UMEC 62.5 mcg or 125 mcg. Across the “All Clinical Trials” grouping of trials, 524 patients were treated with either UMEC 62.5 mcg or 125 mcg for at least 24 weeks, and 133 treated with UMEC 125 mcg for at least 48 weeks. In addition, as part of the UMEC/VI combination product clinical development program, 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 were treated with UMEC/VI 125 mcg/25 mcg 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 a thorough QT trial. This battery of assessments is considered appropriate for the evaluation of the proposed product.

A total of 16 deaths are reported for the UMEC 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 and 4 deaths are reported for the placebo 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 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 efficacy trials,

which are more common in the active treatment groups (1%) 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. Historically there have been concerns about the cardiovascular safety and stroke risk of inhaled anticholinergics; more recent controlled clinical data have been reassuring. 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 are demonstrated. 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. In the cardiovascular AESI analysis, imbalances favoring placebo are observed primarily in the efficacy trials; these include imbalances in serious events overall, as well as in the cardiac ischemia and cardiac arrhythmia subgroups of serious cardiovascular AESIs.

The review of MACE and cardiovascular AESI analyses for the UMEC/VI 125 mcg/25 mcg and 62.5 mcg/25 mcg products revealed similar imbalances in cardiovascular events, particularly those pertaining to cardiac ischemia. However, in both the review of the combination product and in this review, several features of the observed data decrease concern regarding the numerical imbalances observed. The imbalances identified for events pertaining to cardiac ischemia in the cardiovascular AESI analysis are observed in the 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 efficacy trials, but also in the long-term safety trial which evaluated the higher UMEC and UMEC/VI doses 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 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 numerical increase in the percentage of patients with a creatine kinase shift to high in the long-term safety trial. Similar findings were noted in both the efficacy and long-term safety trials in the UMEC/VI clinical program. 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 a thorough QT trial 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 and serious cardiovascular adverse events including those pertaining to ischemia, concern is mitigated by both the reassuring safety profile observed in the long-term safety trial, as well by the low number of overall events. The UMEC 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 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, Efficacy and Exercise Endurance Trials**

Safety evaluations performed in the 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 10, Table 12, Table 13, and Table 14.

In addition, 24-hour Holter monitoring was conducted for a subset of approximately 13% in the 24-week placebo-controlled trials (DB2113361 and DB2113373).

#### **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  $\geq 10$  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):  $\alpha$ -1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease
- Other significant diseases, either past or current; patients with cardiovascular disease were not specifically excluded
- Chest X-ray or CT scan<sup>21</sup> with clinically significant abnormalities not attributable to COPD
- History of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta<sub>2</sub>-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 42

**Table 42. 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

<sup>21</sup> 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.

Oral beta <sub>2</sub> -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 <sub>2</sub> -agonists, short-acting	12 hours
Inhaled short-acting beta <sub>2</sub> -agonists <sup>%</sup>	4 hours
Inhaled short-acting anticholinergics <sup>^</sup>	4 hours
Inhaled short-acting anticholinergic/short-acting beta <sub>2</sub> -agonist combination products	4 hours
Any other investigational medication	30 days or within 5 drug half-lives (whichever is longer)

Source: Applicant's NDA 203-975 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:

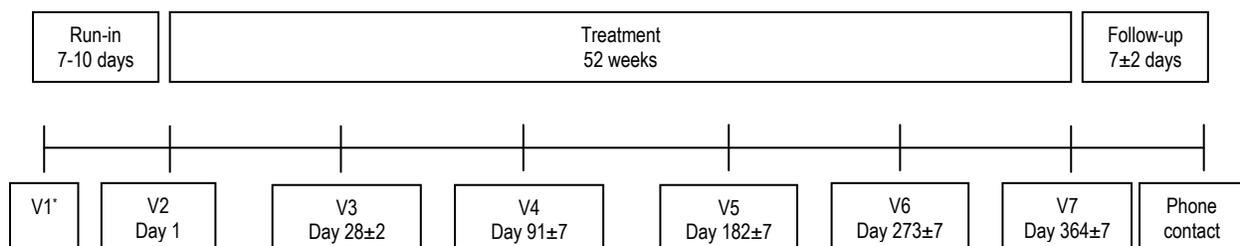
- Clinically important changes in laboratory assessments, per the Investigator's discretion
- Significant abnormal ECG finding
- Significant abnormal finding on 24-hour Holter monitoring
- Protocol-defined liver chemistry stopping criteria

- 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 20.

**Figure 20. Schematic, Long-term Safety Trial**



Source: Applicant's NDA 203-975 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 ( $\leq 14$  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 43.

**Table 43. 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 ( $\pm 2$ ) Month 1	Day 91 ( $\pm 7$ ) Month 3	Day 182 ( $\pm 7$ ) Month 6	Day 273 ( $\pm 7$ ) Month 9	Day 364 ( $\pm 7$ ) 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 Counseling	X	X				X		X	X	
Physical Examination	X	X						X	X	
Reversibility Testing	X	X								
Chest X-ray <sup>1</sup>	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	X	X	X	X	X	X	X			

Card										
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 <sup>2</sup>				X	X	X	X	X	X	
Demonstrate Proper Use of nDPI	X	X	X	X	X	X	X			

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.1 (DB2113359, Protocol Amendment 1), pg. 33-35 (Table 3)

<sup>1</sup> 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

<sup>2</sup> 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 clinical development program:

**Table 44. Applicant's Definitions of Adverse Events**

Category	Abbreviation	Definition	Comments
Adverse Event	AE	Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medical product.	
Serious Adverse Event	SAE	Any untoward medical occurrence that, at any dose, resulted in death, was life-threatening, required hospitalization or prolongation of existing hospitalization, resulted in disability/incapacity, or was a congenital anomaly/birth defect.	Consistent 21 CFR § 312.32(a)
On-treatment	n/a	Events with onset on or after the date of first dose of study drug and up to 1 day after the last recorded dose of study drug	Applies to parallel-group trials
Post-treatment	n/a	Events with an onset 2 days or more after the date of the last recorded dose of study drug	Applies to parallel-group trials

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 90-91

With two exceptions, all trials included in the core clinical development program coded adverse events according to the Medical Dictionary for Regulatory Activities (MedDRA), version 15.0 (Trial AC4115408 used version 14.1, and Trial AC4113589 used version 13.0). 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 10 clinical trials (8 integrated and 2 not integrated) in patients with COPD. These trials are categorized by the Applicant into a number of groups, as described in Table 45. While six of the ten trials evaluated the UMEC/VI combination product in addition to the UMEC, the focus of this review of safety is on the results for the monotherapy.

**Table 45. Applicant's Grouping of Trials**

Grouping	Trials
Efficacy Trials	AC4115408, DB2113361, DB213373, DB2113374
Long-Term Safety Trial	DB21133459
Exercise Trials	DB2114417, DB2114418
Additional Integrated Trial	AC4113589
All Clinical Trials	AC4115408, DB2113361, DB213373, DB2113374, DB21133459, DB2114417, DB2114418, AC4113589
Supportive Trials, not integrated	AC4113073, AC4115321

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 32-34 (Table 1); pg. 38 (Table 2)

## 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 46. These exposure data are organized by the trial groupings defined in Table 45. The main safety database for the proposed product consists of 8 clinical trials in patients with COPD (the "All Clinical Trials" grouping), and includes 2,706 patients across all treatment arms. Across the four efficacy and one long-term safety trials, 1,412 patients were treated with either UMEC 62.5 mcg or 125 mcg.

**Table 46. Summary of Exposure, UMEC Clinical Development Program**

	Placebo	UMEC 62.5	UMEC 125	Treated
	N	N	N	N
Efficacy Trials AC4115408 DB2113361 DB2113373 DB2113374	623	487	698	1808
Long-Term Safety Trial DB2113359	109	--	227	336
Exercise Trials*.# DB2114417 DB2114418	321	89	91	420
Additional Integrated Trial AC4113589	71	--	71	142
All Clinical Trials	1124	576	1087	2706

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 47 (Table 6)

Note: N=Number of patients in the ITT population; some trials included additional treatment arms to those shown here

\*Patients in these crossover trials received more than 1 treatment and are counted for each treatment received and once in the "Treated" column

#Some patients may have been enrolled in a previous trial

The duration of exposure provided by the Applicant's "All Clinical Trials" grouping of trials (i.e., the four efficacy trials, the long-term safety trial, and 3 additional trials as described in Table 45) is summarized in Table 47.

**Table 47. Summary of Exposure, Applicant's "All Clinical Trials" Grouping of Trials**

	Placebo N=1124	UMEC 62.5 N=576	UMEC 125 N=1087
<b>Exposure, days</b>			
Mean (SD)	122 (82)	128 (51)	153 (97)
Median	88	165	166
Min, Max	1, 372	1, 179	1, 375
<b>Range, n(%)</b>			
> 4 weeks	959 (85)	548 (95)	954 (88)
> 8 weeks	901 (80)	522 (91)	900 (83)
> 12 weeks	766 (68)	450 (78)	827 (76)
> 24 weeks	251 (22)	154 (27)	370 (34)
> 36 weeks	73 (6)	0	154 (14)
> 48 weeks	66 (6)	0	133 (12)
> 52 weeks	19 (2)	0	35 (3)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 51 (Table 11)

Notes: N=Number of patients in the ITT population; patients in crossover studies were counted once under each treatment received

Across the “All Clinical Trials” grouping of trials, 524 patients were treated with either UMEC 62.5 mcg or 125 mcg for at least 24 weeks, and 133 treated with UMEC 125 mcg for at least 48 weeks. In addition, as part of the UMEC/VI combination product clinical development program, 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 were treated with UMEC/VI 125 mcg/25 mcg for at least 48 weeks (data not shown). The extent of exposure was adequate for review.

The demographic and COPD disease characteristics of the ITT population from the efficacy trials are discussed in Section 6.1.2 (Table 15 and Table 16). These same characteristics for the ITT population from the long-term safety trial are provided in Table 48 and Table 49 below.

**Table 48. Demographic and selected baseline characteristics for ITT population, Long-Term Safety Trial**

	<b>Placebo N=109</b>	<b>UMEC 125 N=227</b>
<b>Age (years)</b>		
Mean	60.1	61.7
SD	8.3	9.1
Min, Max	41, 82	40, 85
<b>Sex</b>		
Male, n (%)	73 (67)	145 (64)
<b>Race*</b>		
White, n (%)	104 (95)	214 (94)
African America/African heritage, n (%)	3 (3)	13 (6)
Asian, n (%)	2 (2)	0
American Indian or Alaska native, n (%)	0	0
Native Hawaiian or other Pacific Islander, n (%)	0	0
<b>Ethnicity</b>		
Hispanic/Latino, n (%)	7 (6)	17 (7)
Not Hispanic/Latino, n (%)	102 (94)	210 (93)
<b>Height (cm)</b>		
Mean	169.8	168
SD	9.9	8.7
Min, Max	148, 196	143, 188
<b>Weight (kg)</b>		
Mean	79.7	79.0
SD	18.0	16.4
Min, Max	37, 137	47, 130

<b>BMI (kg/m<sup>2</sup>)</b>		
Mean	27.7	28.1
SD	5.9	5.9
Min, Max	13.6, 43.3	17.3, 54.6
<b>Smoking status at Screening</b>		
Current smoker, n (%)	71 (65)	148 (65)
Former smoker, n (%)	38 (35)	79 (35)

Source: Applicant's NDA 203-975 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 49. COPD disease characteristics for ITT population, Long-Term Safety Trial**

	<b>Placebo N=109</b>	<b>UMEC 125 N=227</b>
<b>GOLD stage, n</b>	109	225
I: FEV1 ≥80% predicted, n (%)	1 (<1)	0
II: 50%≤FEV1<80% predicted, n(%)	71 (65)	129 (57)
III: 30%≤FEV1<50% predicted, n (%)	37 (34)	96 (43)
IV: FEV1<30% predicted, n (%)	0	0
<b>ICS use at Screening, n</b>	109	227
ICS user, n (%)	40 (37)	73 (32)
ICS non-user, n (%)	69 (63)	154 (68)
<b>Pre-bronchodilator FEV1 (L), n</b>	108	225
Mean	1.579	1.432
SD	0.5714	0.5120
Median	1.510	1.330
Min, Max	0.46, 3.28	0.55, 3.12
<b>Reversibility to Salbutamol, n</b>	108	224
Not reversible, n (%)	72 (67)	152 (68)
Reversible, n (%)	36 (33)	72 (32)
<b>COPD Type*, n</b>	109	227
Chronic bronchitis, n (%)	74 (68)	162 (71)
Emphysema, n (%)	71 (65)	149 (66)

Source: Applicant's NDA 203-975 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 efficacy trials, the majority of patients were of white race. In contrast to the efficacy trials, more patients in the long-term safety trial were classified as having Gold Stage II disease, 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 efficacy trials (1.2). In addition, whereas the patient population in

the efficacy trials was nearly 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 efficacy and long-term safety trials, with approximately one-third of each patient population demonstrating reversibility. As with the efficacy trials, both chronic bronchitis and emphysema were well-represented.

