CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203975s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	December 18, 2013
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	203975
Applicant Name	GlaxoSmithKline (GSK)
Proprietary / Established (USAN) Names	Anoro Ellipta/umeclidinium and vilanterol inhalation powder
Dosage Forms / Strength	Inhalation powder Umeclidinium/vilanterol 62.5 mcg/25 mcg once daily
Proposed Indication(s)	Long-term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding Anoro Ellipta, a combination of umeclidinium/vilanterol (UMEC/VI), proposed for the long-term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The reader should review the action package for more detail. UMEC/VI is a combination inhalation product of umeclidinium, a new long-acting muscarinic antagonist (LAMA) and vilanterol, a long-acting beta-agonist (LABA) already approved in the United States as a component of the inhalation product Breo Ellipta (fluticasone furoate/vilanterol trifenatate), which is also indicated for COPD.[1]

There are unique aspects to this development program. Presently, there are combination products of short-acting antimuscarinic agents (SAMA) and short-acting beta-agonists (SABA), but UMEC/VI is the first combination product of a LAMA and LABA. Also, similar to the Breo Ellipta development program, UMEC/VI is seeking approval of the combination product before seeking approval of the single individual agents.

There are several drug classes available for the treatment of symptoms of COPD including beta-adrenergic agonists, anticholinergic agents, methylxanthines and phosphodiesterase-4 inhibitors. Beta-adrenergic agonists are also available in combination with corticosteroids. Anticholinergic agents are available as short-acting (ipratropium bromide) and long-acting agents (tiotropium bromide and aclidinium bromide).

[1] Anoro Ellipta is proposed for the maintenance treatment of airflow obstruction in COPD. Breo Ellipta carries this same bronchodilation indication and, in addition, is also indicated for the reduction of exacerbations in patients with COPD.

In the past, meta-analysis and observational study exploration of short-term trials have raised concerns regarding the potential for increased risk of stroke, cardiovascular (CV) death and myocardial infarction (MI) associated with inhaled anticholinergic use.[2,3,4] However, the results of a large, 4-year, randomized, controlled trial (Understanding Potential Long-Term Impacts on Function with Tiotropium; UPLIFT) were published after the results of different meta-analyses and observational studies and the accompanying concern that arose. [5] UPLIFT and all other available data were discussed at a Pulmonary-Allergy Drug Advisory Committee (PADAC) meeting held on November 19, 2009, and committee members (and subsequently the Agency) concluded that the data available at that time did not support an increased risk of stroke, myocardial infarction, or death associated with Spiriva HandiHaler.[6]

However, at that time there were still lingering questions regarding an alternate tiotropium formulation delivered by the Respimat device (foreign marketed) as three, 1-year, placebo-controlled trials presented at the PADAC demonstrated increased all-cause mortality. A meta-analysis of these trials was subsequently published demonstrating the same finding.[7] At that time, a large, prospective safety trial (TIOSPIR) was beginning which ultimately enrolled 17,135 patients with COPD and the primary endpoint compared efficacy (rate of first COPD exacerbation) and safety (rate of death) of tiotropium at a dose of 5 ug and 18 ug delivered by the Respimat and HandiHaler inhalation devices, respectively. The results of TIOSPIR have recently been published.[8] The conclusions of the authors were that tiotropium Respimat at a dose of 5 ug and 2.5 ug[9] had a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 ug in patients with COPD. An editorial critiquing the trial also concluded that "This study clears the air regarding the safety of tiotropium delivered by Respimat."[10,] It should be noted that we have not reviewed TIOSPIR within the agency and have yet to confirm those conclusions.

It is also important to note that another new LAMA, aclidinium bromide, was approved after UPLIFT and before the results of TIOSPIR were known. Partially because of the lingering uncertainty of possible disparate safety effects of tiotropium delivered by different devices (HandiHaler versus Respimat) and because of a limited safety database with single digit CV events, a CV outcome trial was required of aclidinium bromide as a Postmarketing Requirement (PMR).

