Module 1.8.2

European Union Risk Management Plan (EU-RMP) for Umeclidinium bromide/Vilanterol

RMP version to be assessed as part of this application	
RMP Version number	10.0
Data lock point for this RMP	22 December 2023
Date of final sign off	15 March 2024

Rationale for submitting an updated RMP

This EU-RMP update is triggered by the completion of study 201038 "Post-authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients Using Inhaled UMEC/VI Combination, or Inhaled UMEC versus Tiotropium."

Summary of significant changes in this RMP:		
PART	**MODULE**	**Changes made in EU-RMP version 10.0:**
I	S.I	Update to epidemiological data (updated to provide more recent epidemiological data; no substantial changes which can impact benefit/risk profile)
II	S.V	Update to post-authorization exposure
II	S.VII	Proposed removal of risks and missing information update to all sections in consideration of results of PASS 201038 and GVP module Revision 2 guidelines. Relevant data from Study 201038 added where applicable.
III	III	Proposed removal of Study 201038.
V	V.1	Proposed removal of risk minimization measures
V	V.3	Proposed removal of summary of risk minimization measures.
VI	II.A	Summary of risk management plan for ANORO/LAVENTAIR ELLIPTA. Proposed removal of

		List of Important Potential Risks, Missing Information
VI	II.B	Proposed removal of Summary of important risks
VI	II.C	Proposed removal of Studies which are conditions of the marketing authorization

Other RMP versions under evaluation
Not applicable

Details of the currently approved RMP		
Version number	**Approved with procedure**	**Date of approval (opinion date)**
9.0	EMEA/H/C/WS/1850	15/10/2020

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Senior Vice President, Head of Clinical Safety & Pharmacovigilance and EU QPPV
QPPV Signature	Electronic signature on file

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Umeclidinium bromide/Vilanterol trifenatate
Pharmacotherapeutic group(s) (ATC Code)	Adrenergics in combination with anticholinergics (ATC code: R03AL03)
Marketing Authorisation Holder/ Applicant	GlaxoSmithKline (Ireland) Limited
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	ANORO ELLIPTA, LAVENTAIR ELLIPTA
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class Umeclidinium bromide is a long-acting muscarinic receptor antagonist. Vilanterol trifenatate is a long-acting beta2-adrenoceptor agonist.

	Summary of mode of action Inhaled anticholinergic bronchodilators or long-acting muscarinic receptor antagonists (LAMAs) function by blocking endogenous airway smooth muscle cholinergic tone. The principal action of inhaled beta2-agonists is to relax airway smooth muscle by stimulating beta2-adrenergic receptors, which increases cyclic AMP to produce bronchodilatory effects.
	Important information about its composition Contains lactose monohydrate (which contains milk protein).
Reference to the Product Information	Please refer to the approved product information
Indication(s) in the EEA	Current (if applicable): ANORO ELLIPTA/LAVENTAIR ELLIPTA is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease.
	Proposed (if applicable): Not applicable
Dosage in the EEA	Current (if applicable): The recommended dose is one inhalation of ANORO ELLIPTA /LAVENTAIR ELLIPTA 55/22 micrograms once daily. ANORO ELLIPTA /LAVENTAIR ELLIPTA should be administered once daily at the same time of the day each day to maintain bronchodilation. The maximum dose is one inhalation of ANORO ELLIPTA /LAVENTAIR ELLIPTA 55/22 micrograms once daily.
	Proposed (if applicable): Not applicable

Pharmaceutical form(s) and strengths	Current (if applicable): Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 65 micrograms umeclidinium bromide equivalent to 55 micrograms of umeclidinium and 22 micrograms of vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate).
	Proposed (if applicable): Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations

AE	Adverse Event
ADR	Adverse Drug Reaction
AERS	Adverse Event Reporting System
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AMI	Acute myocardial infarction
ATC	Anatomical Therapeutic Chemical
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BMD	Bone mineral density
BMI	Body Mass Index
CAP	Community acquired pneumonia
CAT	COPD Assessment Test
CDC	Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	SARS-CoV-2 virus
CV	Cardiovascular
CVD	Cardiovascular Disease
CPRD	Clinical Practice Research Datalink
CSR	Clinical Study Report
CYP	Cytochrome
DALY	Disability-adjusted life years
sDPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicine Agency
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HR	Hazard Ratio
HV	Healthy Volunteer
ICH	International Conference on Harmonisation
ICS	Inhaled Corticosteroids
IHCIS	Integrated Health Care Information System
IHME	Institute for Health Metrics and Evaluation
IRR	Incidence Rate Ratio
ITT	Intention To Treat
IV	Intravenous
LABA	Long-Acting Beta Agonists
LABD	Long-Acting Bronchodilators
LAMA	Long-Acting Muscarinic Antagonists

LS	Least Square
MACE	Major Adverse Cardiac Events
mcg	micro grams
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council dyspnoea questionnaire
MINOAEL	Myocardial InfarctionNo Observed Adverse Effect Level
OATP	Organic Anion Transporting Polypeptide
OR	Odds Ratio
PASS	Post-Authorization Safety Study
PBO	Placebo
PBRER	Periodic Benefit-Risk Evaluation Report
PD	Pharmacodynamic
PV	Pharmacovigilance
PK	Pharmacokinetic
PRO	Patient Reported Outcomes
PSM	Propensity Score Matched
PSUR	Periodic Safety Updated Report
PT	Preferred Term
PY	Patient Years
QTc(F)	Quaque Die (once daily)
QD	Corrected QT interval using Fridericia's formula
RCT	Randomized Control Trial
RMM	Risk Minimisation Measure
RR	Relative Risk
SABA	Short Acting Beta 2 Agonist
SAE	Serious Adverse Event
SAMA	Short Acting Muscarinic Antagonist
SmPC	Summary of Product Characteristic
SMQ	Standardised MedDRA Query
sNDA	Supplementary New Drug Application
SOC	System Organ Class
SUMMIT	Study to Understand Mortality and Morbidity in COPD
aRMM	Additional Risk Minimisation Measure
THIN	The Health Improvement Network
TIO	Tiotropium
TORCH	Towards a Revolution in COPD Health
UK	United Kingdom
ULN	Upper Limit of Normal
UMEC	Umeclidinium
UMEC/VI	Umeclidinium/Vilanterol
US	United States
USPI	United States Prescribing Information
UTI	Urinary Tract Infection
VI	Vilanterol
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies	Trademarks not owned by the GlaxoSmithKline group of companies
ANORO	SPIRIVA
ELLIPTA	
TRELEGY	
RELVAR	
LAVENTAIR	

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Indication (COPD)

ANORO ELLIPTA /LAVENTAIR ELLIPTA is indicated as a maintenance bronchodilator treatment in adult patients with chronic obstructive pulmonary disease (COPD).