Past and current comorbid conditions of the ITT population from the efficacy trials are discussed in Section 6.1.2 (Table 17). These same characteristics for the ITT population from the long-term safety trial are provided in (Table 50) below.

**Table 50. Comorbid Conditions for ITT population, Long-Term Safety Trial**

	Placebo N=109	UMEC 125 N=227
<b>Common Current Medical Conditions</b>		
Any condition	88 (81)	196 (86)
Cardiovascular risk factors	70 (64)	155 (68)
Cardiac disorders	37 (34)	80 (35)
Musculoskeletal and connective tissue disorders	32 (29)	64 (28)
Metabolism and nutrition disorders	18 (17)	35 (15)
Psychiatric disorders	15 (14)	36 (16)
Vascular disorders	15 (14)	26 (11)
Endocrine disorders	13 (12)	15 (7)
Nervous system disorders	11 (10)	19 (8)
<b>Common Past Medical Conditions</b>		
Any condition	49 (45)	117 (52)
Cardiovascular risk factors	19 (17)	35 (15)
Respiratory, thoracic, and mediastinal disorders	10 (9)	37 (16)
Reproductive system and breast disorders	8 (7)	22 (10)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5 (5)	19 (8)

Source: Applicant's NDA 203-975 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 125 mcg and placebo are noted for current cardiovascular risk factors, but not for current cardiac disorders.

The disposition of patients participating in efficacy trials is discussed in Section 6.1.3 (Table 18 and Table 19); disposition of patients participating in the long-term safety trial is presented in Table 51 below.

**Table 51. Subject Disposition, Long-Term Safety Trial**

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

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 54 (Table 15); Section 5.3.5.1 (DB2113359), pg. 47 (Table 9)

\*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 (39-41%). 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 arm 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 clinical development program evaluated both the dose currently proposed for approval, 62.5 mcg, as well as a higher dose, 125 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 efficacy, exercise endurance, and long-term safety trials included: serum chemistry, hematology, and 12-lead ECGs. In addition, 24-hour Holter monitoring was conducted in the 24-week placebo-controlled trials<sup>22</sup> (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 with verapamil and AC4110106, which evaluated UMEC in normal and poor CYP2D6 metabolizers. 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.

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<sup>22</sup>Trial DB2113361 and Trial DB2113373

## 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 LAMA drug class, to which umeclidinium belongs. The AESI categories included: cardiovascular adverse events, anticholinergic events, 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 16 deaths are reported for the ten trials included in the UMEC clinical development program. There were no deaths in the non-integrated supportive trials. A summary of deaths in the Applicant's "All Clinical Trials" grouping is provided in Table 52; three deaths (a patient on placebo in DB2113373 who died after trial closure, and two patients on tiotropium in Trial DB2113374) are not included in this table.

**Table 52. Summary of Deaths, UMEC Clinical Development Program**

	Placebo	UMEC 62.5	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
Efficacy Trials*	623	487	698
	2# (<1)	3 (<1)	2 (<1)
Long-Term Safety Trial	109	--	227
	1 (<1)	--	4 (2)
Exercise Trials	321	89	91
	0	0	1 (1)
Additional Integrated Trial	71	--	71
	0	--	0
All Clinical Trials	1124	576	1087
	3 (<1)	3 (<1)	7 (<1)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 108 (Table 69)

Note: n (%) = number (percentage) of deaths for each trial grouping

Note: This table includes both on-treatment and post-treatment deaths

\*Two deaths, both for patients in the tiotropium arm of Trial DB2113374, are not included.

\*A post-treatment death reported after trial closure for a patient in the placebo group of Trial DB2113373 is not included in this count

Most notable in these data are the low overall number of events, which limits their interpretability. In the efficacy trials, the percentage of patients with fatal events is <1% across all treatment groups. While the percentage of deaths reported for the UMEC 62.5 mcg treatment arm was slightly higher than that reported for placebo (0.6% vs. 0.3%), no dose-related pattern is observed, as the percentage in the higher UMEC 125 mcg treatment arm (0.3%) is the same as that for placebo. In the long-term safety trial, while there is a numerical imbalance in the number of deaths for UMEC 125 mcg as compared to placebo (4 vs. 1), the overall number of events is low. In addition, there were zero deaths in the UMEC/VI 125 mcg/25 mcg treatment arm during the long-term safety trial (data not shown). Overall, the low absolute number of deaths, the absence of dose dependence, and the lack of corresponding imbalances for the related combination product, are reassuring.

A summary of deaths, by SOC and PT, for the efficacy and long-term safety trials, is provided in Table 53 and Table 54, respectively.

**Table 53. Summary of Deaths, by SOC and PT, Efficacy Trials\*, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
<b>Any fatal AE</b>	<b>2# (&lt;1)</b>	<b>3 (&lt;1)</b>	<b>2 (&lt;1)</b>
Neoplasms benign, malignant and unspecified			
Any event	0	0	2 (<1)
Metastases to bone	0	0	1 (<1)
Metastases to CNS	0	0	1 (<1)
Non-small cell lung cancer	0	0	1 (<1)
Pancreatic carcinoma metastatic	0	0	1 (<1)
General disorders and administration site conditions			
Any event	0	1 (<1)	0
Sudden death	0	1 (<1)	0
Hepatobiliary disorders			
Any event	0	1 (<1)	0
Cholecystitis	0	1 (<1)	0
Infections and infestations			
Any event	1 (<1)	1 (<1)	0
Peritonitis	0	1 (<1)	0
Pneumonia	1 (<1)	0	0
Respiratory, thoracic, and			

mediastinal disorders			
Any event	0	1 (<1)	0
Acute respiratory failure	0	1 (<1)	0
COPD	0	1 (<1)	0
Vascular disorders			
Any event	1 (<1)	0	0
Arteriosclerosis	1 (<1)	0	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 989 (Table 2.50), pg. 110 (Table 71)

Key: AE(s)=adverse event(s); CNS=central nervous system; COPD=chronic obstructive pulmonary disease

Note: This table includes both on-treatment and post-treatment deaths

\*Two deaths, both for patients in the tiotropium arm of Trial DB2113374, are not included.

\*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 54. Summary of Deaths, by SOC and PT, Long-Term Safety Trial, ITT Population**

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

Source: Applicant's NDA 203-975 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 efficacy and long-term safety trials, there were no PTs reported more than once as fatal AEs. 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

55; the results of the adjudication for the efficacy trials and the long-term safety trial follow in Table 56 and Table 57.

**Table 55. 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 NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 120 (Table 78)

**Table 56. Adjudicated Fatal Serious Adverse Reports, Efficacy Trials\*, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
<b>Any fatal AE</b>	<b>3# (&lt;1)</b>	<b>3 (&lt;1)</b>	<b>2 (&lt;1)</b>
Cardiovascular Total	1 (<1)	0	0

Sudden death	1 (<1)	0	0
Respiratory Total	1 (<1)	1 (<1)	0
COPD exacerbation without pneumonia	1 (<1)	1 (<1)	0
Cancer Total	0	0	2 (<1)
Lung cancer	0	0	1 (<1)
Other cancer	0	0	1 (<1)
Other Total	0	1 (<1)	0
Unknown Total	1 (<1)	1 (<1)	0
Inadequate information	1 (<1)	1 (<1)	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 121 (Table 79)

\*Two deaths, both for patients in the tiotropium arm of Trial DB2113374, are not included.

\*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 60 and 61 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 57. Adjudicated Fatal Serious Adverse Reports, Long-Term Safety Trial, ITT Population**

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

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 122 (Table 80)

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 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 58.

**Table 58. Summary of Nonfatal Serious Adverse Events, UMEC Clinical Development Program**

	Placebo	UMEC 62.5	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
Efficacy Trials	623	487	698
	25 (4)	28 (6)	37 (5)
Long-Term Safety Trial	109	--	227
	7 (6)	--	15 (7)
Exercise Trials	321	89	91
	10 (3)	1 (1)	3 (3)
Additional Integrated Trial	71	--	71
	0	--	1 (1)
All Clinical Trials	1124	576	1087
	42 (4)	29 (5)	56 (5)

Source: Applicant's NDA 205-382 Submission dated December 6, 2013, Section 1.11.3 (Efficacy Information Amendment, Response to FDA Request), pg. 3 (Table 1)

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 balanced across treatment arms.

A summary of nonfatal SAEs reported for 2 or more patients in any treatment arm in the efficacy and long-term safety trials, by SOC and PT, is provided in Table 59 and Table 60, respectively.

**Table 59. Nonfatal SAE PTs Reported for ≥ 2 Patients in any Treatment Arm, by SOC and PT Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
<b>Any non-fatal SAE</b>	<b>25 (4)</b>	<b>28 (6)</b>	<b>37 (5)</b>
Respiratory, thoracic, and mediastinal disorders			
Any event	13 (2)	12 (2)	9 (1)
COPD	11 (2)	11 (2)	7 (1)
Cardiac disorders			
Any event	1 (<1)	6 (1)	8 (1)

Atrial fibrillation	0	1 (<1)	2 (<1)
Ventricular extrasystoles	0	0	2 (<1)
Infections and infestations			
Any event	3 (<1)	4 (<1)	6 (<1)
Pneumonia	3 (<1)	0	4 (<1)
Infective exacerbation of chronic airways disease	0	2 (<1)	0
General disorders and administration site conditions			
Any event	1 (<1)	0	3 (<1)
Chest pain	0	0	2 (<1)
Hepatobiliary disorders			
Any event	0	2 (<1)	0
Cholecystitis chronic	0	2 (<1)	0

Source: Applicant's NDA 205-382 Submission dated December 6, 2013, Section 1.11.3 (Efficacy Information Amendment, Response to FDA Request), pg. 5-7 (Table 3)

Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease

Note: This table includes on-treatment events

**Table 60. 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 (%)
<b>Any nonfatal SAE</b>	<b>7 (6)</b>	<b>14 (6)</b>	<b>15 (7)</b>
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)
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Source: Applicant's NDA 203-975 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 efficacy and long-term safety trials, PTs reported as nonfatal SAEs were generally balanced across treatment groups. In the efficacy trials, the PT most commonly reported as a nonfatal SAE was COPD; these events were evenly distributed between the placebo and UMEC 62.5 treatment arms, and somewhat less common for the UMEC 125 mcg arm. Most other PTs in either the efficacy or long-term safety trials were reported for only 2 patients or fewer. An imbalance in cardiac disorders between the active treatment groups (1%) and placebo (0.2%) is noted for the 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 55, 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 efficacy trials and the long-term safety trial are provided in Table 61 and Table 62, respectively.