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[2] Singh S., et al. JAMA 2008; 300:1439-50.
[3] Lee TA, et al. Annals of Internal Medicine 2008; 149:380-390.
[4] Pooled data analysis submitted to the agency by Boehringer Ingelheim in November of 2007 of 29 placebo-controlled tiotropium trials, stratified by study, demonstrated an increase in the rate of stroke leading to an early communication in March 2008.
http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm107272 htm
[5] Tashkin DP, et al. N Engl J Med 2008; 359: 1543-54.
[6] Michele TM, et al. N Engl J Med 2010; 363:1097-99.
[7] Singh S, et al. BMJ 2011; 342:online first pages 1-9.
[8] Wise RA, et al. N Engl J Med 2013; 369:1491-501. According to the published report, Respimat was noninferior to HandiHaler with respect to death (hazard ratio 0.96, 95% CI [0.87, 1.14]), and reported causes of death and the incidence of major cardiovascular adverse events (MACE) were similar in patients who received tiotropium Respimat 2.5 mcg or 5 mcg versus tiotropium HandiHaler 18 mcg.
[9] 2.5 ug was included in trial as well, but was not the primary comparison.
[10] Jenkins CR. N Engl J Med 2013; 369:1555-6

It is also important to note that there are safety concerns of severe asthma exacerbations, some fatal, associated with inhaled beta-2 adrenergic agonists when used for the treatment of asthma.[11] However, this type of signal has never been shown with use of inhaled beta-2 agonists in patients with COPD. In the past, inhaled beta-2 adrenergic agonist agents were developed for both asthma and COPD indications (usually in the asthma population first), but recently the trend has been for sponsors to submit applications for this class of drugs only for COPD indications. This is probably, at least partially, due to sponsors' concerns that the safety signal existing with LABA use in asthma may lead to a perilous approval path. However, past experience with development programs for LABAs has informed us that to date the dose and dosing interval are the same for both asthma and COPD. As such, a traditional development program would include dose-ranging trials performed in subjects with asthma due to their greater airway sensitivity response to adrenergic activation which is necessary to establish separation of dose responses. Once a dose was determined in subjects with asthma, that dose would be carried forward into COPD trials. As such it is important to perform at least some dose-selection trials in subjects with asthma.[12]

As stated above, in the past, single ingredients were developed separately for market introduction. Subsequent to their approval, applications for the combination products containing these individual components were submitted for approval in the same indications. This application is seeking approval of the combination product for COPD (b) (4) However, each component has been studied separately which has resulted in this application being quite large. As noted in Dr. Limb's review, the dose selection for LAMA's can be challenging given the relatively flat dose-response curves and the Agency has recommended that more than one dose be explored in confirmatory trials for COPD. These issues are discussed in thorough detail in Drs. Pippins, Limb and Chowdhury's reviews.

The Division believes that substantial evidence of efficacy and safety has been demonstrated that should allow for marketing of Anoro Ellipta. They also opine that the safety database is large, but not entirely conclusive in regards to CV safety. However, DPARP does not recommend a postmarketing trial. I agree with this assessment and recommend an Approval action. I also do not recommend a postmarketing trial and will elaborate in the conclusions section.

Efficacy

The program was developed to demonstrate efficacy of UMEC and UMEC/VI concurrently. The sponsor sought a bronchodilation claim for the combination of UMEC/VI. The nominal dose and dosing frequency for VI 25 mcg QD were reviewed as part of the Breo Ellipta program. Relevant trials are presented below in tables from Dr. Limb's review (Page 9-10).

[11] A higher dose of inhaled formoterol was not approved because of more severe asthma exacerbations compared to lower doses.

[12] Dose-ranging was performed in both asthma and COPD populations for the Breo Ellipta development program application. The approved vilanterol dose was used in this program.

Table 1 UMEC dose selection					
Trial ***Trial period***	**Design**[a]	**N**[b]	**Treatment**[c]	**Endpoint**	**Sites** *% US subjects*
AC4115321 *Jul 2011-Oct 2011*	R, DB, PC, 7-day XO	60 56 57 58 59 60 56 60	UMEC 15.6 QD UMEC 15.6 BID UMEC 31.25 QD UMEC 31.25 BID UMEC 62.5 QD UMEC 125 QD Tio 18 QD Placebo	Trough FEV1	15 US sites *100%*
AC4113073 *Oct 2009-Mar 2010*	R, DB, PC, 14-day XO	35 34 34 37 36 38 38 32 35 158	UMEC 62.5 QD UMEC 62.5 BID UMEC 125 QD UMEC 125 BID UMEC 250 QD UMEC 250 BID UMEC 500 QD UMEC 1000 QD Tio 18 QD Placebo	Trough FEV1	20 sites (US, Germany) *65%*
AC4115408 *Jul 2011 – Feb 2012*	12-wk, R, DB, PC PG	69 69 68	UMEC 62.5 QD UMEC 125 QD Placebo	Trough FEV1	27 sites (US, Germany, Japan)
AC4113589 *Dec 2009 – Jul 2010*	28-day, R, DB, PC, PG	71 72 71 71	UMEC 125 QD UMEC 250 QD UMEC 500 QD Placebo	Trough FEV1	21 sites (US, E. Europe, W. Europe) *33%*