Incidence

Data from the Global Burden of Disease Study suggested that the global incidence rate in 2019 of COPD was 210 per 100,000 and that the number of new cases diagnosed in 2017 totaled over 16 million [IHME 2020; Vos, 2020]. Estimates of incidence vary with patient characteristics. The one-year, age-standardised incidence rate of COPD in the UK is 274 per 100,000 persons [IHME 2020]. Age-standardised incidence rates across Europe range as high as 303 per 100,000 persons in Denmark to as low as 83 per 100,000 in Latvia. One-year, age-standardised incidence rates from other countries of note include: United States with 254 per 100,000 persons, Australia with 228 per 100,000 persons, Canada with 209 per 100,000 persons, and Japan with 111 per 100,000 persons [IHME 2020]. When stratified by sex, the one-year, age-standardised incidence rate is generally higher among men across Europe (Table 2). Notable exceptions include Denmark (female vs male; 305 vs 301 cases per 100,000 persons), Iceland (female vs male; 224 vs 211 cases per 100,000), Norway (female vs male; 265 vs 260 cases per 100,000), and Sweden (female vs male; 241 vs 226 cases per 100,000) [IHME 2020].

The incidence rate of COPD increases with age. In the UK, for example, the incidence rate is: 139 per 100,000 for adults aged 25-49, 717 per 100,000 for adults aged 50-70, and 1,848 for adults over age 70 [IHME 2020]. COPD affects approximately 7.5% of the UKs population. A little over 4 million of the UK's 4.7 million cases in 2019 were among adults over the age of 50 [IHME 2020]. Given COPD association with age, countries with a greater proportion of elderly populations will be more impacted by COPD incidence.

Sex and age trends in the prevalence and incidence of COPD in the UK are also seen throughout Europe and across the globe [IHME 2020]. On average, the one-year incidence rate of COPD has increased 30-40 per 100,000 since 2010.

Table 2 Age-standardized incidence rates of COPD stratified by sex and select global regions [IHME 2020]

Region	Male age-standardised incidence rate (new cases per 100 000 population)	Female age-standardised incidence rate (new cases per 100 000 population)
Western Europe	242	196
Central Europe	219	122

Eastern Europe	177	77
North America	260	241
East Asia	205	207
South Asia	270	263
Southeast Asia	235	139

Within Europe, specifically, incidence rates of COPD range from 120-546 cases per 100,000 [IHME 2020]. (Table 3) lists the 10 countries in Europe with the highest COPD incidence rates with the estimated percentage of population affected.

Table 3 Highest incidence rates of COPD in Europe [IHME 2020]

Country	Incidence rate (new cases per 100,000 population)	Prevalence in the total population (%)
Denmark	546	8.72
Monaco	518	7.78
Netherlands	510	7.86
Belgium	489	7.93
Greece	476	6.67
Germany	474	7.58
United Kingdom	467	7.47
Spain	465	6.68
Portugal	463	6.20
Sweden	445	6.79

Prevalence

Country specific data from the Global Burden of Disease Study in 2019 suggested considerable variation in the incidence and prevalence rates of COPD between countries (Table 4).

In a systematic literature review of 60 published researched studies, the authors estimated that across both sexes and all ages the prevalence of COPD Gold Stage I and II was each about 7% across the globe [Varmaghani 2019]. The global prevalence of COPD Gold Stage III/IV was

about 2%. As seen in other data sources, the authors also concluded that the prevalence of COPD increases drastically with age.

Table 4 Incidence and Prevalence rates of COPD in selected countries [IHME 2020]

Country	Incidence rate (new cases per 100 000 population)	Prevalence rate (total cases per 100 000 population)	Prevalence (estimated total number of cases in 2017)
Germany	474	7 220	6 130 746
United Kingdom	467	7 033	4 727 607
Spain	466	6 314	2 905 818
Italy	429	5 394	3 253 110
United States	403	6 143	20 147 917
Canada	384	4 979	1 818 278
Australia	367	5 229	1 284 616
Japan	328	3 748	4 789 562
France	300	3 841	2 543 487

SI.1.1 Demographics of the population in the authorized indication and risk factors for the disease

Patients with COPD tend to be above 40 years of age with significant smoking history. Previously, COPD has tended to occur more predominantly in men, but in recent studies, prevalence in women (especially in the US) appeared to be becoming comparable or even higher than among men (Global: 2.85% in males vs 2.86 in females; US: 6.11% vs 6.83%) [Landis 2014; IHME 2020].

People aged above 40 years, who are heavy smokers, appear to be at higher risk of developing COPD. However, the disease may also develop after exposure to dust, chemicals and fumes. Genetic risk factors may contribute, such as α1-antitrypsin deficiency. Other risk factors are low birth weight, history of severe respiratory infection in childhood and lower socioeconomic status [Global Initiative for Obstructive Lung Disease (GOLD) 2024].

Based on data from the US Behavioral Risk Factor Surveillance System, the reported COPD prevalence is highest among adults age ≥65 (12.8%), among multiracial adults (9.3%) and among

American Indian/Alaskan Native (11.9%) [Wheaton 2019]. COPD prevalence in the US is higher among current smokers (15.2%) versus former smokers (7.6%) or never smokers (2.8%).

SI.1.2 The main existing treatment options

COPD treatment guidelines recommend an incremental approach to pharmacological treatment as the disease state worsens, involving the use of combinations of drug classes with different or complementary mechanisms of action. Currently, a more personalised approach based on the individualised assessment of symptoms and future risk of exacerbation is preferred [GOLD, 2024].

Bronchodilators, such as beta2-agonists and anti-muscarinic, are central to improving lung function and symptoms, including exercise tolerance and health status in COPD. Long-acting agents are convenient and more effective at producing maintained symptom relief than short-acting ones. Although, long-term monotherapy treatment with ICS is not recommended, the addition of inhaled corticosteroids to bronchodilators leads to reductions in the frequency of exacerbations, improves symptoms and quality of life and produces small improvements in lung function [GOLD, 2024]. Factors unfavourable to ICS use are recurrent pneumonia, history of mycobacterial infection, and eosinophils (<100 cells/μL) [GOLD, 2024].

For the treatment of exacerbations, short-acting inhaled beta2-antagonist, with or without anticholinergics, are recommended as the initial bronchodilator to treat an acute mild-moderate exacerbation. Oral corticosteroids or antibiotics may be added to the treatment regimen for moderate exacerbations [GOLD, 2024]. Treatment of severe exacerbations would additionally include considerations of increased short-acting bronchodilator dosage, oxygen therapy, or non-invasive mechanical ventilation. For all patients hospitalised for exacerbations, they should be assessed for severe Vitamin D deficiency and supplemented if required [GOLD, 2024]. The goals of pharmacologic therapy in COPD should be to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance, with differing treatment recommendations according to GOLD group [GOLD, 2024]. For patients in the GOLD Group E category the choice of therapy is a combination of long-acting beta2-agonist/long-acting anticholinergics (LABA/LAMA) or an inhaled corticosteroid plus long-acting beta2 agonist and long-acting anticholinergic (ICS/LABA/LAMA) if blood eosinophil levels ≥ 300 [GOLD, 2024].) See recommended initial pharmacological treatment in Table 5.