**Table 61. Adjudicated Non-fatal SAEs, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
<b>Any nonfatal SAE</b>	<b>26 (4)</b>	<b>28 (6)</b>	<b>39 (6)</b>
Cardiovascular, Total	2 (<1)	4 (<1)	12 (2)
Myocardial infarction/ischemic heart disease	0	3 (<1)	5 (<1)
Congestive heart failure	0	0	1 (<1)
Stroke	1 (<1)	0	1 (<1)
Hemorrhagic	0	0	0
Thromboembolic	1 (<1)	0	0
Indeterminate	0	0	1 (<1)
Other cardiovascular	1 (<1)	1 (<1)	5 (<1)
Respiratory, Total	13 (2)	14 (3)	11 (2)
COPD exacerbation with pneumonia	3 (<1)	1 (<1)	4 (<1)
COPD exacerbation without pneumonia	9 (1)	12 (2)	4 (<1)
Pneumonia/RTI without COPD exacerbation	0	0	1 (<1)

Asthma-associated	0	0	0
Pulmonary embolism	0	0	1 (<1)
Other respiratory	2 (<1)	1 (<1)	1 (<1)
Other, Total	10 (2)	12 (2)	16 (2)
Unknown, Total	2 (<1)	0	0
Inadequate information	0	0	0
Indeterminate	2 (<1)	0	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 128 (Table 84)

Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease; RTI=respiratory tract infection

Note: This table includes both on-treatment and post-treatment events

**Table 62. Adjudicated Non-fatal SAEs, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
	n (%)	n (%)
<b>Any nonfatal SAE</b>	<b>7 (6)</b>	<b>15 (7)</b>
Cardiovascular, Total	2 (2)	3 (1)
Myocardial infarction/ischemic heart disease	1 (<1)	2 (<1)
Congestive heart failure	1 (<1)	0
Stroke	0	0
Hemorrhagic	0	0
Thromboembolic	0	0
Indeterminate	0	0
Other cardiovascular	1 (<1)	1 (<1)
Respiratory, Total	3 (3)	5 (2)
COPD exacerbation with pneumonia	0	1 (<1)
COPD exacerbation without pneumonia	3 (3)	2 (<1)
Pneumonia/RTI without COPD exacerbation	0	1 (<1)
Asthma-associated	0	0
Pulmonary embolism	0	0
Other respiratory	0	1 (<1)
Other, Total	2 (2)	7 (3)
Unknown, Total	1 (<1)	0
Inadequate information	0	0
Indeterminate	1 (<1)	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 1341 (Table 2.142)

Abbreviations: AE(s)=adverse event(s); COPD=chronic obstructive pulmonary disease; RTI=respiratory tract infection

Note: This table includes both on-treatment and post-treatment events

In general, adjudicated nonfatal SAEs were balanced across treatment arms in the 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 (0.6-

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) in the UMEC clinical development program is provided in Table 63. Adverse events leading to dropout reported for three or more patients (in any treatment arm) are presented in Table 64 and Table 65 for the efficacy and long-term safety trials, respectively.

**Table 63. Summary of Adverse Events Leading to Dropout, UMEC Clinical Development Program**

	Placebo	UMEC 62.5	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
Efficacy Trials	623	487	698
	26 (4)	32 (7)	44 (6)
Long-Term Safety Trial	109	--	227
	12 (11)	--	20 (9)
Exercise Trials	321	89	91
	17 (5)	2 (2)	3 (3)
Additional Integrated Trial	71	--	71
	0	--	1 (1)
All Clinical Trials	1124	576	1087
	55 (5)	34 (6)	68 (6)

Source: Applicant's NDA 205-382 Submission dated December 6, 2013, Section 1.11.3 (Efficacy Information Amendment, Response to FDA Request), pg. 10 (Table 5)

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

	Placebo	UMEC 62.5	UMEC 125
	N=623	N=487	N=698
	n (%)	n (%)	n (%)
Any AE leading to dropout	26 (4)	32 (7)	44 (6)

Respiratory, thoracic, and mediastinal disorders			
Any event	16 (3)	14 (3)	11 (2)
COPD	14 (2)	11 (2)	9 (1)
Infections and infestations			
Any event	5 (<1)	7 (1)	10 (1)
Pneumonia	4 (<1)	1 (<1)	6 (<1)
Cardiac disorders			
Any event	2 (<1)	9 (2)	8 (1)
Tachycardia	1 (<1)	3 (<1)	1 (<1)
General disorders and administration site conditions			
Any event	0	2 (<1%)	8 (1%)
Chest discomfort	0	0	3 (<1%)
Chest pain	0	0	3 (<1%)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 918-921 (Table 2.34)

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 65. 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 125 N=227
	n (%)	n (%)
<b>Any AE leading to dropout</b>	<b>12 (11)</b>	<b>20 (9)</b>
Cardiac disorders		
Any event	8 (7)	12 (5)
Ventricular extrasystoles	1 (<1)	4 (2)
Supraventricular tachycardia	1 (<1)	3 (1)
Sinus tachycardia	1 (<1)	3 (1)

Source: Applicant's NDA 203-975 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 slightly higher for the active treatment arms (6-7%) compared to placebo (4%) in the efficacy trials, but the opposite pattern is observed in the long-term safety trial. In the efficacy trials, COPD

and pneumonia are the most commonly reported AEs leading to dropout; similar percentages of patients in the placebo and UMEC treatment arms withdrew as a result of these events. Pneumonia is reviewed as an adverse event of special interest (AESI) in Section 7.3.5 of this review. An imbalance in the overall category of cardiac disorders between UMEC (1-2%) and placebo (<1%) is noted for the efficacy trials, but the opposite pattern is observed in the long-term safety trial. A detailed analysis of cardiovascular adverse events of special interest is provided in Section 7.3.5 of this review. Overall, most PTs associated with adverse events leading to dropout, in either the efficacy or long-term safety trials, were reported for fewer than 3 patients.

#### 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 efficacy and long-term safety trials. The overall incidence of adverse events by severity, for the 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 LAMA drug class, to which umeclidinium belongs. The AESI categories included: cardiovascular adverse events, anticholinergic events, 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 66.

**Table 66. Applicant's MACE criteria**

	<b>Broad Criteria</b>	<b>Narrow Criteria</b>
Ischemia/Infarction	Cardiac Ischemia Special Interest AE Subgroup <ul style="list-style-type: none"> <li>• Myocardial Infarction SMQ (excluding fatalities)</li> <li>• Other Ischemic Heart Disease SMQ (excluding fatalities)</li> </ul>	Myocardial ischemia PT Acute myocardial infarction PT
Stroke	Stroke Special Interest AE Subgroup <ul style="list-style-type: none"> <li>• CNS Hemorrhages and Cerebrovascular Conditions SMQ (excluding fatalities)</li> </ul>	Stroke Special Interest AE Subgroup <ul style="list-style-type: none"> <li>• CNS Hemorrhages and Cerebrovascular Conditions SMQ (excluding fatalities)</li> </ul>
Cardiovascular Death	Adjudicated Cardiovascular Deaths	Adjudicated Cardiovascular Deaths

The Applicant's MACE analyses were conducted using a pooled ITT population from trials evaluating UMEC with a treatment duration of at least 12 weeks: the four efficacy trials, the long-term safety trial, and the two exercise endurance trials. Results from these analyses are presented in Table 67.

**Table 67. MACE Analyses, Trials DB2113361, DB2113373, DB2113360, DB2113374, DB2114417, DB2114418, DB2113359, AC4115408, ITT Population**

	<b>Placebo</b>	<b>UMEC</b>	<b>UMEC</b>
	<b>N=1053</b>	<b>62.5</b>	<b>125</b>
	<b>SY=369</b>	<b>N=576</b>	<b>N=1016</b>
		<b>SY=202</b>	<b>SY=449</b>
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Broad-definition MACE	20 (2)	9 (2)	14 (1)
Narrow-definition MACE	7 (<1)	2 (<1)	7 (<1)
Adjudicated CV death	2 (<1)	0	1 (<1)
Non-fatal cardiac ischemia AESI	14 (1)	8 (1)	11 (1)
Non-fatal MI	1 (<1)	1 (<1)	4 (<1)
Non-fatal stroke AESI	4 (<1)	1 (<1)	2 (<1)
<b>Incidence Rate</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Broad-definition MACE	54.3	44.5	31.2

Narrow-definition MACE	19.0	9.9	15.6
Adjudicated CV death	5.4	0	2.2
Non-fatal cardiac ischemia AESI	38.0	39.5	24.5
Non-fatal MI	2.7	4.9	8.9
Non-fatal stroke AESI	10.9	4.9	4.5
<b>Total Number of MACE Events</b>	<b>Number of Events</b>		
Total broad-definition MACE Events	22	11	15
Total narrow-definition MACE Events	8	2	7

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 164 (Table 111)  
 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. Similarly, the incidence rate for adjudicated cardiovascular death and non-fatal stroke is higher for placebo compared to both UMEC 62.5 mcg and 125 mcg. 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 UMEC 125 mcg) or comparable between placebo and active treatment (for UMEC 62.5 mcg), an imbalance favoring placebo is observed for the narrow category of non-fatal myocardial infarction. This imbalance is true for both doses of UMEC compared to placebo, with incidence rates of 8.9, 4.9, and 2.7 for the UMEC 125 mcg, UMEC 62.5 mcg, and placebo arms, respectively. Similar patterns were observed in MACE analyses for UMEC/VI 125 mcg/25 mcg and UMEC/VI 62.5 mcg/25 mcg (data not shown). 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 68.

**Table 68. Cardiovascular AESI: Subgroups and Terms**

<b>Subgroup</b>	<b>Terms</b>
Acquired Long QT	PTs: conduction disorder electrocardiogram QT prolonged

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

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 134 (Table 89)

The Applicant's cardiovascular AESI analysis was conducted for the ITT populations from the efficacy trials, long-term safety trial, exercise endurance trials, and the Applicant's "All Clinical Trials" grouping of trials. The overall incidence and exposure-adjusted frequency for on-treatment cardiovascular AESIs, by trial grouping, are presented in Table 69.

**Table 69. Cardiovascular AESIs, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623 41 (7)	N=487 43 (9)	N=698 56 (8)
Long-term Safety	N=109 25 (23)	-- --	N=227 49 (22)
Exercise	N=321 8 (2)	N=89 2 (2)	N=91 1 (1)
All Clinical Trials	N=1124 78 (7)	N=576 45 (8)	N=1087 107 (10)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220 186.5	SY=183 235.6	SY=263 213.2
Long-term Safety	SY=80 311.0	-- --	SY=167 293.1
Exercise	SY=68 117.0	SY=20 100.8	SY=19 51.7
All Clinical Trials	SY=374 208.6	SY=202 222.4	SY=454 235.5

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 136 (Table 90)

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 efficacy trials the frequency is higher for UMEC versus placebo, but the magnitude of difference is greater for the UMEC 62.5 mcg to placebo comparison (235.6 vs. 186.5) and smaller for the UMEC 125 mcg to placebo comparison (213.2 vs. 186.5). In the long-term safety trial the exposure-adjusted frequency is lower for the UMEC arm compared to placebo. For the Applicant's broad grouping of "All Clinical Trials", the exposure-adjusted frequency is somewhat greater in the active treatment arms compared to placebo.

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 efficacy and long-term safety trials are presented in Table 70 and Table 71, respectively.

**Table 70. Cardiovascular AESIs (On-treatment) by Subgroup, Efficacy Trials, ITT Population**

	Placebo N=623 SY=220	UMEC 62.5 N=487 SY=183	UMEC 125 N=698 SY=263
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Acquired long QT	0	1 (<1)	0
Cardiac arrhythmias	19 (3)	22 (5)	22 (3)
Cardiac failure	6 (<1)	7 (1)	7 (1)
Cardiac ischemia	5 (<1)	7 (1)	6 (<1)
Hypertension	11 (2)	12 (2)	22 (3)
Sudden death	0	0	0
Stroke	2 (<1)	1 (<1)	1 (<1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Acquired long QT	0	5.5	0
Cardiac arrhythmias	86.4	120.5	83.8
Cardiac failure	27.3	38.3	26.7
Cardiac ischemia	22.7	38.3	22.8
Hypertension	50.0	65.7	83.8
Sudden death	0	0	0
Stroke	9.1	5.5	3.8

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 137 (Table 92)

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

	Placebo N=109 SY=80	UMEC 125 N=227 SY=167
<b>Incidence</b>	<b>Number (%) of Subjects</b>	
Acquired long QT	0	0
Cardiac arrhythmias	17 (16)	39 (17)
Cardiac failure	1 (<1)	4 (2)
Cardiac ischemia	4 (4)	4 (2)
Hypertension	7 (6)	6 (3)
Sudden death	0	0
Stroke	0	1 (<1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>	
Acquired long QT	0	0
Cardiac arrhythmias	211.5	233.3
Cardiac failure	12.4	23.9
Cardiac ischemia	49.8	23.9
Hypertension	87.1	35.9
Sudden death	0	0
Stroke	0	6.0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 150 (Table 101)

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 efficacy trials the results for the comparison between UMEC 62.5 mcg and placebo demonstrate small imbalances favoring placebo for acquired long QT, cardiac arrhythmias, cardiac failure, and cardiac ischemia, but comparable frequencies between placebo and the UMEC 125 mcg arm. An imbalance favoring placebo compared to both UMEC arms is noted for the hypertension subgroup; mean change in blood pressure is discussed in Section 7.4.3. In contrast, the frequency of stroke was higher for placebo compared to active treatment. There were no cases of sudden death observed in any of the treatment arms. In the long-term safety trial, imbalances favoring placebo are seen in the cardiac arrhythmias, cardiac failure, and stroke subgroups, while the opposite trend (imbalances favoring active) are observed for cardiac ischemia and hypertension. There were no cases of acquired long QT or sudden death in the long-term safety trial.