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

[b] modified ITT

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

Table 2 UMEC/VI clinical development program					
Trial ***Trial period***	**Design**[a]	**N**[b]	**Treatment**[c]	**Endpoint**	**Sites** ***% US patients***
24-week primary efficacy and safety trials					
DB2113361 *Mar 2011 – Sep 2012*	R, DB, PC, PG	403 407 404 275	UMEC/VI 125/25 UMEC 125 VI 25 Placebo	Trough FEV1	153 site (US, E and W Europe, Japan, Philippines *21%*
DB2113373 *Mar 2011 – Apr 2012*	R, DB, PC, PG	413 418 421 280	UMEC 62.5/25 UMEC 62.5 VI 25 Placebo	Trough FEV1	163 sites (US, E and W Europe, Chile, S Africa, Japan, Mexico, Thailand *28%*
DB2113360 *Mar 2011 – Apr 2012*	R, DB, DD, AC, PG	214 212 209 208	UMEC/VI 125/25 UMECVI 62.5/25 VI 25 Tio 18	Trough FEV1	91 sites (US, E and W Europe, Peru, Mexico) *27%*
DB2113374 *Mar 2011 – Apr 2012*	R, DB, DD, AC, PG	215 217 222 215	UMEC/VI 125/25 UMEC/VI 62.5/25 UMEC 125 Tio 18	Trough FEV1	95 sites (US, E and W Europe, S. America, Australia, Canada, Mexico, S Korea, S Africa) *26%*
12-week exercise trials					
DB2114417 *Mar 2011 – Jun 2012*	R, DB, PC, XO	144 152 76 50 49 170	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 UMEC 125 UMEC 62.5 Placebo	Exercise endurance time Trough FEV1	31 sites (US, W Eur, E Eur) *56%*
DB2114418 *Mar 2011 – Jul 2012*	R, DB, PC, XO	128 130 64 41 40 151	UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 UMEC 125 UMEC 62.5 Placebo	Exercise endurance time Trough FEV1	42 sites (US, E Eur, W Eur, S Africa, Canada) *45%*
52-week safety trial					
DB2113359 Jan 2011 – Jul 2012	R, DB, PG, PC	226 227 109	UMEC/VI 125/25 UMEC 125 Placebo	Safety parameters	53 sites (US, Chile, E Eur, S Africa) *28%*

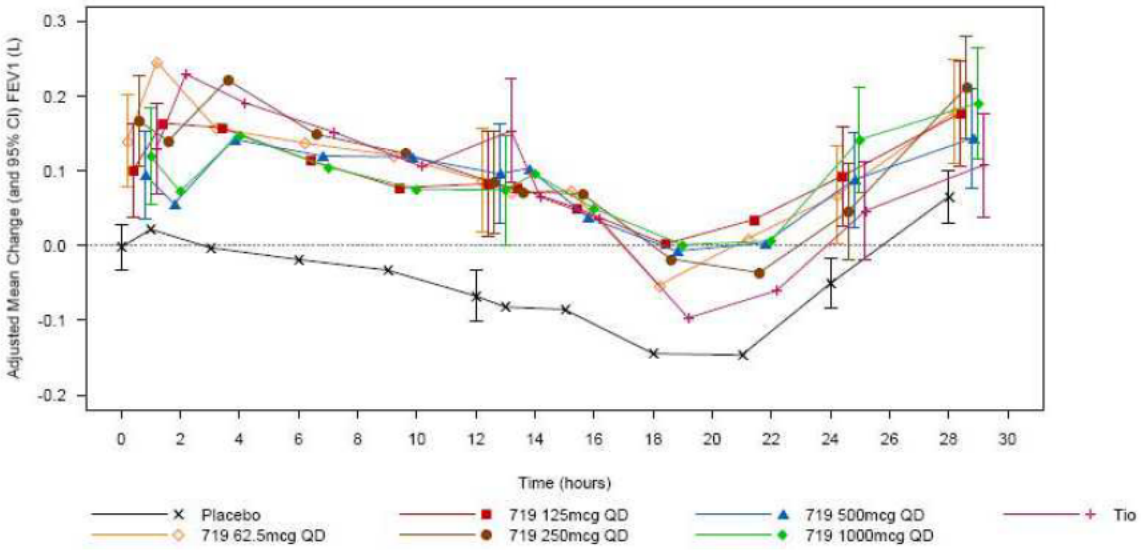
[a] AC= active-controlled, DB=double-blind, DD=double dummy, PG=parallel group, PC=placebo-controlled, R=randomized, SD=single dose, XO=crossover