Table 5 Recommended initial pharmacological treatment by GOLD group [GOLD, 2024]

INITIAL PHARMACOLOGICAL TREATMENT		
≥ 2 moderate exacerbations or ≥ 1 leading to hospitalization	**GROUP E** LABA+LAMA* (consider LABA+LAMA+ICS* if blood eosinophils ≥300)	
0 or 1 moderate exacerbations (not leading to hospital admission)	**GROUP A** A bronchodilator	**GROUP B** LABA+LAMA*
	mMRC 0-1 CAT<10	mMRC ≥ 2 CAT ≥ 10

*single inhaler therapy may be more convenient and effective than multiple inhalers; mMRC=modified Medical Research Council dyspnoea questionnaire; CAT= COPD Assessment Test; LABA = long-acting beta2 agonist; LAMA = long-acting muscarinic antagonist; ICS = inhaled corticosteroids

SI.1.3 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

Globally in 2019, COPD was the 3rd leading cause of death, with WHO estimating over 3.2 million deaths due to COPD. According to most recent World Health Organization (WHO) estimates, 65 million people have moderate to severe COPD. Mortality rates in patients with COPD increase substantially with age. COPD was the 6th leading cause of mortality in the US in 2020 [Murphy 2021; CDC 2021]. Before the global pandemic of COVID-19, chronic lower respiratory disease was the 4th leading cause of death in the US.

Age-standardised mortality rates in Europe varied from 8.4 per 100,000 to 33.5 per 100,000 persons [IHME 2020]. In Europe, the overall mortality rate for COPD was about 19.7 per 100 000 persons. There is a general trend for countries with higher prevalence of cigarette smoking to have higher mortality from COPD. In the US, the age-standardised mortality rate for COPD in 2019 was 32.5 per 100,000 overall and higher in men (37.8 per 100,000) than women (28.7 per 100,000) [IHME 2020].

Disease severity and COPD exacerbations increase the risk of mortality. In a nationwide Danish study from 2018 3-year mortality increased with increasing exacerbations and dyspnoea from group A (all-cause mortality 10.0%, respiratory mortality 3.0%) to group D (all-cause mortality 36.9%, respiratory mortality 18.0%). However, 3-year mortality was higher for group B patients (all-cause mortality 23.8%, respiratory mortality 9.7%) than for group C patients (all-cause mortality 17.4%, respiratory mortality 6.4%). Compared with group A, adjusted HRs for all-cause mortality ranged from 2.05 (95% CI 1.87–2.26) for group B, to 1.47 (1.31–1.65) for group C, and to 3.01 (2.75–3.30) for group D [Gedebjerg, 2018].

Just as smoking status is associated with higher prevalence of COPD, it is also associated with greater mortality. Tobacco use is the #1 contributor to COPD mortality and was associated with 1.41 million COPD deaths [Li, 2017]. The second highest contributor to COPD mortality is ambient air pollution or particulate matter. Others important risk factors and comorbidities include anaemia, sleep disturbance, and having anxiety or depression symptoms [Cavaillès 2013].

COPD is associated with considerable morbidity. In European countries, the average age-standardised admission rate for COPD is around 200 per 100,000 people per year, with large variation in rates (as high as 10-fold) between European countries due to differences in the average age of the population and availability of hospital beds [European Lung White Book 2013]. In 2019, age-standardised disability-adjusted life years (DALYs) for COPD were 1149 per 100,000 men globally and 744 per 100,000 females [IHME 2020].

SI.1.4 Important co-morbidities

Important Co-morbidity	Incidence, prevalence, and mortality
Smoking-Related Co-morbidities: Cardiovascular Disease	Patients with COPD tend to be older and have significant smoking history; therefore, patients with COPD have more co-morbid CV disease than patients without COPD. In a qualitative review of over 100 published research studies examining major comorbidities in patients with COPD, the authors calculated the weighted average prevalences of several important cardiovascular disease comorbidities. The authors calculated a weighted average prevalence of: 43% for hypertension, 29% for ischemic heart disease, 23% for pulmonary hypertension, and 18% for heart failure [Smith 2014]. A longitudinal study in the Netherlands of 13,471 adults (including 1615 with COPD) showed that those with COPD were at higher risk of sudden cardiac death compared with participants without COPD (HR=1.34, 95% CI 1.06-1.70); risk of death was even higher for COPD patients with frequent exacerbations (HR=3.58, 95% CI 2.35-5.44) [Lahousse, 2015]. In a systematic review and meta-analysis of 29 datasets from 27 observational studies (~11 million COPD cases), evidence was found for a 2- to 5-fold increase in risk of ischemic heart disease, cardiac dysrhythmia, heart failure, diseases of the pulmonary circulation, and diseases of the arteries in those with COPD compared with the population with no COPD [Chen, 2015]. In the TORCH trial, 27% of deaths among participants were attributed to cardiovascular causes [Calverley, 2007]. From these types of data, it is clear that CV disease represents a significant co-morbidity of COPD. In the FF/VI clinical studies approximately 60% of the participants had a concurrent CV condition on entry into the study. This is consistent with the findings in other large studies in the COPD population.

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In prior studies in COPD, cardiovascular events, including those with a serious outcome were frequently observed across all treatment arms including placebo. The table below shows the experience from the TORCH study with salmeterol/fluticasone propionate and the incidence rates of CV events [Calverley 2010].

Incidence Rate of Cardiovascular (CV) Events per 1000 person years
<table>
<tr><th>Adverse Event</th><th>Placebo (n=1544)</th><th>Salmeterol (n=1542)</th><th>FP (n=1552)</th><th>FP/Salmeterol (n=1546)</th></tr>
<tr><td>Any CV event</td><td>142</td><td>141</td><td>130</td><td>110</td></tr>
<tr><td>Serious CV event</td><td>75</td><td>66</td><td>66</td><td>57</td></tr>
<tr><td>Ischemia CV event</td><td>68</td><td>70</td><td>62</td><td>54</td></tr>
<tr><td>Stroke-related</td><td>17</td><td>13</td><td>16</td><td>12</td></tr>
</table>

In a sub-cohort analysis of the SUMMIT trial, the hazard ratio for CVD events after an acute exacerbation of COPD was increased, particularly in the first 30 days after exacerbation (HR: 3.8; 95% CI: 2.7, 5.5). The 30-day hazard ratio for a CVD event after an acute exacerbation of COPD requiring hospitalization was more than 2-fold greater (HR: 9.9; 95% CI: 6.6, 14.9) [Kunisaki 2018].
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<tr>
<td>Smoking-Related Co-morbidities: Lung Cancer</td>
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Lung cancer is a frequent co-morbidity among patients with COPD, with incidence rates as high as 16.7 cases per 1000 person-years [Smith 2014].
A review examining published studies of COPD comorbidities calculated a weighted average prevalence of lung cancer in COPD patients to be about 9% [Smith 2014].