Serious Cardiovascular AESIs

The overall incidence and exposure-adjusted frequency of serious on-treatment cardiovascular AEs observed in the efficacy and long-term safety trial is provided in Table 72.

**Table 72. Serious Cardiovascular AEs, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	2 (<1)	7 (1)	10 (1)
Long-term Safety	N=109	--	N=227
	2 (2)	--	5 (2)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	9.1	38.3	38.1
Long-term Safety	SY=80	--	SY=167
	24.9	--	29.9

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 148 (Table 99); pg. 1309 (Table 2.125); pg. 155 (Table 104); pg. 1314 (Table 2.127)

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 efficacy trials an imbalance favoring placebo is seen for both doses of UMEC. In the long-term safety trial, the exposure-adjusted frequency for serious cardiovascular AEs is slightly higher for the UMEC 125 mcg monotherapy compared to placebo.

Serious on-treatment cardiovascular AEs by subgroup, for the efficacy and long term safety trials, are presented in Table 73 and Table 74, respectively.

**Table 73. Serious Cardiovascular AEs, by Subgroup, Efficacy Trials, ITT Population**

	Placebo N=623 SY=220	UMEC 62.5 N=487 SY=183	UMEC 125 N=698 SY=263
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Acquired long QT	0	1 (<1)	0
Cardiac arrhythmias	0	4 (<1)	4 (<1)
Cardiac failure	0	0	0
Cardiac ischemia	1 (<1)	4 (<1)	4 (<1)
Hypertension	0	0	1 (<1)
Sudden death	0	0	0

Stroke	1 (<1)	0	1 (<1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Acquired long QT	0	5.5	0
Cardiac arrhythmias	0	21.9	15.2
Cardiac failure	0	0	0
Cardiac ischemia	4.5	21.9	15.2
Hypertension	0	0	3.8
Sudden death	0	0	0
Stroke	4.5	0	3.8

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 148 (Table 99); pg. 1309 (Table 2.125)

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 74. Serious Cardiovascular AESIs by Subgroup, Long-term Safety Trial, ITT Population**

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

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 155 (Table 104); pg. 1314 (Table 2.127)

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 observed in the efficacy trials is largely driven by an imbalance in the cardiac arrhythmias and cardiac ischemia subgroups. No such patterns are observed for the long-term safety trial. To explore these imbalances

further, these two subgroups of serious cardiovascular AEs, by preferred term, are presented for the efficacy trials in Table 75 and Table 76.

**Table 75. Serious Cardiovascular AEs, Cardiac Ischemia Subgroup, by Preferred Term, Efficacy Trials, ITT Population**

	Placebo N=623 SY=220	UMEC 62.5 N=487 SY=183	UMEC 125 N=698 SY=263
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Any term	1 (<1)	4 (<1)	4 (<1)
Acute myocardial infarction	0	0	1 (<1)
Angina pectoris	1 (<1)	0	0
Angina unstable	0	1 (<1)	1 (<1)
Coronary artery disease	0	2 (<1)	0
Coronary artery stenosis	0	0	1 (<1)
Myocardial infarction	0	0	1 (<1)
Troponin increased	0	1 (<1)	0
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Any term	4.5	21.9	15.2
Acute myocardial infarction	0	0	3.8
Angina pectoris	4.5	0	0
Angina unstable	0	5.5	3.8
Coronary artery disease	0	11.0	0
Coronary artery stenosis	0	0	3.8
Myocardial infarction	0	0	3.8
Troponin increased	0	5.5	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 148 (Table 99); pg. 1309 (Table 2.125)

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. Serious Cardiovascular AEs, Cardiac Arrhythmias Subgroup, by Preferred Term, Efficacy Trials, ITT Population**

	Placebo N=623 SY=220	UMEC 62.5 N=487 SY=183	UMEC 125 N=698 SY=263
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Any term	0	4 (<1)	4 (<1)
Atrial fibrillation	0	1 (<1)	2 (<1)
Bradycardia	0	1 (<1)	0

Electrocardiogram QT prolonged	0	1 (<1)	0
Syncope	0	1 (<1)	0
Tachycardia	0	1 (<1)	0
Ventricular extrasystoles	0	0	2 (<1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Any term	0	21.9	15.2
Atrial fibrillation	0	5.5	7.6
Bradycardia	0	5.5	0
Electrocardiogram QT prolonged	0	5.5	0
Syncope	0	5.5	0
Tachycardia	0	5.5	0
Ventricular extrasystoles	0	0	7.6

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 148 (Table 99); pg. 1309 (Table 2.125)

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 the preferred terms for “acute myocardial infarction” and “myocardial infarction” were observed only for the UMEC 125 mcg arm; however, most striking is the very low number of events (n=1 for each term). There were no notable patterns on examination of the preferred terms for the cardiac arrhythmia subgroup.

### **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 are demonstrated. 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. In the cardiovascular AESI analysis, imbalances favoring placebo are observed primarily in the efficacy trials; these include imbalances in serious events overall, as well as in the cardiac ischemia and cardiac arrhythmia subgroups of serious cardiovascular AESIs.

The review of MACE and cardiovascular AESI analyses for the UMEC/VI 125 mcg/25 mcg and 62.5 mcg/25 mcg products revealed similar imbalances in cardiovascular events, particularly those pertaining to cardiac ischemia. However, in both the review of the combination product and in this review, several features of the observed data decrease concern regarding the numerical imbalances observed. The imbalances identified for events pertaining to cardiac ischemia in the cardiovascular AESI analysis are observed in the 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 efficacy trials, but also in

the long-term safety trial which evaluated the higher UMEC and UMEC/VI doses 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 51 for placebo and UMEC data; data for UMEC/VI not shown); 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 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 77 and

Table 78, 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 77. Anticholinergic Effects AESIs, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	25 (4)	18 (4)	30 (4)
Long-term Safety	N=109	--	N=227
	2 (2)	--	5 (2)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	113.7	98.6	114.2
Long-term Safety	SY=80	--	SY=167
	24.9	--	29.9

Source: Applicant’s NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 176 (Table 117)

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 78. Urinary Retention AESIs, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	0	0	2 (<1)
Long-term Safety	N=109	--	N=227
	0	--	0
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	0	0	7.6
Long-term Safety	SY=80	--	SY=167
	0	--	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 1270 (Table 2.113); pg. 1276 (Table 2.115); pg. 1286 (Table 2.117); pg. 1294 (Table 2.119)

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 79). A small numerical imbalance favoring placebo was observed for the UMEC 125 mcg in the efficacy trials, but not in the long-term safety trial.

**Table 79. Ocular AESIs, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	5 (<1)	3 (<1)	8 (1)
Long-term Safety	N=109	--	N=227
	1 (<1)	--	1 (<1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	22.7	16.4	30.5
Long-term Safety	SY=80	--	SY=167
	12.4	--	6.0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 166 (Table 112)

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 80). The overall incidence of gallbladder disorders AESIs was low across the clinical program.

**Table 80. Gallbladder Disorders AESI, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	1 (<1)	3 (<1)	0
Long-term Safety	N=109	--	N=227
	0	--	2 (<1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	4.5	16.4	0
Long-term Safety	SY=80	--	SY=167
	0	--	12.0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 170 (Table 115)

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 81). The overall incidence of intestinal obstruction AESIs was low across the clinical program.

**Table 81. Intestinal Obstruction AESI, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	2 (<1)	0	0
Long-term Safety	N=109	--	N=227
	0	--	0
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	9.1	0	0
Long-term Safety	SY=80	--	SY=167
	0	--	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 1271 (Table 2.113); pg. 1277 (Table 2.115); pg. 1288 (Table 2.117)

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)

### **Pneumonia and Lower Respiratory Tract Infection**

Adverse events related to pneumonia and lower respiratory tract infections excluding pneumonia (LRTI) 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. The overall results for pneumonia and LRTI (excluding pneumonia), each by trial grouping, are provided in Table 82 and Table 83, respectively.

**Table 82. Pneumonia AESI, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	4 (<1)	3 (<1)	10 (1)
Long-term Safety	N=109	--	N=227
	0	--	7 (3)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	18.2	16.4	38.1
Long-term Safety	SY=80	--	SY=167
	0	--	41.9

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 182 (Table 122)

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 83. LRTI AESI (excluding pneumonia), by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	4 (<1)	3 (<1)	12 (2)
Long-term Safety	N=109	--	N=227
	2 (2)	--	6 (3)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	18.2	21.9	45.7
Long-term Safety	SY=80	--	SY=167
	24.9	--	35.9

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 183 (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)

For both pneumonia and LRTI (excluding pneumonia) AESIs an imbalance favoring placebo compared to the higher UMEC dose is observed; this is seen in both the efficacy and long-term safety trials. To further explore these findings, serious pneumonia and LRTI (excluding pneumonia) AESI were examined. These data, by trial grouping, are presented in Table 84 and Table 85.

**Table 84. Serious Pneumonia AESI, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	4 (<1)	3 (<1)	5 (<1)
Long-term Safety	N=109	--	N=227
	0	--	3 (1)
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	18.2	16.4	19.0
Long-term Safety	SY=80	--	SY=167
	0	--	17.9

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 187 (Table 128); pg. 187 (Table 129); pg. 1305 (Table 2.123); pg. 1315 (Table 2.127)

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)

**Table 85. Serious LRTI (excluding pneumonia) AESI, by Trial Grouping, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
<b>Incidence</b>	<b>Number (%) of Subjects</b>		
Efficacy	N=623	N=487	N=698
	0	2 (<1)	0
Long-term Safety	N=109	--	N=227
	0	--	0
<b>Exposure-adjusted frequency</b>	<b>Number of Subjects with Events per 1000 Subject-Years</b>		
Efficacy	SY=220	SY=183	SY=263
	0	11.0	0
Long-term Safety	SY=80	--	SY=167
	0	--	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 187 (Table 128); pg. 187 (Table 129); pg. 1305 (Table 2.123); pg. 1315 (Table 2.127)

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)

When serious pneumonia AESIs are examined, the imbalance between active and placebo in the efficacy and long-term safety trial persists, but the magnitude of the imbalance is attenuated. The number of serious LRTI (excluding pneumonia) AESIs is too small to discern any patterns.

Similar findings were observed in the UMEC/VI clinical development program, although those analyses combined the evaluation of pneumonia and LRTI AESIs.

Given the known association between ICS/LABA combination products and pneumonia in COPD, it is useful to examine the incidence of pneumonia AESIs by ICS use. This specific analysis was not provided in the NDA for umeclidinium; however, an analysis of pneumonia and LRTI AESIs combined, by ICS use, was provided in the NDA for UMEC/VI (data not shown). For the overall category of LRTI and Pneumonia AESIs, the patterns observed were generally irrespective of ICS use, with small numerical imbalances favoring placebo noted for several treatment groups.

In summary, while an imbalance in overall Pneumonia and LRTI (excluding pneumonia) AESIs favoring placebo is noted in the UMEC clinical development program, the attenuated magnitude of the imbalance for serious pneumonia AESIs, along with the overall low number of serious events, 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 efficacy and long-term safety trials are presented in Table 86 and Table 87.