[b] Intent-to-treat

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

Data regarding the nominal dose are presented in the figure below from Dr. Limb's review (Page 11).

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



Source: CSR AC4113073, Figure 6

Four main efficacy trials (3361, 3373, 3360, and 3374) were conducted to support the proposed indication. The change from baseline in mean trough FEV1 at day 169 was the primary endpoint for placebo- and active-controlled trials. The results are listed below in tables from Dr. Limb's review (pages 18, 19).

Table 3 Trials 3361 and 3373: Mean change from baseline in trough FEV1 at Day 169 (ITT)

Treatment	N	LS mean (L)	LS mean change	Difference from UMEC (95% CI)	P	Difference from VI (95% CI)	P
3361							
UMEC/VI 125/25	403	1.484	0.207	0.079 (0.046, 0.112)	<0.001	0.114 (0.081, 0.148)	<0.001
UMEC 125	407	1.405	0.129	-	-	-	-
VI 25	404	1.379	0.093	-	-	-	-
Placebo	275	1.245	-0.031	0.160 (0.122, 0.198)	<0.001	0.124 (0.086, 0.162)	<0.001
3373							
UMEC/VI 62.5/25	413	1.406	0.171	0.052 (0.017, 0.087)	0.002	0.095 (0.060, 0.130)	<0.001
UMEC 62.5	418	1.354	0.119	-	-	-	-
VI 25	421	1.311	0.076	-	-	-	-
Placebo	280	1.239	0.004	0.115 (0.076, 0.155)	<0.001	0.072 (0.032, 0.112)	<0.001

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

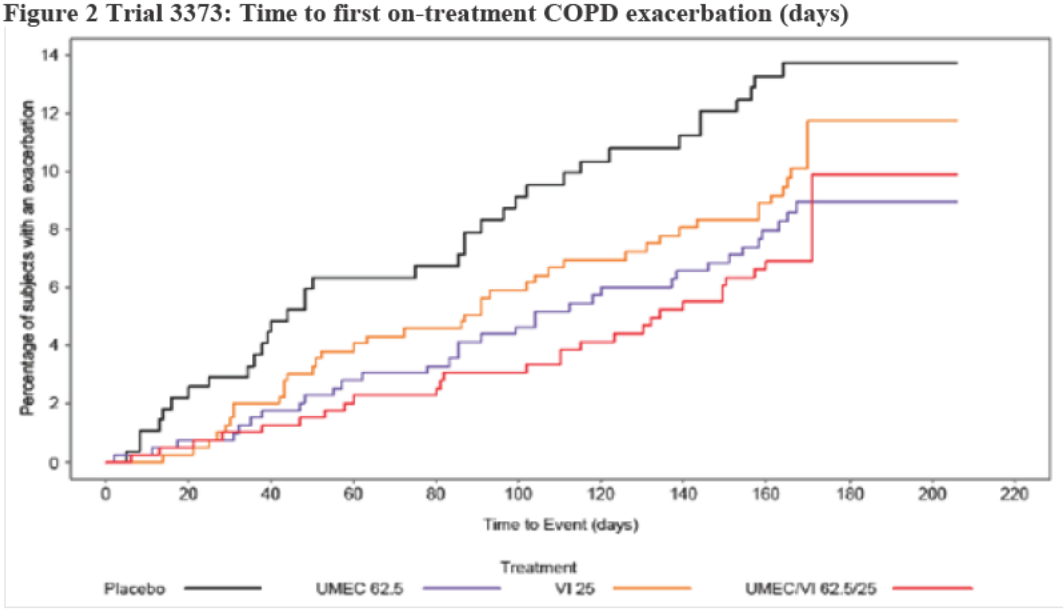
Table 4 Trials 3360 and 3374: Mean change from baseline in trough FEV1 at Day 169 (ITT)							
Treatment	**N**	**LS mean (L)**	**LS mean change**	**Difference from UMEC (95% CI)**	**P**	**Difference from VI (95% CI))**	**P**
3360							
UMEC/VI 62.5/25	207	1.521	0.211	-	-	0.088 (0.037, 0.139)	<0.001
UMEC/VI 125/25	208	1.519	0.209	-	-	0.093 (0.041, 0.144)	<0.001
VI 25	205	1.431	0.121	-	-	-	-
Tiotropium 18	203	1.431	0.121	-	-	-	-
3374							
UMEC/VI 62.5/25	217	1.355	0.208	0.022 (-0.027, 0.072)	0.377	-	-
UMEC/VI 125/25	215	1.369	0.223	0.037 (-0.012, 0.087)	0.142	-	-
UMEC 125	222	1.332	0.186	-	-	-	-
Tiotropium 18	215	1.295	0.149	-	-	-	-