Not only is COPD frequently diagnosed among lung cancer patients, but it is also underdiagnosed. A study in Spain reported that 71.6% of COPD cases among all lung cancer patients over a 2 year period were underdiagnosed [Mouronte-Roibas 2018]. In 73.9% of these COPD+lung cancer cases, the patients were GOLD stage I and II. Results from this study also suggested that patients with both COPD and lung cancer died, on average, 6 months earlier than lung cancer patients without COPD. In a UK study of high-risk individuals for lung cancer, 67% of participants were underdiagnosed for COPD [Ruparel 2020].
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<tr>
<td>Age-Related Co-morbidities: Diabetes,</td>
<td>Most COPD patients are above 65 years of age, and older age can be an independent risk factor for diseases.</td>
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</table>

Cataracts, Glaucoma	A review calculated a weighted average prevalence (25 studies) of 15% for cataracts in COPD patients [Smith 2014]. In a study specific to inhaled corticosteroids-induced cataracts and glaucoma, the prevalence of cataracts was 16.2% and the prevalence of glaucoma was 3.9% [Nath 2017]. A review cited a range (4 studies) for the prevalence of diabetes in COPD patients from 10.3-18.7%, depending on the stage of COPD and age of the patients [Cavaillès 2013]. Diabetes has also been shown to affect the prognosis of COPD. The hazard ratio for COPD-related death in diabetes patients was 1.27 compared to patients without diabetes [Cavaillès 2013].
Pneumonia	The incidence of pneumonia including pneumonia requiring hospitalization in a COPD population is dependent upon several patient characteristics, and is greater with increasing age, increasing COPD disease severity, lower BMI (<20), being male, and the presence of co-morbid conditions [Williams 2017]. In a COPD cohort of 40,414 patients in the UK, the incidence of pneumonia was 22.4 per 1,000 person years [Müllerova, 2012], and it increased with disease severity. A separate COPD cohort of 13,513 in the UK had an incidence of pneumonia of 37.6 per 1,000 person years [Williams 2017]. The risk of acquiring pneumonia also increases markedly with age after the age of 60 (age 60-79, OR:1.67, 95% CI: 1.30-2.16; ≥80, OR: 4.10, 95% CI: 3.05-5.94). Risk also increases with GOLD Stage when compared to GOLD Stage I (GOLD II OR: 1.29, GOLD III OR: 2.24, GOLD IV OR: 2.86) [Williams 2017]. Due to difficulties in distinguishing COPD exacerbations from pneumonia with COPD, the prevalence of pneumonia in COPD patients has a wide range across studies. An older (1979-2001), but comprehensive study of over 22 years of hospital discharge data from the United States suggested that approximately 11% of COPD patients also had an pneumonia infection [Holguin 2005]. More recent studies from Europe also suggest a similar prevalence range of 13-15% of COPD patients having a pneumonia infection [Williams 2017; Boixeda 2014]. The background mortality of pneumonia in this population is high, and is often one of the complications of COPD that results in death. A review of COPD admissions (n=9,338) in the UK in 2008 [Myint 2011] showed that only 16% had a chest X-ray consistent with pneumonia. COPD exacerbations with pneumonia were associated with worse outcomes, with a mortality rate of 11% for those with pneumonia, compared with 7% in those without radiographic evidence of pneumonia. A Danish study reported similar 30-day mortality rates for pneumonic (12.1%) and non-pneumonic (8.4%) COPD patients hospitalized for their first acute exacerbation [Søgaard 2016]. In a systematic review and meta-analysis of 18 observational studies (>100,000 observations) examining mortality in community-acquired pneumonia in COPD patients, the authors concluded that co-existing CAP was associated with increased mortality in hospitalized COPD patients [Yu 2021]. The pooled RR for all mortality metrics (in-hospital mortality, short-term (≤3 mo post discharge), long-term (>3 mo post discharge)) was 1.85 (95% CI: 1.50, 2.30).

	Inhaled corticosteroids have been linked to increased pneumonia incidence. Multiple pooled and meta-analyses have been conducted over time with a variety of treatment groups in COPD patients from clinical trials, including active treatments and placebo. There appears to be an increased risk of pneumonia among patients with COPD who are treated with ICS-containing medications relative to those treated with non-corticosteroid-containing medications or placebo [Drummond 2008; Spencer 2011; Zhang 2020]. In the most recently published meta-analysis of 18 RCTs of associations between pneumonia and ICS utilization, the authors estimated a pooled RR of 1.43 (95% CI: 1.31, 1.56) suggesting a clear increase in risk of pneumonia with ICS use [Zhang 2020]. The authors also examined risk by different ICS types: fluticasone propionate (RR: 1.79, 95% CI: 1.49-2.16), fluticasone furoate (RR: 1.37, 95% CI: 1.23-1.52), budesonide (RR: 1.07, 95% CI: 0.78-1.47), beclomethasone (RR: 1.46, 95% CI: 0.91-2.35). An article 31 referral procedure on the risk of pneumonia with inhaled corticosteroids in COPD concluded on 28 April 2016 (EMEA/H/A-31/1415). Following a review of the available data, EMA confirmed the risk of pneumonia with inhaled corticosteroids (ICS) in patients with COPD. There is no conclusive clinical evidence for intra-class differences in the magnitude of the risk among ICS products (EMA/285392/2016 EMA 2016). There were two year-long exacerbation studies in COPD examining FP/Salmeterol vs. Salmeterol. Patients were aged 40 years or more and had an established clinical history of COPD, a pre-bronchodilator $FEV_1 \leq 50\%$ of predicted normal, a pre-bronchodilator FEV_1/forced vital capacity (FVC) ratio of ≤70%, a cigarette smoking history of ≥10 pack-years, and a documented history of at least one COPD exacerbation in the past year prior to screening that required treatment with oral corticosteroids, antibiotics, or resulted in hospitalization [Anzueto, 2009; Ferguson 2008]. In these replicate 12-month studies of 1,579 patients with COPD (n=788 FP/Salmeterol, n=791 Salmeterol), there was a higher incidence of pneumonia reported in patients receiving FP/Salmeterol (7%) than in those receiving Salmeterol 50 mcg (3%) [Anzueto, 2009; Ferguson, 2008]. The proportion of these AEs due to pneumonia that were serious was 32 of 55 (58%) on FP/Salmeterol and 15 of 18 (72%) on Salmeterol. One AE resulted in death (FP/Salmeterol treatment arm). Although COPD participants on ICS-containing regimens are more likely to develop pneumonia, those that do appear not to have an increased risk of mortality relative to patients on other treatments; however, the data are not definitive. In a meta-analysis of studies examining pneumonia-associated mortality and ICS use, there was no significant differences between ICS and non-ICS arms in either pneumonia-associated mortality or pneumonia fatality in RCTs and observational studies [Festic 2016]. Pooled risk ratios from [Festic 2016]