**Table 86. Common Adverse Events Reported for ≥ 3% Patients in any Treatment Arm, by PT, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
<b>Any AE</b>	<b>288 (46)</b>	<b>243 (50)</b>	<b>376 (54)</b>
Headache	65 (10)	37 (8)	72 (10)
Nasopharyngitis	55 (9)	37 (8)	50 (7)
Cough	24 (4)	16 (3)	34 (5)
URTI	21 (3)	23 (5)	25 (4)
Back pain	24 (4)	10 (2)	27 (4)
Hypertension	10 (2)	10 (2)	19 (3)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 97 (Table 58)

Note: This table includes on-treatment AEs

Abbreviations: AE(s)=adverse event(s); URTI=upper respiratory tract infection

**Table 87. Common Adverse Events Reported for ≥ 3% Patients in any Treatment Arm, by PT, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
	n (%)	n (%)
<b>Any AE</b>	<b>57 (52)</b>	<b>132 (58)</b>
Headache	9 (8)	25 (11)
Nasopharyngitis	5 (5)	20 (9)
Ventricular Extrasystoles	5 (5)	12 (5)
Extrasystoles	4 (4)	10 (4)
Back pain	3 (3)	9 (4)
Hypertension	5 (5)	4 (2)
Sinusitis	3 (3)	6 (3)
Influenza	5 (5)	5 (2)
Cough	1 (<1)	6 (3)
URTI	3 (3)	8 (4)
COPD	3 (3)	6 (3)
Ventricular tachycardia	4 (4)	3 (1)
Supraventricular tachycardia	1 (<1)	6 (3)
Supraventricular extrasystoles	1 (<1)	6 (3)
Sinus tachycardia	1 (<1)	6 (3)
Dyspnea	3 (3)	0
Pneumonia	0	6 (3)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 100 (Table 60)

Note: This table includes on-treatment AEs

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

A small imbalance favoring placebo in the overall percentage of patients reporting AEs is noted in both the efficacy and long-term safety trials. An imbalance of at least 1% favoring placebo over either UMEC group is observed for the events of cough, upper respiratory tract infection, and hypertension in the efficacy trials, and for the events of headache, nasopharyngitis, back pain, cough, upper respiratory tract infection, supraventricular tachycardia, supraventricular extrasystoles, sinus tachycardia, and pneumonia in the long-term safety trial.

#### 7.4.2 Laboratory Findings

**Chemistry**

The percentages of patients with shifts to low or high values in chemistry parameters are presented in Table 88 for the efficacy trials and in Table 89 for the long-term safety trial.

**Table 88. Shift Table of Chemistry Parameters, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
Alanine aminotransferase N	585	457	667
To High, n (%)	17 (3)	10 (2)	22 (3)
Albumin N	585	457	668
To Low, n (%)	1 (<1)	1 (<1)	1 (<1)
To High, n (%)	8 (1)	3 (<1)	9 (1)
Alkaline phosphatase N	585	457	667
To High, n (%)	18 (3)	16 (4)	18 (3)
Aspartate aminotransferase N	584	457	668
To High, n (%)	13 (2)	9 (2)	20 (3)
Bicarbonate N	584	457	668
To Low, n (%)	43 (7)	47 (10)	55 (8)
To High, n (%)	0	2 (<1)	1 (<1)
Bilirubin, Total N	585	457	668
To High, n (%)	4 (<1)	3 (<1)	9 (1)
Bilirubin, Direct N	585	457	668
To High, n (%)	3 (<1)	2 (<1)	3 (<1)
Bilirubin, Indirect N	585	457	668
To High, n (%)	0	1 (<1)	3 (<1)
Calcium N	584	457	668
To Low, n (%)	12 (2)	13 (3)	14 (2)
To High, n (%)	16 (3)	11 (2)	25 (4)
Chloride N	585	457	667
To Low, n (%)	14 (2)	3 (<1)	6 (<1)
To High, n (%)	25 (4)	19 (4)	31 (5)

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Creatine kinase			
N	584	457	668
To High, n (%)	20 (3)	10 (2)	28 (4)
Creatinine			
N	585	457	668
To Low, n (%)	42 (7)	41 (9)	51 (8)
To High, n (%)	7 (1)	9 (2)	3 (<1)
GGT			
N	585	457	667
To High, n (%)	34 (6)	16 (4)	39 (6)
Glucose			
N	585	457	668
To Low, n (%)	16 (3)	18 (4)	30 (4)
To High, n (%)	79 (14)	65 (14)	91 (14)
Phosphorus			
N	585	457	667
To Low, n (%)	30 (5)	16 (4)	17 (3)
To High, n (%)	28 (5)	25 (5)	35 (5)
Potassium			
N	584	457	668
To Low, n (%)	10 (2)	5 (1)	5 (<1)
To High, n (%)	23 (4)	16 (4)	21 (3)
Sodium			
N	585	457	667
To Low, n (%)	18 (3)	14 (3)	14 (2)
To High, n (%)	11 (2)	5 (1)	9 (1)
Total Protein			
N	585	457	668
To Low, n (%)	6 (1)	1 (<1)	2 (<1)
To High, n (%)	3 (<1)	0	2 (<1)
Urea (BUN)			
N	585	457	668
To Low, n (%)	6 (1)	3 (<1)	11 (2)
To High, n (%)	23 (4)	16 (4)	19 (3)
Uric acid			
N	583	455	668
To Low, n (%)	21 (4)	15 (3)	19 (3)
To High, n (%)	34 (6)	14 (3)	22 (3)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 1508-1527 (Table 3.01)

Note: This includes labs performed at any time post-baseline, including at scheduled, unscheduled, and early withdrawal visits

**Table 89. Shift Table of Chemistry Parameters, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
Alanine aminotransferase		
N	99	217
To High, n (%)	6 (6)	15 (7)
Albumin		
N	99	217
To Low, n (%)	0	1 (<1)
To High, n (%)	3 (3)	5 (2)
Alkaline phosphatase		
N	99	217
To Low, n (%)	0	0
To High, n (%)	7 (7)	7 (3)
Aspartate aminotransferase		
N	99	217
To High, n (%)	6 (6)	12 (6)
Bicarbonate		
N	99	217
To Low, n (%)	14 (14)	19 (9)
To High, n (%)	0	0
Bilirubin, Total		
N	99	217
To High, n (%)	1 (1)	7 (3)
Bilirubin, Direct		
N	99	217
To High, n (%)	0	3 (1)
Bilirubin, Indirect		
N	99	217
To High, n (%)	0	2 (<1)
Calcium		
N	99	216
To Low, n (%)	1 (1)	4 (2)
To High, n (%)	11 (11)	11 (5)
Chloride		
N	99	217
To Low, n (%)	1 (1)	3 (1)
To High, n (%)	12 (12)	20 (9)
Creatine kinase		
N	99	217
To High, n (%)	6 (6)	23 (11)

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Creatinine		
N	99	217
To Low, n (%)	12 (12)	33 (15)
To High, n (%)	1 (1)	7 (3)
GGT		
N	99	217
To High, n (%)	8 (8)	20 (9)
Glucose		
N	99	217
To Low, n (%)	6 (6)	3 (1)
To High, n (%)	13 (13)	37 (17)
Phosphorus		
N	98	216
To Low, n (%)	6 (6)	8 (4)
To High, n (%)	9 (9)	17 (8)
Potassium		
N	99	217
To Low, n (%)	1 (1)	5 (2)
To High, n (%)	9 (9)	22 (10)
Sodium		
N	99	217
To Low, n (%)	4 (4)	5 (2)
To High, n (%)	5 (5)	4 (2)
Total Protein		
N	99	217
To Low, n (%)	1 (1)	2 (<1)
To High, n (%)	0	3 (1)
Urea (BUN)		
N	99	217
To Low, n (%)	3 (3)	8 (4)
To High, n (%)	6 (6)	9 (4)
Uric acid		
N	99	216
To Low, n (%)	1 (1)	6 (3)
To High, n (%)	14 (14)	19 (9)

Source: Applicant's NDA 203-975 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 efficacy and long-term safety trials, with some exceptions, which are noted below.

### ***Creatine kinase***

In the long-term safety trial there is an increase in the percentage of patients with a creatine kinase shift to high (11% vs. 6% for UMEC 125 mcg and placebo, respectively). Similar findings were noted in both the efficacy and long-term safety trials in the UMEC/VI clinical program (data not shown). 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 efficacy trials alone there was a small increase in the percentage of patients with a bicarbonate shift to low. In the long-term safety trial alone there was a small increase in the percentage of patients with a creatinine shift to low, and a glucose shift to high. In general, the small magnitude of these imbalances is reassuring.

### **Hematology**

The percentages of patients with shifts to low or high values in chemistry parameters are presented in Table 90 for the efficacy trials and in Table 91 for the long-term safety trial.

**Table 90. Shift Table of Hematology Parameters, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
WBC Count			
N	583	451	668
To Low, n (%)	6 (1)	5 (1)	6 (<1)
To High, n (%)	47 (8)	27 (6)	51 (8)
Lymphocytes (percentage)			
N	579	449	666
To Low, n (%)	57 (10)	54 (12)	71 (11)
To High, n (%)	10 (2)	6 (1)	14 (2)
Neutrophils (percentage)			
N	579	449	666
To Low, n (%)	7 (1)	12 (3)	18 (3)
To High, n (%)	63 (11)	55 (12)	75 (11)
Neutrophils (ANC)			
N	579	449	666
To Low, n (%)	3 (<1)	8 (2)	17 (3)
To High, n (%)	37 (6)	33 (7)	44 (7)
Eosinophils (percentage)			
N	579	449	666

To High, n (%)	40 (7)	25 (6)	39 (6)
Monocytes (percentage)			
N	579	449	666
To High, n (%)	23 (4)	25 (6)	31 (5)
Basophils (percentage)			
N	579	449	666
To High, n (%)	0	0	2 (<1)
Hemoglobin			
N	584	452	670
To Low, n (%)	30 (5)	25 (6)	17 (3)
To High, n (%)	15 (3)	14 (3)	11 (2)
Platelet Count			
N	571	442	658
To Low, n (%)	7 (1)	7 (2)	11 (2)
To High, n (%)	14 (2)	5 (1)	6 (<1)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 1548-1558 (Table 3.03)

Note: This includes labs performed at any time post-baseline, including at scheduled, unscheduled, and early withdrawal visits

**Table 91. Shift Table of Hematology Parameters, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
WBC Count		
N	99	217
To Low, n (%)	1 (1)	5 (2)
To High, n (%)	9 (9)	20 (9)
Lymphocytes (percentage)		
N	99	217
To Low, n (%)	11 (11)	21 (10)
To High, n (%)	5 (5)	12 (6)
Neutrophils (percentage)		
N	99	217
To Low, n (%)	3 (3)	12 (6)
To High, n (%)	11 (11)	30 (14)
Eosinophils (percentage)		
N	99	217
To High, n (%)	9 (9)	14 (6)
Monocytes (percentage)		
N	99	217
To High, n (%)	5 (5)	18 (8)
Basophils (percentage)		

N	99	217
To High, n (%)	0	0
Hemoglobin		
N	99	217
To Low, n (%)	8 (8)	27 (12)
To High, n (%)	2 (2)	11 (5)
Platelet Count		
N	99	217
To Low, n (%)	4 (4)	6 (3)
To High, n (%)	1 (1)	3 (1)

Source: Applicant's NDA 203-975 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 efficacy and long-term safety trials. Several numerical imbalances are noted in the long-term safety trial (neutrophils to either low or high, monocytes to high, and hemoglobin to low or high), but the magnitude of these imbalances is generally small.

### 7.4.3 Vital Signs

Mean changes from baseline in systolic blood pressure, diastolic blood pressure, and heart rate observed in the efficacy and long-term safety trials are provided in Table 92 and Table 93, respectively.