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

The combination of UMEC/VI 62.5/25 demonstrates statistically significant increased bronchodilation compared to the individual components.

While not designed to assess COPD exacerbations as a primary endpoint, data on exacerbations were collected during the four main efficacy trials. Exacerbation data from Trial 3373 on UMEC/VI 62.5/25 and the individual components are presented in the figure below from Dr. Limb's review (page 22).

Figure 2 Trial 3373: Time to first on-treatment COPD exacerbation (days)



Factorial comparisons favored the combination of UMEC/VI 62.5/25 over the components and placebo.

The data presented demonstrate evidence of efficacy for UMEC 62.5/25 and UMEC 62.5 compared to placebo for bronchodilation in COPD when evaluated by trough FEV1. Efficacy for VI 25 was previously established in the Breo Ellipta program and was reconfirmed in this program. The criteria for the combination policy were fulfilled demonstrating that each individual component of UMEC 62.5/25 makes a contribution to the primary efficacy evaluation. Exacerbation evaluations were conducted as an additional endpoint and not as a primary in a dedicated trial.

Safety

Main safety issues with the LABA component were discussed above and safety issues associated with VI use in COPD have been evaluated in the Breo Ellipta application. The main focus of this section will be on the LAMA component (UMEC) and the combination UMEC/VI.

Deaths and non-fatal serious adverse events (SAE)[13] were evenly reported across all treatment arms. The main safety issue requiring consideration is possible adverse cardiovascular events, specifically MACE events[14], with use of LAMA's in general and whether there may be an increase in adverse cardiovascular events with the use of UMEC or UMEC/VI. Two MACE analyses (a "broad" analysis and a "narrow" analysis") were conducted to capture possible ischemia/infarction, stroke and CV death: these analyses differed only in the definition used for the ischemia/infarction category, with the narrow analysis using the preferred terms of "myocardial ischemia" and "acute myocardial infarction" while the broad analysis used the Myocardial Infarction Standard MedDRA Queries (SMQ) and Other Ischemic Disease SMQ. The MACE analyses were conducted on all COPD studies of at least 12 weeks duration and the results are present in the table below from Dr. Limb's review (Page 26).

Table 5 MACE analyses in integrated COPD database

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

[13] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

[14] Major Adverse Cardiac Events, typically defined as CV death and Non-fatal MI and stroke.

Narrow-definition	19.0	12.3	10.5	9.9	15.6	18.1	5.8
Adjudicated CV death	5.4	4.9	0	0	2.2	4.5	0
Non-fatal cardiac ischemia	38.0	31.9	33.2	39.5	24.5	27.2	28.9
Non-fatal MI	2.7	7.4	5.2	4.9	8.9	4.5	0
Non-fatal stroke	10.9	0	5.2	4.9	4.5	9.1	5.8

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

There are few events, and limited duration of exposure, so any results are fragile at best and conclusion would be tenuous. The most that can be said is that there is not a consistent trend of MACE events indicating harm with drug use compared to placebo (or dose-response increase). Dr. Limb mentions that a small imbalance is noted in cardiac ischemia for the narrow-definition MACE analysis. While technically this is true, the result is on the basis of 4 events (placebo vs. UMEC/VI 62.5/25) and also after many subgroup analyses. It is not possible with any confidence to render a conclusion based on 4 events. To put this into context, over 600 events are required in diabetic drug development trials designed to evaluate CV safety in order to have sufficient power to exclude an increase of 30% for MACE events.[15] This scenario assumes a HR of 1.0 and an annual event rate of 2 to 3%. It should be noted that, although individual components are viewed with interest, we typically evaluate overall MACE events and not the individual components. If validity were placed to a possible concern that an imbalance in 4 cardiac ischemia events may have, the opposite (favoring UMEC/VI) should also be considered regarding non-fatal stroke risk, also based on 4 events. Neither result can be used as reassurance or concern.