<table>
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<tr><td></td><td>Pneumonia-associated mortality (95% CI)
(sample size of pooled estimate)</td><td>Pneumonia fatality (95% CI)
(sample size of pooled estimate)</td></tr>
<tr><td>RCTs</td><td>1.50 (0.85, 2.67)
(n=12,958; 6 studies)</td><td>0.91 (0.52, 1.59)
(n=1,159; 6 studies)</td></tr>
<tr><td>Observational studies</td><td>1.09 (0.98, 1.21)
(n=146,175; 2 studies)</td><td>0.72 (0.59, 0.88)
(n=37,701; 8 studies)</td></tr>
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<tr><td>Decreased Bone Mineral Density</td><td>
Risk factors for osteoporosis in COPD patients include older age, smoking, low body mass index (BMI) and physical inactivity [Inoue 2016]. Further, COPD-related systemic inflammation, vitamin D deficiency, and the use of systemic corticosteroids in treatment of COPD may enhance the decline in bone mineral density [Inoue, 2016].

In a recent reviews of the literature, it has been shown that there is wide variability in the prevalence of osteoporosis, defined as low bone mineral density, in COPD, from 9% to 69%, while the prevalence of vertebral fractures was as high as 79%, both estimates reply on the choice of diagnostic methods, population studied, and the severity of the underlying respiratory disease [Inoue 2016; Chen 2019]. The pooled odds ratio (58 studies) for having osteoporosis in COPD patients vs comparison/control patients was 2.99 (95% CI: 2.09, 4.27) [Chen 2019]. One of the reviews also identified several studies demonstrating an association between lower levels of FEV_1, which is sometimes coupled with greater COPD severity, and reduced bone mineral density [Inoue, 2016].

The incidence of fracture seen over 3 years in a COPD population in the TORCH study was 5.1 to 6.3% across all treatment groups [Calverley 2007].

Historically, studies among adults with COPD yield varied evidence for the direct effect of ICS on BMD and fracture. There appears to be a modest increase in risk of fracture among patients with COPD treated with ICS, but results are not consistent across individual studies [Legrand, 2000; Lehouck, 2011; Weldon, 2009; Christensson, 2008]. One study reported that long-term ICS decelerated annual BMD loss in bronchitic patients [Mathioudakis 2013]. Overall, the relationship between long-term ICS use and risk of bone fracture is unclear [Caramori 2019]. Due to data deficiencies and use of inconsistent terminology, it is difficult to fully elucidate the nature of this relationship across studies.

A systematic review and meta-analysis of 16 randomized clinical trials (n=17 513 participants) and 7 observational studies (n=69,000 participants) suggest a modest increase in the risk of fracture among COPD patients treated with ICS relative to those not treated with a steroid [Loke, 2011]. ICS were associated with a significantly increased risk of fractures (Peto OR 1.27; 95% CI 1.01-1.58 and OR=1.21; 95% CI 1.12-1.32) in randomized trials and observational studies, respectively. There was a dose-response relationship, a 9% increase in risk with
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</table>

	each 500 mcg increase in beclomethasone dose equivalents. Results looking at patients with asthma or patients with asthma or COPD produced similar findings [Hubbard, 2006]. COPD and osteoporosis are associated and share common risk factors such as age, smoking, and inactivity. At baseline in the TORCH randomized clinical trial, 18% of men and 30% of women had osteoporosis, and 42% of men and 41% of women had osteopenia based on BMD assessments [Ferguson, 2009]. Bisphosphonate use was 7% at baseline and 23% for other BMD therapies, where users of BMD therapies were disproportionately female. There is an increased risk of additional fracture or mortality in the period immediately following a fracture, particularly in the frail elderly [van den Bergh 2012]. As BMD worsens (BMD T-score decrease) in COPD patients, there is an increasing risk of all-cause mortality (HR: 1.04; 95% CI: 1.00, 1.08) [Vikjord 2019].

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies and relevance to human usage:

Key safety findings (from non-clinical studies)	Relevance to human usage
Single and repeat dose toxicity: • In accordance with ICH M3 (R2), single dose, acute inhaled toxicity studies have not been conducted with UMEC or VI. In single dose tolerability studies in the rodent, UMEC was well tolerated following oral, intravenous or subcutaneous administration. In single dose tolerability studies with VI, dose-related clinical signs were seen following high single intravenous doses in rats, high oral doses in rats were well tolerated and in dogs, single inhaled doses were associated with vasodilatation and increased pulse rate. • In repeat dose inhalation toxicity studies, the principal toxicities seen with UMEC of relevance to risk assessment were irritant effects in the respiratory tract and expected pharmacology-related CV effects (see below). • Other effects, seen only in some studies, were considered of less importance. Effects in the lung (granuloma formation) observed in one dog study only were considered to be secondary to excessive anti-muscarinic pharmacology. Gall bladder distension accompanied by myofibre degeneration/regeneration was observed in one 14 day dog study only, and has not been observed in longer term studies in the dog either with UMEC alone or in combination with VI, which achieved similar systemic exposures. Accumulations of alveolar macrophages were only observed in the lung of rats, including controls, in longer-term studies; small variations in incidences were either only at a high dose (26 week study, small shift in severity at high dose) or generally similar to historical background data. Given the characteristics of the	• In clinical trials for UMEC/VI, the incidence of symptoms associated with local irritancy (*e.g.* cough, nasopharyngitis, and oropharyngeal pain) were reported across all treatment arms, including UMEC and placebo. These events were commonly reported and were not associated with any sequelae. • A diagnostic ultrasound of the gall bladder in two Phase 2b studies (AC4113073 and AC4113589) and a Phase 2a study (DB2113120) was performed for participants who developed Right Upper Quadrant (RUQ) pain in which a gall bladder-related adverse event could not be excluded. Results from these studies and additional clinical pharmacology studies indicated that treatment with UMEC or UMEC/VI did not result in an increased incidence of RUQ pain and/or gall bladder-related adverse events nor was UMEC associated with abnormal findings for gall bladder length and width compared with placebo. In addition, in the clinical studies, the incidence of on-treatment events in the gallbladder disorders adverse events of special interest (AESI) category which includes AEs of cholecystitis, acute cholecystitis, chronic cholecystitis, and cholelithiasis, was low and similar across both doses of UMEC/VI, UMEC, VI and placebo treatment groups • In clinical trials for UMEC/VI, the incidence of symptoms associated with local irritancy (*e.g.* cough, nasopharyngitis, and oropharyngeal pain) were reported across all active treatment arms, including VI, and placebo.