**Table 92. Least Squares Mean Changes from Baseline in Vital Signs, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
<b>Systolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline</b>			
Day 1			
10 min	-0.4 (0.38)	-0.1 (0.47)	0.5 (0.38)
45 min	-0.9 (0.40)	-0.7 (0.49)	-0.2 (0.39)
Day 84			
Predose	0.0 (0.56)	-1.5 (0.67)	-0.9 (0.55)
10 min	-1.2 (0.56)	-1.9 (0.67)	-1.2 (0.54)
45 min	-1.6 (0.55)	-2.0 (0.66)	-1.0 (0.54)
Day 168			
Predose	0.6 (0.67)	1.2 (0.83)	0.2 (0.65)
10 min	-0.3 (0.64)	-0.4 (0.78)	0.3 (0.61)
45 min	-0.1 (0.65)	0.7 (0.79)	-0.6 (0.62)

<b>Diastolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline</b>			
Day 1			
10 min	0.0 (0.26)	0.3 (0.33)	0.2 (0.26)
45 min	-0.1 (0.27)	-0.2 (0.34)	-0.1 (0.27)
Day 84			
Predose	0.2 (0.36)	-0.7 (0.43)	-1.0 (0.35)
10 min	-0.5 (0.36)	-0.6 (0.43)	-1.1 (0.35)
45 min	-0.6 (0.35)	-0.8 (0.42)	-1.0 (0.34)
Day 168			
Predose	0.2 (0.42)	0.2 (0.51)	-0.2 (0.40)
10 min	-0.5 (0.41)	-0.9 (0.51)	-0.1 (0.40)
45 min	-0.9 (0.40)	-0.1 (0.49)	-1.0 (0.39)
<b>Heart Rate (bpm), LS Mean Change (SE) from Baseline</b>			
Day 1			
10 min	-2.3 (0.25)	-2.8 (0.31)	-2.7 (0.25)
45 min	-3.3 (0.28)	-3.8 (0.34)	-3.8 (0.27)
Day 84			
Predose	0.5 (0.42)	0.2 (0.5)	-0.9 (0.40)
10 min	-2.0 (0.41)	-2.8 (0.49)	-3.7 (0.39)
45 min	-3.1 (0.41)	-3.9 (0.49)	-4.4 (0.40)
Day 168			
Predose	1.1 (0.47)	0.2 (0.58)	-0.7 (0.45)
10 min	-1.4 (0.46)	-2.6 (0.56)	-2.8 (0.44)
45 min	-2.4 (0.47)	-3.1 (0.57)	-3.9 (0.45)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 217 (Table 155)

**Table 93. Least Squares Mean Change from Baseline in Vital Signs, Long-Term Safety Trial, ITT Population**

	<b>Placebo N=109</b>	<b>UMEC 125 N=227</b>
<b>Systolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline</b>		
Day 1		
10 min	-0.9 (0.8)	-0.2 (0.6)
45 min	-0.5 (0.9)	-1.1 (0.6)
Month 12		
Predose	0.4 (1.6)	-0.4 (1.2)
10 min	-0.3 (1.4)	0.1 (1.0)
45 min	-1.0 (1.6)	-1.2 (1.2)
<b>Diastolic Blood Pressure (mmHg), LS Mean Change (SE) from Baseline</b>		
Day 1		
10 min	0.4 (0.6)	-0.2 (0.4)
45 min	-0.2 (0.6)	-1.0 (0.4)

Month 12		
Predose	0.7 (1.1)	-0.2 (0.8)
10 min	-1.4 (1.0)	-0.4 (0.7)
45 min	-1.4 (1.0)	-0.7 (0.7)
<b>Heart Rate (bpm), LS Mean Change (SE) from Baseline</b>		
Day 1		
10 min	-2.8 (0.6)	-2.5 (0.4)
45 min	-4.1 (0.6)	-4.1 (0.4)
Month 12		
Predose	-0.5 (1.2)	-0.2 (0.8)
10 min	-1.3 (1.1)	-1.4 (0.8)
45 min	-2.0 (1.1)	-3.2 (0.8)

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 336-337 (Table 240)

For both the 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 a dedicated study evaluating potential effects on cardiac conduction (i.e. "Thorough QT" study); 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 efficacy and long-term safety trials are provided in Table 94 and Table 95, respectively.

**Table 94. Least Squares Mean Changes from Baseline in ECG Parameters, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
<b>Heart Rate (bpm), LS Mean Change (SE) from Baseline</b>			
Day 1			
10 min	-3.4 (0.24)	-3.0 (0.30)	-3.6 (0.24)
45 min	-4.3 (0.26)	-5.0 (0.33)	-5.4 (0.26)
Day 84			

Predose	0.9 (0.43)	0.6 (0.52)	-1.0 (0.42)
10 min	-2.8 (0.43)	-4.2 (0.51)	-4.8 (0.41)
45 min	-4.2 (0.42)	-4.4 (0.50)	-5.6 (0.41)
Day 168			
Predose	0.8 (0.48)	0.2 (0.59)	-0.4 (0.46)
10 min	-2.5 (0.49)	-3.3 (0.60)	-3.5 (0.47)
45 min	-3.2 (0.48)	-3.8 (0.58)	-5.0 (0.46)
<b>PR (msec), LS Mean Change (SE) from Baseline</b>			
Day 1			
10 min	0.4 (0.39)	0.8 (0.48)	-0.4 (0.38)
45 min	0.1 (0.41)	0.6 (0.51)	0.6 (0.41)
Day 84			
Predose	-1.1 (0.58)	-0.3 (0.69)	0.5 (0.56)
10 min	-0.61 (0.61)	0.7 (0.73)	-0.2 (0.59)
45 min	-1.0 (0.60)	1.0 (0.72)	0.8 (0.58)
Day 168			
Predose	-1.2 (0.67)	-0.8 (0.82)	0.6 (0.65)
10 min	-1.6 (0.71)	0.5 (0.87)	0.8 (0.68)
45 min	-0.9 (0.70)	0.1 (0.85)	0.9 (0.67)
<b>QTcF (msec), LS Mean Change (SE) from Baseline</b>			
Day 1			
10 min	-0.4 (0.49)	0.7 (0.60)	-0.8 (0.48)
45 min	-0.7 (0.48)	0.5 (0.60)	0.2 (0.48)
Day 84			
Predose	-1.1 (0.68)	-0.7 (0.81)	0.5 (0.65)
10 min	-0.6 (0.71)	-1.4 (0.84)	0.4 (0.68)
45 min	-0.7 (0.70)	0.0 (0.83)	0.7 (0.67)
Day 168			
Predose	-0.4 (0.77)	-1.2 (0.94)	0.3 (0.74)
10 min	-1.0 (0.82)	-1.4 (1.00)	-0.6 (0.78)
45 min	-1.1 (0.82)	-2.1 (1.00)	0.1 (0.79)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 227 (Table 164); pg. 229 (Table 166); pg. 230 (Table 167)

**Table 95. Least Squares Mean Changes from Baseline in ECG Parameters, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
<b>Heart Rate (bpm), LS Mean Change (SE) from Baseline</b>		
Day 1		
10 min	-2.4 (0.5)	-2.8 (0.3)
45 min	-4.0 (0.6)	-4.5 (0.4)
Month 12		

Predose	0.9 (1.1)	0.4 (0.8)
10 min	-0.2 (1.1)	-1.1 (0.8)
45 min	-1.5 (1.2)	-2.6 (0.9)
<b>PR (msec), LS Mean Change (SE) from Baseline</b>		
Day 1		
10 min	0.4 (0.9)	1.5 (0.6)
45 min	1.0 (1.0)	1.4 (0.7)
Month 12		
Predose	-3.9 (1.6)	-3.8 (1.1)
10 min	-5.1 (1.6)	-2.6 (1.1)
45 min	-3.8 (1.7)	-2.6 (1.1)
<b>QTcF (msec), LS Mean Change (SE) from Baseline</b>		
Day 1		
10 min	-0.6 (1.0)	-1.0 (0.7)
45 min	-0.3 (1.1)	-0.2 (0.8)
Month 12		
Predose	-2.8 (2.1)	-0.1 (1.5)
10 min	-3.3 (2.0)	0.5 (1.5)
45 min	-2.6 (2.0)	-0.5 (1.4)

Source: Applicant's NDA 203-975 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 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 96 for the efficacy trials and Table 97 for the long-term safety trial.

**Table 96. Clinically Significant Abnormalities on ECG at Any Time Post-Baseline, Overall and Reported for  $\geq$  3% of Patients, Efficacy Trials, ITT Population**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
	n (%)	n (%)	n (%)
<b>Any clinically significant abnormality</b>	<b>135 (22)</b>	<b>89 (18)</b>	<b>127 (18)</b>
ST depression	37 (6)	29 (6)	32 (5)
Frequent VPD $\geq$ 3	27 (4)	17 (3)	24 (3)
Ectopic supraventricular beats	16 (3)	16 (3)	23 (3)
RBBB with QTcF <530 msec	24 (4)	10 (2)	20 (3)
T waves flat	16 (3)	10 (2)	17 (2)
Ectopic supraventricular rhythm	12 (2)	10 (2)	18 (3)

Short PR interval	15 (2)	15 (3)	10 (1)
Occasional VPD<3	11 (2)	13 (3)	14 (2)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 234-235 (Table 169)

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 97. Clinically Significant Abnormalities on ECG at Any Time Post-Baseline, Overall and Reported for ≥ 3% of Patients, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
	n (%)	n (%)
<b>Any clinically significant abnormality</b>	<b>25 (23)</b>	<b>58 (26)</b>
ST depression	13 (12)	16 (7)
Frequent VPD≥3	1 (<1)	13 (6)
T waves flat	5 (5)	11 (5)
T wave inversion	3 (3)	10 (4)
RBBB with QTcF <530 msec	2 (2)	7 (3)
Ectopic supraventricular beats	1 (<1)	9 (4)
First degree AV block	1 (<1)	6 (3)
Short PR interval	3 (3)	6 (3)
Ectopic supraventricular rhythm	3 (3)	7 (3)

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 365-366 (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 is slightly higher for patients receiving placebo compared to active treatment in the efficacy trials; the reverse is observed in the long-term safety trial. 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 efficacy trials; several small numerical imbalances favoring placebo are noted for the long-term safety trial (frequent ventricular premature depolarizations, ectopic supraventricular beats).

### **24-hour Holter Monitoring**

Twenty-hour Holter monitoring was conducted in the 24-week placebo-controlled trials<sup>23</sup> (for a subset of approximately 13% of patients) as well as in the long-term safety trial. In the 24-week 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 98 and Table 99 for the 24-week placebo-controlled and long-term safety trials, respectively.

<sup>23</sup>Trial DB2113361 and Trial DB2113373

**Table 98. Summary of 24-Hour Holter Interpretations, 24-week Placebo-Controlled Trials, Subset Population**

	Placebo N=73	UMEC 62.5 N=54	UMEC 125 N=53
	n (%)	n (%)	n (%)
<b>Screening</b>			
n	73	54	53
Any clinically significant abnormality	26 (36)	18 (33)	15 (28)
<b>Post-baseline*</b>			
n	72	54	53
Any clinically significant abnormality	43 (60)	30 (56)	29 (55)
<b>Change from Screening to Post-baseline*</b>			
n	72	54	53
Unfavorable clinically significant change	28 (39)	20 (37)	22 (42)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 256 (Table 188)

\*This includes Holters conducted at any time after screening, both scheduled and unscheduled

**Table 99. Summary of 24-Hour Holter Interpretations, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
	n (%)	n (%)
<b>Screening</b>		
n	109	227
Any clinically significant abnormality	26 (24)	62 (27)
<b>Post-baseline*</b>		
n	90	198
Any clinically significant abnormality	47 (52)	109 (55)
<b>Change from Screening to Post-baseline*</b>		
n	90	198
Unfavorable clinically significant change	39 (43)	86 (43)

Source: Applicant's NDA 203-975 Submission dated December 18, 2012, Section 5.3.5.3 (ISS), pg. 394 (Table 286)

\*Includes both scheduled and unscheduled Holters

The percentage of patients with an unfavorable clinically significant change on 24-hour Holter monitoring is generally balanced across treatment arms in both the 24-week placebo-controlled trials and 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 100 for the 24-week placebo-controlled trials and in Table 101 for the long-term safety trial.