Another broader analysis was performed of cardiovascular AEs of special interest (AESI) consisting of terms for cardiac ischemia, stroke, sudden death and additionally acquired long QT, cardiac arrhythmia, cardiac failure, and hypertension. The results are in the table below from Dr. Limb's review (Page 27).

[15] It should also be noted that MACE is a composite of three different events. While we do look at each composite, from a statistical standpoint we would not expect each point estimate to at unity or below.

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

Source: Module 5.3.5.3, ISS, Table 113
SY=subject-years
Exposure-adjusted frequency was calculated as (1000*Number of Patients with AE) divided by (Total duration of exposure in days/365.25)

There are very few events upon which to draw conclusions, but with the available data there does not appear to be an increase in cardiac arrhythmias between placebo and UMEC/VI. This table illustrates the risk however of drawing conclusions based upon few events. If one were to compare placebo to UMEC 62.5 for cardiac arrhythmias (based on subject-year exposure) the conclusion would be that there is a signal with drug use. However, UMEC/VI use appears favorable for the same adverse event compared to placebo. It does not make sense that UMEC 62.5 would be arrhythmogenic while UMEC/VI 62.5/25 was not unless VI provided protection. The table above however would suggest the converse as there are more cardiac arrhythmia events associated with VI 25 compared to placebo. Therefore, when few events are involved and many categories are explored, it is hard to draw any conclusions from imbalances, particularly when there are disparate and inconsistent results observed across multiple analyses. Further analysis was performed on Trial 3359 (one-year placebo-controlled) by itself, but again few events were captured, although cardiac ischemia imbalances favored UMEC/VI 125/25[16].

The clinical program performed ECG in all patients and 24-hour Holter monitoring in approximately 13%. No clear treatment-related effects were demonstrated for the clinical program as a whole, or for the primary efficacy trials, although there was a relative imbalance of discontinuations for ECG protocol-defining stopping criteria in Trial 3359 (6% UMEC/VI 125/25, 5% UMEC 125, 0% placebo). This was also noted for Holter abnormalities (11-12% in the UMEC and UMEC/VI vs 7% in placebo).

[16] 2% vs 4% or 29.8 vs 22.7 per 1000 subject-years, placebo vs UMEC/VI 125/25.

In summary, based on a limited number of events, there is not sufficient evidence to either confirm or refute possible adverse CV effects from UMEC either as a single agent or in combination with VI. Other adverse events identified for UMEC/VI appear consistent with the general safety profile associated with LAMA and LABA drug classes.[17]

Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on September 10, 2013. The committee voted 11-yes, 2-no for approval. There were concerns regarding generalizability of the efficacy and safety results as the committee questioned if patients with CV disease and more severe pulmonary disease were included in the trials. Some committee members expressed that a post-marketing outcome trial may be necessary. Further questioning from Agency personnel regarding what kind of trial, what comparators, what margin for safety would be necessary, were not responded to by panel members.

Conclusions and Recommendations

UMEC/VI has demonstrated substantial evidence as a bronchodilator when used in COPD. This application has also demonstrated the contribution from UMEC and VI to the combination product.

In regard to safety, the database is fairly large and this combination product has adverse effects that would be expected from the components. However, if one were to be of the opinion that there is still uncertainty regarding a possible class effect (or individual effect) of LAMA products in regards to thromboembolic effects as evaluated by MACE events, this program did not have enough CV events for reassurance. The main question to answer is whether there should be concern that LAMA agents or UMEC may increase MACE events. In the past, questions have been raised based on meta-analyses and observational studies whether a different member of the class of SAMA (ipratropium) or LAMAs (tiotropium), or even tiotropium delivered by a different device, may have adverse CV effects by increasing MACE events (or individual components of MACE). However, subsequent large, randomized trials (UPLIFT, TIOSPIR[18]) seem to have put this controversy to rest (for most).