Key safety findings (from non-clinical studies)	Relevance to human usage
response and the overages based on lung deposited dose and given alveolar macrophages in the lung are a common finding in inhalation studies, including controls, this is not considered to be of clinical significance. • In repeat dose inhalation toxicity studies, the principal toxicities seen with VI were upper respiratory tract irritancy and pharmacology-driven CV effects (see below), metabolic changes, rodent reproductive changes and minor skeletal muscle effects. • UMEC had no effects on male or female mating performance or fertility, nor any effects on embryofetal survival and development in either the rat or rabbit. In a rat pre-and post-natal study, apart from slightly decreased pre-weaning pup body weights in litters from dams where UMEC caused decreased maternal body weight gain and food consumption, there were no other effects on pre-natal or post-natal development. • VI did not affect male or female rat fertility, nor did it produce any adverse effects on the developing rat fetus. However, in the rabbit, inhaled doses of VI caused a number of class-related but inconsistent findings such as cleft palate, open eyelids, sternebral fusion and abnormal frontal bone ossification. A NOAEL of 30 mcg/kg (AUC: 22.4 ng.h/mL) was established by the subcutaneous route, providing a safety margin of 36-fold relative to the AUC in adult humans following a dose of 25 mcg/day. This spectrum of changes has been observed with other beta$_2$-receptor agonists and appears dependent on high exposures. • No novel toxicity was identified nor any evidence of exacerbation of toxicity when UMEC was given in combination with VI for up to 13 weeks duration in dogs. The 4-week combination study in rats did not show any novel toxicity and only a modest exacerbation	These events were commonly reported and were not associated with any sequelae. • The metabolic changes observed with VI in the nonclinical species have not been observed in COPD subjected with UMEC/VI. • The minor microscopic changes in skeletal muscle observed were observed in one rat 4 week combination study with the GSK ICS (GW685698). Although similar findings have been reported with other beta$_2$-agonists (*e.g.* clenbuterol), they were not seen in other rat studies of similar or longer duration or in any dog studies. • The ovarian changes observed with VI are considered to be rodent-specific and are of no relevance to humans because a similar beta$_2$-related mechanism for cyst formation has not been identified over many patient years of clinical use with other beta$_2$-agonists. • An extensive search of salmeterol and Seretide/Advair clinical and post-marketing GSK databases, the FDA AERS database and literature, was conducted, and the review of the data has not identified any clinically relevant signals for proliferative uterine changes. • Extensive clinical use of beta$_2$-agonists over many years, including their inevitable and deliberate use in pregnancy (to prevent pre-term labor), has established the safety of therapeutic doses of this class of medicine. Follow-up studies on children whose mothers had received beta$_2$-agonists during pregnancy have not shown an association of treatment with adverse developmental effects. • In clinical trials for UMEC/VI, the incidence of symptoms associated with local irritancy (*e.g.* cough, nasopharyngitis, oropharyngeal pain) were reported across all treatment arms and placebo. These events were commonly

Key safety findings (from non-clinical studies)	Relevance to human usage
of the irritant effects of both UMEC and VI was observed in the upper respiratory tract. The 4 week dog combination study specifically investigating the effect of the use of the pre-adaptation phase on the heart did not show any significant differences (*i.e.* effects on the heart) between pre-adapted and non-adapted groups, indicating pre-adaptation did not protect the heart from any unexpected effects. • There were no hepatotoxicity or nephrotoxicities identified with either UMEC or VI alone or in combination. Genotoxicity: • *In vitro* or *in vivo* genotoxicity studies with either UMEC, VI or GI179710 (the counter-ion of VI M triphenylacetate salt), indicate that neither UMEC nor VI represent a genotoxic hazard to humans. Carcinogenicity: • There were no treatment-related increases in tumor incidence following lifetime administration of UMEC by the inhalation route. • In the inhaled carcinogenicity studies with VI, proliferative changes were seen in the female reproductive tract of rats and mice and pituitary gland in rats; all effects observed in both species have been observed following administration of other marketed beta$_2$-agonists and are considered not to be human relevant. Developmental Toxicity: • UMEC had no effects on male or female mating performance or fertility, nor any effects on embryofetal survival and development in either the rat or rabbit. In a rat pre- and post-natal study, apart from slightly decreased pre-weaning pup body weights in litters from dams where UMEC caused decreased maternal body weight gain and food	reported and were not associated with any sequelae. • Leiomyomas (and other proliferative changes of the reproductive tract) have not shown increased incidence in women over years of extensive use of beta$_2$-agonists in the treatment of bronchial asthma, and their formation at high multiples of human therapeutic exposure to VI indicates no relevance to therapeutic use in humans. • Based on a review of salmeterol and associated clinical and post-marketing databases, the FDA AERS database and available literature, the extensive human experience with beta$_2$-agonists over 40 years (including approximately 70 million patient-years exposure to salmeterol), there is no evidence that the pituitary findings caused by salmeterol in rat are relevant in humans. It is, therefore, considered unlikely that GW642444 use in humans would lead to

Key safety findings (from non-clinical studies)	Relevance to human usage
consumption, there were no other effects on pre-natal or post-natal development. • VI did not affect male or female rat fertility nor did it produce any adverse effects on the developing rat fetus. However, in the rabbit, inhaled doses of VI caused a number of class-related but inconsistent findings such as cleft palate, open eyelids, sternebral fusion and abnormal frontal bone ossification. A NOAEL of 30 mcg/kg (AUC: 22.4 ng.h/mL) was established by the subcutaneous route, providing a safety margin of 36-fold relative to the AUC in adult humans following a dose of 25 mcg/day. These spectrum of changes has been observed with other $beta_2$-receptor agonists and appear dependent on high exposures. The use of LABAs (*e.g.* salmeterol, formoterol) during pregnancy was not associated with any particular adverse event.	similar pathology to that observed in the rat carcinogenicity study. • As there are no studies with this combination in pregnant women, UMEC/VI should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.
<u>Safety Pharmacology</u>: • There were no respiratory or central nervous systems safety pharmacology findings of concern with UMEC. UMEC caused altered ion channel activities *in vitro* and as expected from the pharmacology of muscarinic antagonists, a number of CV effects, including tachycardia in dogs. In repeat dose inhaled studies, increased pulse rates/heart rates were generally accompanied with the secondary loss of respiratory sinus arrhythmia but no additional treatment-related waveform abnormalities were observed. • There were no respiratory or central nervous systems safety pharmacology findings of concern with VI. As with other $beta_2$-agonists, a single dose of VI causes tachycardia in dogs, which is considered to be a reflex effect in response to vasodilatation. In repeat dose inhaled studies in dogs, this tachycardia response can lead to morphologic damage, particularly papillary muscles, but the	• Heart changes in dog have been seen with other $beta_2$-agonists and are thought to be due to localized areas of hypoxia, resulting from vasodilatation lowering the coronary perfusion and tachycardia increasing oxygen demand on the heart. The dog appears to be particularly sensitive to papillary muscle damage with sustained tachycardia. • There were no clinically relevant changes from baseline in heart rate in the participants with COPD with UMEC/VI, UMEC or VI compared with placebo at the proposed commercial dose. In the thorough QT study in healthy volunteers, the maximum mean time-matched change in heart rate for UMEC 500 mcg compared with placebo was 2.1 bpm at 8 hours post-dose (90% CI: 0.7, 3.5). • Transient increases in heart rate in participants with asthma with UMEC/VI or VI