**Table 100. Clinically Significant Abnormalities on 24-Hour Holter Monitoring at Any Time Post-Randomization Reported for ≥ 3% of Patients, 24-week Placebo-Controlled Trials, Subset Population**

	Placebo N=73	UMEC 62.5 N=54	UMEC 125 N=53
	n (%)	n (%)	n (%)
<b>Patients post-randomization*, n</b>	72	54	53
<b>Any clinically significant abnormality</b>	43 (60)	30 (56)	28 (53)
Ventricular couplets	27 (38)	16 (30)	17 (32)
Bigeminy	29 (40)	18 (33)	11 (21)
NSVT (>100 bpm, 3-30 beats)	11 (15)	4 (7)	7 (13)
PVC > 1000/24 hr	9 (13)	4 (7)	6 (11)
Ectopic supraventricular beats	1 (1)	4 (7)	3 (6)
Trigeminy	4 (6)	3 (6)	1 (2)
RBBB	1 (1)	2 (4)	2 (4)
Idioventricular rhythm (≤100 bpm, wide QRS)	1 (1)	3 (6)	0
PVC >4000 in 24 hr	2 (3)	2 (4)	0
Sustained supraventricular tachycardia (>100 bpm, >30 beats)	1 (1)	2 (4)	0
Sinus pause ≥ 2 seconds	2 (3)	0	1 (2)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 257-258 (Table 189)

Key: NSVT=non-sustained ventricular tachycardia; PVC=premature ventricular complex; RBBB=right bundle branch block

\*Includes both scheduled and unscheduled Holters

**Table 101. Clinically Significant Abnormalities on 24-Hour Holter Monitoring at Any Time Post-Randomization Reported for ≥ 3% of Patients, Long-Term Safety Trial, ITT Population**

	Placebo N=109	UMEC 125 N=227
	n (%)	n (%)
<b>Patients post-randomization#, n</b>	90	198

<b>Any clinically significant abnormality</b>	47 (52)	109 (55)
Bigeminy	25 (28)	60 (30)
Ventricular couplets	32 (36)	54 (27)
NSVT (<100 bpm, 3-30 beats)	11 (12)	16 (8)
PVC >1000/24 hr	5 (6)	16 (8)
Ectopic supraventricular beats	4 (4)	17 (9)
Trigeminy	5 (6)	10 (5)
Sustained supraventricular tachycardia (>100 bpm, >30 beats)	2 (2)	9 (5)
RBBB	0	7 (4)
PVC >4000/24 hr	2 (2)	4 (2)
Idioventricular rhythm (≤100 bpm, wide QRS)	2 (2)	8 (4)
Ectopic supraventricular rhythm	2 (2)	7 (4)

Source: Applicant's NDA 203-975 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

The overall percentage of patients with clinically significant abnormalities on 24-hour Holter monitoring post-randomization was somewhat higher for placebo compared to active treatment in the 24-week placebo-controlled trials, while a small imbalance favoring placebo is observed for the long-term safety trial. Among the most common (occurring in 3% or more of patients) clinically significant Holter abnormalities observed in the 24-week placebo-controlled trials, numerical imbalances favoring placebo are noted for ectopic supraventricular beats, RBBB, idioventricular rhythm, and sustained supraventricular tachycardia. The absolute number of patients with these findings is small. Similar findings are observed for the long-term safety trial, although the absolute number of events is somewhat higher.

### **Studies of Cardiac Conduction (i.e. “Thorough QT” study)**

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.

#### 7.4.5 Special Safety Studies/Clinical Trials

See 7.4.4 for a description of DB2114635 (“Thorough QT” study).

#### 7.4.6 Immunogenicity

Umeclidinium, a small molecule, is not anticipated to induce an immune response; therefore, 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 102 and by age in Table 103. 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 102. Summary of Adverse Events, by Gender, Efficacy Trials, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
<b>Any AE</b>			
Female	211	145	238
	110 (52)	78 (54)	145 (61)
Male	412	342	460
	178 (43)	165 (48)	231 (50)
<b>Any SAE</b>			
Female	211	145	238
	9 (4)	8 (6)	14 (6)
Male	412	342	460
	18 (4)	20 (6)	25 (5)
<b>Any AE Leading to Dropout*</b>			
Female	211	145	238
	9 (4)	11 (8)	15 (6)
Male	412	342	460
	17 (4)	21 (6)	29 (6)

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 270 (Table 200); pg. 272 (Table 202)

\*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 each of the treatment arms; however, the percentage of any SAE and any AE leading to dropout was similar across the two genders.

**Table 103. Summary of Adverse Events, by Age, Efficacy Trials, ITT Population**

	Placebo	UMEC 62.5	UMEC 125
	N	N	N
	n (%)	n (%)	n (%)
<b>Any AE</b>			
<64 years	370	257	371
	173 (47)	126 (49)	204 (55)
65-74 years	200	171	256
	89 (45)	88 (51)	136 (53)
75-84 years	52	56	69
	26 (50)	28 (50)	35 (51)

≥85 years	1	3	2
	0	1 (33)	1 (50)
<b>Any SAE</b>			
<64 years	370	257	371
	10 (3)	15 (6)	13 (4)
65-74 years	200	171	256
	13 (7)	12 (7)	22 (9)
75-84 years	52	56	69
	4 (8)	1 (2)	4 (6)
≥85 years	1	3	2
	0	0	0
<b>Any AE Leading to Dropout*</b>			
<64 years	370	257	371
	9 (2)	17 (7)	22 (6)
65-74 years	200	171	256
	14 (7)	9 (5)	16 (6)
75-84 years	52	56	69
	3 (6)	6 (11)	6 (9)
≥85 years	1	3	2
	0	0	0

Source: Applicant's NDA 205-382 Submission dated April 30, 2013, Section 5.3.5.3 (ISS), pg. 270 (Table 200); pg. 273 (Table 203)

\*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.

In general, the percentage of patients with any AE leading to dropout increase with age, but the magnitude of change is modest. No consistent relationship with age is observed for the other categories of AEs.

#### 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 and UMEC was evaluated in trial DB2114636. The effect of hepatic function on the pharmacokinetics of UMEC/VI and UMEC was evaluated in trials DB2114637. These trials were reviewed by Clinical Pharmacology under NDA 203-975 (UMEC/VI), which recommended 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 with verapamil, and AC4110106, which evaluated UMEC in normal and poor CYP2D6 metabolizers. These results were reviewed by the Clinical Pharmacology team, which does not recommend any dose adjustments in the context of co-administration with verapamil, or in patients using concomitant CYP2D6 inhibitors or with genetic polymorphisms of CYP2D6 metabolism.

## 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 NDA 205-382 nonclinical review by Dr. Matthew Whittaker, December 12, 2013).

### 7.6.2 Human Reproduction and Pregnancy Data

No pregnancies occurred in the UMEC COPD clinical development program. Umeclidinium is also being developed as a combination product with fluticasone furoate (UMEC/FF) for use in asthma. In the ongoing UMEC/FF program there have been four pregnancies: two occurred prior to study medication administration, and two occurred while on blinded UMEC/FF, FF, or FF/VI. Of the two pregnancies that occurred while on blinded study medication, one pregnancy was ongoing at the time of this NDA submission, and the other had an outcome of spontaneous abortion.

### 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 substance, drug abuse, withdrawal, and rebound are not anticipated for this product. Additionally, the mode of administration makes abuse less likely.

## 7.7 Additional Submissions / Safety Issues

The Applicant provided a 120-Day Safety Update on August 22, 2013, which covers the reporting period from December 11, 2012, through April 30, 2013. This submission includes safety data from 7 clinical trials (2 concluded and 5 ongoing), which are summarized in Table 104. With the exception of one trial (ILA116524, a clinical pharmacology trial in healthy subjects), all of these trials are for COPD. The original NDA also noted an additional two ongoing trials (ALA116402 and ILA115938); these trials are not included in the 120-Day Safety Update as they are evaluating UMEC for a different indication (asthma).

**Table 104. Trials Included in 120-Day Safety Update**

Trial	Objective	Design	N*	Arms	Duration	Type of Safety Data
<b>Concluded Trials</b>						
DB2116133	Lung function	R, DB, CO	182/159	UMEC/VI 62.5/25 UMEC 62.5 VI 25	14 days	Blinded
ILA116524	Safety, tolerability, PK	R, DB, CO	18/17	UMEC 500 FF 400 UMEC/FF 500/400	Single dose	Unblinded
<b>Ongoing Trials</b>						
AC4115361	Long-term safety in Japanese patients	OL	131 <sup>#</sup>	UMEC 125	52 weeks	Unblinded (open-label)
AC4116135	Efficacy, safety	R, DB, PG, PC	616 <sup>#</sup>	UMEC 62.5 UMEC 125 FSC 250/50 BID Placebo	12 weeks	Blinded
AC4116136	Efficacy, safety	R, DB, PG, PC	441 <sup>#</sup>	UMEC 62.5 UMEC 125	12 weeks	Blinded

				FSC 250/50 BID Placebo		
CRT116277	Exercise endurance	R, DB, CO	24/5	UMEC/VI 125/25 UMEC 125	4 weeks	Blinded
DB2116132	Lung function	R, DB, CO	207#	UMEC/VI 62.5/25 UMEC 62.5 VI 25	14 days	Blinded

Source: Applicant's NDA 205-382 Submission dated August 22, 2013, Section 5.2 (Tabular Listing of All Clinical Studies – 120-Day Safety Update)

\*N=number randomized/number completed (unless otherwise noted)

#Trial ongoing: N=estimated number of planned randomized subjects

Note: All treatments are once-daily (unless otherwise noted)

Key: FSC=fluticasone propionate/salmeterol combination

A total of two deaths (associated with three preferred terms [PT]) are reported in this 120-Day Safety Update. One death (associated with the PTs of esophageal carcinoma and pancreatic carcinoma) occurred in Trial DB2116133, and is not likely to be associated with trial medication. The second death (associated with the PT of “death”) occurred in Trial AC4116135 in a patient receiving run-in therapy.

A total of 38 non-fatal SAEs in 28 patients are reported in this 120-Day Safety Update, and are summarized in Table 105.

**Table 105. Non-fatal SAEs, 120-Day Safety Update**

Trial	Patients with non-fatal SAEs, n	Non-fatal SAEs, n	PTs (n)
<b>Concluded Trials</b>			
DB2116133	7	7	Angina pectoris Breast cancer COPD (2) Spinal fracture Bladder cancer Abscess limb
ILA116524	0	0	--
<b>Ongoing Trials</b>			
AC4115361	10	15	COPD (3) Cerebral infarction Gastric cancer Colon adenoma Fractured ischium Pubis fracture Pneumonia (3)

Clinical Review  
 Jennifer Rodriguez Pippins, MD, MPH  
 NDA 205-382  
 TBD Ellipta (umeclidinium)

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			Pneumothorax (2) Hypothermia (2)
AC4116135	7	8	COPD (5) Acute coronary syndrome Myocardial infarction Acute myocardial infarction
AC4116136	2	3	COPD (2) Pneumonia
CRT116277	0	0	--
DB2116132	2	5	Circulatory collapse Dehydration Gastroenteritis Hypotension Orchitis
<b>Total</b>	<b>28</b>	<b>38</b>	<b>--</b>

Source: Applicant's NDA 205-382 Submission dated August 22, 2013, Section 5.3.5.3 (120-Day Safety Update Report Body)

In general, the SAE PTs reported for the trials included in the 120-Day Safety Update are similar to those reported in the original application.

## 8 Postmarket Experience

Umeclidinium is not available for marketing in any country.

## 9 Appendices

### 9.1 Literature Review/References

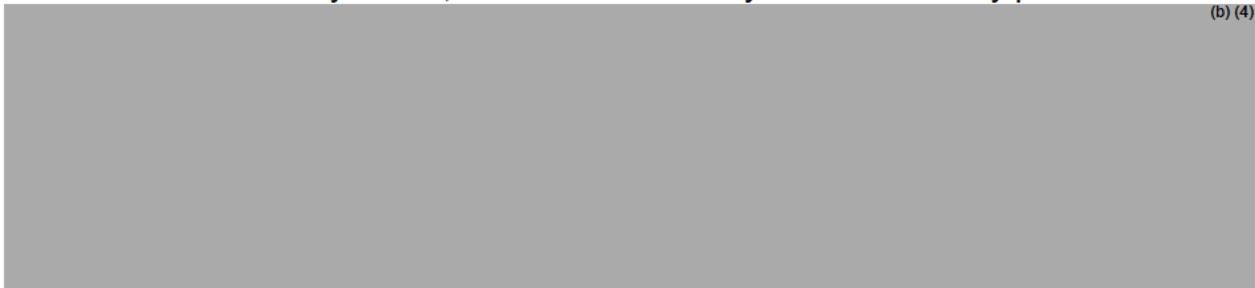
A PubMed search performed by this Reviewer [search term: umeclidinium; no limits] was conducted on December 2, 2013, and yielded 15 references. A brief review of these publications was performed. No new safety signals were identified.

### 9.2 Labeling Recommendations

Preliminary labeling recommendations include the following:

- Removal of  (b) (4)  

- Presentation of UMEC dose-ranging data
  - Section 14.1 should be revised to include a summary of UMEC dose-ranging data.
- Confirmatory Trials
  - Section 14.2 should be revised to emphasize the results of the pivotal 24-week trial (DB2113373). The description of results from the 12-week trial (AC4115408) should be abbreviated.
  - The figure depicting serial spirometry results from Trial DB2113373 should include Day 1 data, in addition to the Day 168 data already present.