It is important to reflect on the past in making decisions for the future regarding the requirement of CV outcome trials. The history of LAMAs is analogous to that of rosiglitazone and drugs being developed for Type-2 Diabetes Mellitus, so it may be informative to review this history to date. Meta-analyses of rosiglitazone trials, one of short, randomized trials (not designed to capture CV events) and one including long-term trials, revealed a possible CV effect.[19,20] Because of the high background rate of CV events in patients with Type-2 diabetes

[17] Please see Drs. Pippins, Limb and Chowdhury's reviews for discussions of other AE.
[18] Given the caveat noted above that TIOSPIR has not undergone internal review yet.
[19] Nissen SE, et al. NEJM. 2007; 356:2457-2471. This meta-analysis included long-term controlled clinical trials.
[20] FDA meta-analysis of 42 controlled clinical trials presented in July 2007 at a joint advisory committee meeting and the sponsor also conducted a meta-analysis of their internal data which was presented.

mellitus and the public health implications if a drug had an effect that increased that rate, external scientific input (advisory committee meetings) and internal discussion led to requirements for all agents being developed for use in Type 2 diabetes mellitus to conduct a CV outcome trial. After these requirements were implemented, a subsequent open-label randomized trial (RECORD) seems to have called some of the original conclusions upon which the mandatory outcome study requirement was based into question and has led some to call this requirement into question.[21, 22, 23] However, it is important to note that despite some calling the requirement into question, the definitive trial that would have ultimately answered the question (TIDE) was placed on hold. So while RECORD may have lessened concern, due to its open-label design, it could not definitively define a possible CV risk.

LAMA development could be seen as heading down the same path but there are some important differences that may cause one to consider a different approach than mandatory outcome trials for these agents. In a large picture view, there were meta-analyses of SAMA and LAMA agents which suggested a CV signal. The sponsor conducted a meta-analysis of all their trials (mostly small, short and not designed to capture CV events), which also suggested some potential problems. Then, randomized trials (UPLIFT, TIOSPIR) were completed which seem to have contradicted the meta-analysis results and repudiate any potential CV problems (although some panel members at the Anoro AC meeting were calling for more safety data or an outcome trial). The blinded study design of UPLIFT and TIOSPIR increases the strength of the findings, in contrast to the open-label design of RECORD.

The diabetic CV outcome trial requirement started in large part due to decisions made on meta-analysis. If one is to consider large, well-conducted, blinded, randomized trials as the best standard (truth), it is instructive to review their concordance with meta-analysis examining the same scientific issue. Over time, there have been (unfortunately) many examples of discrepancies between meta-analyses and subsequent large randomized trials. A report by LeLorier, highlights this where he compared 12 randomized trials to 19 meta-analyses of the same question.[24] If a later randomized trial had not been performed, the meta-analysis would have led to adoption of an ineffective treatment in 32% of cases and rejection of useful treatment in 33%. Another example besides the tiotropium experience described above includes the discrepancies noted in the Women's Health Initiative (WHI) study. Before initiation of the definitive trial, it was known that female replacement hormones had a positive effect on all lipid parameters, and most published meta-analyses at the time supported well-established dogma that treatment provided CV benefit. Ultimately, the randomized trial demonstrated that estrogen plus progestin resulted in an increased risk of heart attacks, strokes, and blood clots while estrogen alone increased the risk of strokes and blood clots and is no longer recommended for heart disease prevention.

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[21] This is a very incomplete description of all that has transpired (including a readjudication of the RECORD trial) but is used for illustrative purposes.
[22] Hiatt WR, et al. N Engl J Med. 2013 Oct 3;369(14):1285-7.
[23] Home PD, et al. Lancet 2009; 373:2125-35.
[24] LeLorier J, Gregoire G, Benhaddad A, et al. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. NEJM 1997; 337:536-542.