Key safety findings (from non-clinical studies)	Relevance to human usage
tachycardia was shown to decrease on repeat dosing (tachyphylaxis). • When a single, intravenous dose of UMEC and VI in combination was given to dogs, whilst there was a minimal increase in mean, systolic and diastolic blood pressure (which was not seen with the individual components), there was no exacerbation of the increase in heart rate in combination compared to the individual components alone. There were no ECG changes that were unique to the UMEC/VI combination in following either single or repeated administration to dogs.	were modest and were not associated with adverse effects. • A placebo and moxifloxacin- controlled thorough QT study was conducted in 103 healthy volunteers (DB2114635). At a supratherapeutic UMEC/VI dose (500/100 mcg for 10 days), there was evidence of an effect on QTc(F) during the first hour after dosing. The largest mean time-matched difference from placebo was 8.2 msec (90% CI: 6.2, 10.2) at 30 minutes after dosing. This was the only time point where the upper limit of the 90% CI exceeded 10 msec and QTc(F) differences from placebo declined rapidly afterwards. In a concentration-QT analysis there was a dose dependent increase in QTc(F) estimated for VI when comparing the low dose combination (UMEC/VI 125/25 mcg) to the high dose combination (500/100 mcg).
<u>Mechanisms for drug interactions</u> • *In vitro*, UMEC is a substrate of CYP2D6 and the P-gp transporter and organic cation transporters; OCT1 and OCT2. • *In vitro* studies conducted using human recombinant cytochrome P450 (CYP) enzymes showed that UMEC was metabolized mainly by CYP2D6. The contribution of OCT1 to the clearance of UMEC is unclear as there was no evidence of an increase in systemic exposure for UMEC following inhaled UMEC (125 mcg) in participants with moderate hepatic impairment compared to healthy controls (Study DB2114637). It can therefore be implied that an interaction with a transporter such as OCT1 would not result in a clinically significant increase in systemic exposure of UMEC. • In an additional *in vitro* study, UMEC and VI were found not to be substrates of BCRP, OATP1B1 or OATP1B3 transporters. UMEC	• There was no evidence of a difference in systemic exposure UMEC in healthy normal metabolizers and healthy human participants, which were poor metabolizers (CYP2D6). • The extent of the role of OCT1 or OCT2 in the clearance of UMEC in humans is unclear and there is no clear guidance on clinical probes to study inhibition of OCTs in humans. It is considered that any mechanism (including an interaction) which limits the clearance of UMEC by one of these routes will be compensated for by another route of clearance. This is supported by the lack of a clinically significant increase in systemic exposure of UMEC in studies performed in participants with severe renal impairment (DB2114636), participants with moderate hepatic impairment (DB2114637) or in a healthy population of CYP450 isoenzyme 2D6 poor metabolizers (AC4110106).

Key safety findings (from non-clinical studies)	Relevance to human usage
is also not a substrate for OAT1 and BSEP transporter but is a weak substrate of OAT3. Based on this *in vitro* information, there should be no risk regarding an *in vivo* interaction in humans should a potent inhibitor of one of these transporter systems be co-administered with UMEC and/or VI. • VI is an *in vitro* substrate of CYP3A4 and the transporter P-gp. • The binding of UMEC and VI to human liver microsomal protein was investigated *in vitro* with approximately 47% and 49%, respectively, of the compound being bound to protein following equilibration. This binding has been taken into account in evaluating the possible interaction on any CYP450's which UMEC or VI may inhibit. The Cmax of UMEC at its commercial dose of 62.5 mcg/day (<0.2 ng/mL or 0.5 nM) is at least 200-fold lower than the lowest IC_{50} for CYP2D6 inhibition (0.1 mcM or 100 nM). The estimated Ki for CYP2D6 as a worse case (50 nM), equivalent to a free concentration 26.5 nM (based on binding to microsomal protein of 47%) is 378-fold higher than the unbound Cmax, which is above the accepted threshold of concern (CHMP guidance recommended threshold of concern is <50 fold higher) and does not therefore warrant further clinical investigation. For VI, the Cmax at 25 mcg/day (<0.2 ng/mL or 0.5 nM) is at least 3 orders of magnitude lower than the lowest IC_{50} for CYP3A4 inhibition (4 mcM or 4000 nM). Likewise the estimated Ki for CYP3A4 as a worse case (2000 nM) is 34,000 fold higher than the unbound Cmax taking into account the microsomal binding being 49%. This is above the accepted threshold of concern and does not therefore warrant further clinical investigation.	• The hepatic route has been determined as the major route of elimination of UMEC. Following intravenous administration of [^{14}C]-UMEC, 58% of total radioactivity was recovered in the feces, suggesting biliary secretion of total drug related material. This was further confirmed by detection of radioactive drug-related material following IV dosing in duodenal bile samples captured using the Entero-test device. • Renal clearance of UMEC was assessed in both healthy participants and participants with COPD. Across studies in healthy participants, at steady state renal clearance (CLr) generally ranged from 7 to 12 L/h, suggesting primary renal elimination by glomerular filtration with potential contribution from tubular secretion. These clinical findings are consistent with the *in vitro* finding that UMEC is a substrate for OCT2. In study AC4105211 UMEC CLr in COPD participants, was 7L/h, suggesting no differential CLr for UMEC in COPD participants. • Low renal clearance is also consistent with renal elimination being a minor clearance pathway for UMEC, with 3-4% of dose excreted unchanged in urine. Interference with this clearance route as assessed in renally impaired participants (DB2114636) showed no evidence of an increased systemic exposure for UMEC compared to healthy controls, implying that an interaction with the renal OCT2 transporter would not result in a clinically significant increase in UMEC systemic exposure. This was also corroborated by population pharmacokinetic analysis of combined data from 1467 COPD participants from two phase 3 clinical studies (DB2116975). This analysis showed no difference in systemic exposure of UMEC in mild (n=640), moderate (n=204) or severe (n=4) renally impaired COPD participants compared to COPD participants with normal