### 9.3 Advisory Committee Meeting

An advisory committee meeting was not held for the application.

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was held on September 10, 2013, for the related combination product UMEC/VI (NDA 203-975). One of the major topics of discussion was the cardiovascular safety profile of the product, particularly given the history of concern regarding potential cardiovascular signals for inhaled LAMA products. While the vast majority of the PADAC voted affirmatively in response to the question posed about the adequacy of the safety data for UMEC/VI, both assenting and dissenting members alike expressed concerns about the generalizability of the safety data to patients with more significant cardiovascular disease, comorbid conditions, or more severe pulmonary disease. Several members recommended that additional data for a broader population be obtained in the postmarket setting, but did not provide specifics as to trial design. Further internal discussion of the UMEC/VI application took place at a CDER Regulatory Briefing held on December 6, 2013. The consensus was that the small numerical imbalances observed for cardiovascular adverse events in the UMEC/VI clinical program did not warrant further exploration with a required postmarketing trial.

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JENNIFER R PIPPINS  
12/19/2013

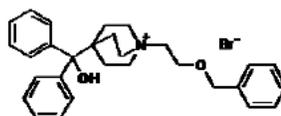
SUSAN L LIMB  
12/19/2013

<b>MEDICAL OFFICER REVIEW</b>			
<b>Division Of Pulmonary and Allergy Drug Products (HFD-570)</b>			
<b>APPLICATION:</b>	NDA 205-382	<b>TRADE NAME:</b>	TBD
<b>APPLICANT/SPONSOR:</b>	GlaxoSmithKline	<b>USAN NAME:</b>	umeclidinium
<b>MEDICAL OFFICER:</b>	Jennifer Rodriguez Pippins, MD, MPH		
<b>TEAM LEADER:</b>	Susan Limb, MD	<b>CATEGORY:</b>	LAMA
<b>DATE:</b>	June 14, 2013	<b>ROUTE:</b>	Oral inhalation
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
4/30/2013	4/30/2013	NDA 205-382 SD# 1 eCTD# 0	Original NDA
<b><u>REVIEW SUMMARY:</u></b>			
<p>GlaxoSmithKline (GSK) has submitted a 505(b)(1) New Drug Application (NDA) for umeclidinium, a long-acting muscarinic antagonist (anticholinergic). 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.” A 62.5 mcg once daily dose is proposed for approval. A related product, umeclidinium/vilanterol (NDA 203-975) is also currently under review for the same indication.</p> <p>Three key UMEC dose-ranging trials were all conducted in a COPD population. The phase 3 clinical program is comprised primarily of three placebo-controlled trials (one 12-week and two 24-week trials), one 24-week active control trial, two 12-week exercise endurance trials, and one 52-week long-term safety trial. While the clinical program provides replicate evidence of a statistically significant result for the primary endpoint of trough FEV1, with a treatment effect of approximately 120 mL, the data do not appear to provide adequate support for the proposed labeling claims related to (b) (4). The extent of exposure provided by the safety database appears adequate, and the application addresses adverse events of special interest (i.e. cardiovascular and anticholinergic events).</p> <p>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.</p>			
<b>RECOMMENDED REGULATORY ACTION:</b>			
<b>FILEABLE <input checked="" type="checkbox"/></b>		<b>NOT FILEABLE <input type="checkbox"/></b>	

## 1. GENERAL INFORMATION

### 1.1 Active Drug

Generic name:	umeclidinium
Chemical name:	1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide
Proposed Trade name:	(b) (4) Ellipta
Pharmacologic category:	LAMA
Route of administration:	Oral inhalation
Proposed doses:	62.5 mcg once daily
Molecular Formula:	C <sub>29</sub> H <sub>34</sub> NO <sub>2</sub> ·Br
Molecular Weight:	508.5
Molecular Structure:	



### 1.2 Background

GlaxoSmithKline (GSK) has submitted a 505(b)(1) New Drug Application (NDA) for umeclidinium, a long-acting muscarinic antagonist (anticholinergic). 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.” A 62.5 mcg once daily dose is proposed for approval. 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	Application Number	Interaction/Date/Topic
UMEC	104,479	<ul style="list-style-type: none"> <li>preIND May 26, 2009</li> </ul>
UMEC/VI	IND 106,616 NDA 203-975	<ul style="list-style-type: none"> <li>EOP2 October 29, 2010, dose and dosing interval discussed</li> <li>preNDA January 18, 2012</li> <li>NDA submitted December 18, 2012; PDUFA December 18, 2013</li> </ul>
SOBDA*		<ul style="list-style-type: none"> <li>Meetings on August 29, 2006, June 16, 2008, May 10, 2010, July 27, 2010</li> <li>Written feedback provided by Agency on June 30, 2010</li> </ul>

\*SOBDA=Shortness of Breath with Daily Activities Questionnaire

## 2. CLINICAL DEVELOPMENT PROGRAM: Dose-Ranging

Three key UMEC dose-ranging trials were all conducted in a COPD 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
<b>UMEC</b>						
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

## 3. CLINICAL DEVELOPMENT PROGRAM: Phase 3 Trials

The phase 3 clinical program for UMEC is comprised primarily of three placebo-controlled trials (one 12-week and two 24-week trials), one 24-week active control trial, 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
<b>Placebo-controlled Trials</b>						
AC4115408	Efficacy, safety	R, DB, PC, PG	COPD	UMEC 62.5 125 P	12 weeks	Trough FEV1
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
<b>Active Comparator Trials (tiotropium)</b>						
DB2113374	Efficacy, safety	R, DB, DD, AC	COPD	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 Tio 18	24 weeks	Trough FEV1
<b>Exercise Endurance Trials</b>						
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
<b>Long-term safety</b>						
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

Results for mean change in trough FEV1 are provided in Table 4.

**Table 4. Trough FEV1 (L) at Day 85 (Trial AC4115408) or 169 (Trials DB2113361 and DB2113373), ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>AC4115408</b>						
UMEC 62.5	69	1.363 (0.026)	0.120 (0.026)	0.127	0.052, 0.202	<0.001
Placebo	68	1.235 (0.028)	-0.007 (0.028)			
<b>DB2113361</b>						
UMEC 125	40 7	1.405 (0.012)	0.129 (0.012)	0.160	0.122, 0.198	<0.001
Placebo	27 5	1.245 (0.015)	-0.031 (0.015)			
<b>DB2113373</b>						
UMEC 62.5	41 8	1.354 (0.013)	0.119 (0.013)	0.115	0.076, 0.155	<0.001
Placebo	28 0	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. 863 (Table 6.05); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 793 (Table 6.05); Section 5.3.5.1 (AC411508, Study Report Body), pg. 299 (Table 6.05)

Key: BL=baseline

**Reviewer's Comment:**

*The clinical program provides replicate evidence of a statistically significant result for the primary endpoint of trough FEV1, with a treatment effect of approximately 120 mL for the proposed UMEC 62.5 mcg product.*

**Results for Additional Endpoints**

**SGRQ**

Results for mean change in trough SGRQ are provided in Table 5.

**Table 5. SGRQ Total Score at Day 84 (Trial AC4115408) or 168 (Trials DB2113361 and DB2113373), ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>AC4115408</b>						
UMEC 62.5	69	42.43 (1.47)	-3.14 (1.47)	-7.9	-12.2, -3.6	<0.001
Placebo	68	50.33 (1.60)	4.74 (1.60)			
<b>DB2113361</b>						
UMEC 125	40 7	43.48 (0.66)	-4.14 (0.66)	-0.31	-2.46, 1.85	0.778
Placebo	27 5	43.69 (0.88)	-3.83 (0.88)			
<b>DB2113373</b>						
UMEC 62.5	41 8	41.93 (0.75)	-7.25 (0.75)	-4.69	-7.07, -2.31	<0.001
Placebo	28 0	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); Section 5.3.5.1 (AC411508, Study Report Body), pg. 92 (Table 33)

Key: BL=baseline

Reviewer's Comment:



**SOBDA**

Results for mean change in trough SGRQ are provided in Table 6.

**Table 6. Mean SOBDA Score at Week 24 (Trials DB2113361, DB2113373), ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>DB2113361</b>						
UMEC 125	407	1.81 (0.029)	-0.15 (0.029)	-0.08	-0.17, 0.02	0.106
Placebo	275	1.89 (0.038)	-0.07 (0.038)			
<b>DB2113373</b>						
UMEC 62.5	418	1.84 (0.029)	-0.16 (0.029)	-0.10	-0.19, 0.00	0.043
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); Section 5.3.5.1 (DB2113373, Study Report Body), pg. 129 (Table 44)

Key: BL=baseline

Reviewer's Comment:

The SOBDA instrument is a novel PRO, and is currently under review as part of NDA 203-975. The Applicant has identified a MCID of -0.1 to -0.2 for this instrument; only one trial demonstrates a result for this endpoint that is both statistically significant and meets the Applicant's identified threshold for a clinically meaningful difference. These (b) (4)

**Table 7. Mean number of puffs of rescue medication per day at Week 12 (Trial AC4115408) and at Week 24 (Trials DB2113361, DB2113373), ITT Population**

Treatment Arm	N	BL	Change from BL	Treatment Difference from Placebo		
		LS Mean (SE)	LS Mean (SE)	Difference	95% CI	p-value
<b>AC4115408</b>						
UMEC 62.5	69	2.2 (0.2)	-0.7 (0.2)	-0.7	-1.3, -0.1	0.025
Placebo	68	2.9 (0.2)	0.0 (0.2)			
<b>DB2113361</b>						
UMEC 125	407	2.8 (0.1)	-1.5 (0.1)	-0.8	-1.3, -0.4	<0.001
Placebo	275	3.7	-0.7			

		(0.2)	(0.2)			
<b>DB2113373</b>						
UMEC 62.5	418	3.8 (0.2)	-1.7 (0.2)	-0.3	-0.8, 0.2	0.276
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); Section 5.3.5.1 (AC411508, Study Report Body), pg. 87 (Table 29)

Key: BL=baseline

Reviewer's Comment:

(b) (4)

**5. OVERVIEW OF SAFETY**

The primary safety database includes four primary efficacy trials (12-24 weeks in length), one 52-week long-term safety trial, two 12-week exercise trials, and three additional supportive trials (7-28 days in length).

Pre-specified AEs of interest include the following:

- Cardiovascular:
  - MACE analysis: non-fatal cardiac ischemia, stroke, adjudicated cardiovascular death
  - AESI analysis: acquired long QT, cardiac arrhythmia, cardiac failure, cardiac ischemia, hypertension, sudden death, stroke
- Anticholinergic: urinary retention, ocular effects, other anticholinergic effects
- COPD-related: pneumonia

A summary of exposure from the primary efficacy trials (12-24 weeks in duration) and 52-week long-term safety trial is provided in Tables 8 and 9.

**Table 8. Exposure in the primary efficacy trials**

	Placebo N=623	UMEC 62.5 N=487	UMEC 125 N=698
Range			
≥ 1 day	623	487	698
> 12 weeks	472	390	568
> 24 weeks	169	154	200

**Table 9. Exposure in the long-term safety trial**

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

Reviewer's Comment

*The extent of exposure appears to be adequate.*

**6. ITEMS REQUIRED FOR FILING**

See attached Clinical Filing Checklist (Appendix A).

**7. BRIEF REVIEW OF PROPOSED LABELING**

As discussed above, the clinical program does not appear to provide adequate evidence to support the (b) (4) (b) (4) included in the proposed labeling.

**8. OSI Audit**

No OSI audit is recommended for this application, given that two relevant sites are already being audited under the purview of NDA 203-975:

- 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. The adequacy of the data to support labeling claims related to (b) (4) (b) (4) 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:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
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			
<b>LABELING</b>					
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			
<b>SUMMARIES</b>					
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			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				<b>505(b)(1)</b>
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product	X			<b>The application includes appropriate</b>



	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	current worldwide knowledge regarding this product?				
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) 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 <sup>2</sup> 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			
<b>OTHER STUDIES</b>					
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	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
<b>DATASETS</b>					

<sup>1</sup> 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.

<sup>2</sup> 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).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
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			
<b>CASE REPORT FORMS</b>					
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	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
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. The adequacy of the data to support labeling claims related to (b) (4) (b) (4) (b) (4) will be a review issue.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER R PIPPINS  
06/18/2013

SUSAN L LIMB  
06/18/2013