These examples are to demonstrate that meta-analysis should for the most part be viewed as hypothesis generation tools whose results require further evaluation. For the diabetes example, unfortunately, the large randomized trial which would have definitively answered this question (TIDE) was placed on hold. Therefore we will need to collect a more substantial body of evidence (continued outcome trials) upon which to base further possible regulatory action. In this situation with LAMAs, we had a meta-analysis for tiotropium that caused a signal of concern, which was refuted later by a large randomized trial that does not suffer the design issues noted with RECORD. There was also a meta-analysis questioning whether tiotropium by a different delivery device could have adverse CV effects. A large randomized trial (that has undergone peer review, but not internal FDA review) seems to have answered that question as well (if our internal analysis reaches the same conclusion). With these results in hand, the question becomes at what point we feel that a hypothesized safety issue caused by a class of drugs has been answered and further exploration is not necessary? Put another way, when a concern is discovered by meta-analysis, when is there enough data from randomized trials to assuage this concern?

It is an important question as Tudorza Pressair (aclidinium bromide) was approved 7/23/2012, between the publication of UPLIFT and TIOSPIR and we required an outcome trial to be completed by September 30, 2017. At the time of my review for aclidinium I concluded:

I do not find the CV events in the application of a sufficient number to make any conclusions. However, pending the final results of the Respimat safety study discussed above, it is not unreasonable to be concerned that different types of formulations, or anticholinergics, may have different effects on the cardiovascular system. As such, and considering that we have required outcome studies for a variety of drugs used in a variety of disorders, it is reasonable to require a study that generates enough events upon which to form conclusions. I do not find the data compelling enough to require an outcome study prior to approval.

I also noted that the safety database was small and there were single digit numbers of MACE events.[25] At the time of the review for aclidinium, I did not believe we had enough data to exonerate tiotropium, thereby casting a shadow on the LAMA class. However, if the published results for TIOSPIR withstand FDA scrutiny, I believe that tiotropium does not have excess MACE events regardless of whether it is delivered by RESPIMAT or HANDIHALER devices. Therefore, it would seem that the realization needs to be made that the advice for outcome trials for LAMA agents was based on a meta-analysis for tiotropium/ipratropium (and possible concerns of class effects), which has proven to be a false signal. If this is a logical progression of thought, then contemplation must occur regarding at what point CV outcome trials should no longer be required of LAMA agents. I believe we are at that point. As previously noted, we have not reviewed TIOSPIR yet, and if we come to a different conclusion

[25] The safety population for aclidinium 400 mcg BID includes a total of 1471 COPD patients exposed to at least one dose or more of aclidinium 400 mcg BID. At the time of NDA submission, a total of 462 patients had been exposed for at least 6 months, and 97 patients had been exposed for ≥1 year. Following an October 21, 2011, safety update, these numbers were increased to 733 and 329 patients. For comparison, the safety database for the UMEC/VI application included a total of 2454 patients receiving UMEC/VI 62.5/25 or 125/25 and 1663 patients received UMEC 62.5 or 125. 1312 patients were exposed to UMEC 62.5, UMEC 125, UMEC/VI 62.5/25, or UMEC/VI 125/25 for 24 weeks or longer. A total of 279 patients were exposed to UMEC 125 or UMEC 125/25 for 48 weeks or longer.

from the published results, then we may need to revisit this conclusion. To be more specific, if we were to come to a different conclusion on TIOSPIR than published reports, I would regard this as new safety information which would allow us to require a CV outcome trial for the UMEC component of UMEC/VI under a PMR.

Finally, the sponsor has proposed to conduct observational studies to try to explore any possible CV risks. To this point, we have not felt that observational studies can definitively answer questions regarding a drug's potential to cause increased MACE events.[26] I have not seen evidence that would change this determination.[27] As such, we either think that this needs further evaluation, which would be in the form of a large, randomized trial, or we do not.

I recommend approval of UMEC/VI without a PMR for an outcome trial.

[26] For a required post-marketing trial, it must first be determined that observational studies will not adequately explore the concern.

[27] In the diabetes arena, there are now reports from CVOT trials of two drugs (saxagliptin, alogliptin) that had meta-analysis of their programs (we have not reviewed the outcome trials internally yet). The published reports for the outcome trials have different point estimates from what the meta-analysis demonstrated which may have led to very different conclusions based on which analysis was relied upon. This may give further credibility that if there is a concern the only way to arrive at a definitive conclusion is by performing a large randomized trial. On the other hand, the published reports of both of these CV trials did not demonstrate CV harm, also giving some evidence to the critics that the broad application of CV outcome trials to all treatments of type-2 DM based on a meta-analysis was reactionary. Also noted for each trial are that some of the MACE components point estimates are above unity and some are below, while the confidence intervals include unity.

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/s/

CURTIS J ROSEBRAUGH
12/18/2013