Key safety findings (from non-clinical studies)	Relevance to human usage
	renal function (n=781) and creatinine clearance was not identified as an influential covariate for UMEC pharmacokinetic parameters. GSK considers that UMEC is cleared systemically by more than one mechanism, including metabolism (involving CYP2D6) and by direct elimination in the bile, as demonstrated in study AC4112014, with only a minor renal contribution (<3-4% of unchanged drug in urine following inhaled administration). • A clinical study showed a moderate interaction of VI with verapamil (a moderate inhibitor of P-gp and CYP3A4). • Clinical studies showed a weak interaction of VI with ketoconazole (a strong inhibitor of CYP3A4 and potent inhibitor of P-gp) but no interaction with verapamil (a moderate CYP3A4 inhibitor and potent P-gp inhibitor) suggesting that its pharmacokinetics are unaffected by P-gp inhibition. • UMEC is not an *in vitro* substrate, or is only a weak *in vitro* substrate for the transporters, BCRP, OATP1B1/3, OAT1/3 and BSEP. Co-administration with inhibitors of these transporters should not, therefore, result in a clinically meaningful change in UMEC systemic exposure. • Vilanterol is not an *in vitro* substrate for the transporters BCRP and OATP1B1/3. Co-administration with inhibitors of BCRP and OATP1B1/3 should not, therefore, result in a clinically meaningful change in VI systemic exposure.
Other toxicity-related information or data	
None	

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Safety information from 14 completed clinical studies in COPD participants from the Phase 3 clinical development programs for UMEC/VI and fluticasone furoate (FF)/VI[1] were used to support the initial global regulatory filings for UMEC/VI in patients with COPD (Table 6).

Table 6 Clinical studies to support safety profile of UMEC/VI (ITT population)

	Number of Participants						
Study ID	Placebo	UMEC 62.5	UMEC 125	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25	TIO 18
Primary Efficacy and Safety Studies							
DB2113361	275	-	407	404	-	403	-
DB2113373	280	418	-	421	413	-	-
DB2113360	-	-	-	209	212	214	208
DB2113374	-	-	222	-	217	215	215
Supportive Studies							
DB2113359	109	-	227	-	-	226	-
DB2114417[a]	170	49	50	76	152	144	-
DB2114418[a]	151	40	41	64	130	128	-
HZC112206	207	-	-	205	-	-	-
HZC112207	205	-	-	203	-	-	-
HZC102871	-	-	-	409	-	-	-
HZC102970	-	-	-	409	-	-	-
B2C111045	101	-	-	101	-	-	-
AC4113589	71	-	71	-	-	-	-
AC4115408	68	69	69	-	-	-	-
Total	**1637**	**576**	**1087**	**2501**	**1124**	**1330**	**423**

Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol; TIO=tiotropium; ITT – Intent to treat population
a = Two-period, incomplete block design cross-over study; participants are counted once under each treatment received
Note: All strengths are in micrograms (mcg)
Source: DB2_ISS Table 1.01

Four Phase 3 studies with UMEC/VI Inhalation Powder conducted over a 24-week period are considered Primary Efficacy Studies for the COPD indication.

Studies DB2113361 and DB2113373 were 24-week, randomized double-blind, parallel-group studies comparing UMEC/VI to UMEC, VI and placebo.

- DB2113361 – UMEC/VI 125/25 mcg, UMEC 125 mcg, VI 25 mcg, and placebo QD

[1] FF/VI is a combination of the inhaled corticosteroid fluticasone furoate (FF) and long-acting beta2-agonist (VI) under development for the treatment of COPD (EMEA/H/C/0002673). Studies from this program were included in the integrated analysis because they contained a VI monotherapy treatment group.

- DB2113373 – UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, VI 25 mcg and placebo QD

These studies provide safety data, including 12-lead ECG, vital signs, 24-hour Holter monitoring (in a subset) and clinical chemistry and hematology assessments over a 24-week treatment period.

Studies DB2113360 and DB2113374 were 24-week, randomized double-blind, parallel-group studies comparing UMEC/VI to UMEC, VI and TIO.

- DB2113360 - UMEC/VI 125/25 mcg, UMEC/VI 62.5/25 mcg, VI 25 mcg, and TIO 18 mcg QD
- DB2113374 - UMEC/VI 125/25 mcg, UMEC/VI 62.5/25 mcg, UMEC 125 mcg, and TIO 18 mcg QD

These studies provide safety data, including 12-lead ECG, vital signs and clinical chemistry and hematology assessments over a 24-week treatment period.

Two exercise endurance studies were conducted as part of the Phase 3 clinical development for UMEC/VI:

- DB2114417 and DB2114418 were replicate two period, incomplete block design cross-over exercise endurance studies, conducted to evaluate the effects of UMEC/VI treatment in COPD participants over 12 weeks. Both studies evaluated UMEC/VI 125/25 mcg, UMEC/VI 62.5/25 mcg, UMEC 125 mcg, UMEC 62.5 mcg, VI 25 mcg and placebo. These studies provide safety data including 12-lead ECG, vital signs and clinical chemistry and hematology assessments

One 12-month Safety Study was conducted with UMEC/VI:

- Study DB2113359 was designed to evaluate the safety and tolerability of UMEC/VI (125/25 mcg) and UMEC (125 mcg) compared with placebo administered once daily over 12 months. This study provides safety data including 12-lead ECG, 24-hour Holter monitoring, vital signs and clinical chemistry and hematology assessments

Two additional studies were conducted with FF/VI and included a VI treatment group:

- Studies HZC102871 and HZC102970 were 12 month, efficacy and safety studies to assess COPD exacerbations conducted as part of the development program for FF/VI in COPD and provide safety data from the VI Inhalation Powder monotherapy arm.

The following five studies were also included in the safety analysis as they included a treatment group for UMEC or VI at the strength proposed for marketing and were at least 4 weeks in duration:

- Studies HZC112206 and HZC112207 were 6-month pivotal efficacy and safety studies conducted as part of the development program for FF/VI in COPD. Only safety data from the VI Inhalation Powder (25 mcg QD) monotherapy and placebo groups were used.

- Study B2C111045, a Phase 2b study that evaluated the dose-response of VI inhalation powder over 28 days in participants with COPD. Only data from the VI 25 mcg and placebo groups were used.
- Study AC4113589, a Phase 2b study that evaluated the dose response of UMEC over 28 days. Only data from the UMEC 125 mcg and placebo groups were used.
- Study AC4115408, a Phase 3 study evaluating the safety and efficacy of UMEC at 62.5 mcg and 125 mcg once daily over 12 weeks in participants with COPD.

Safety data from an additional 7 studies in asthma are included from the FF/VI development program, where VI was used alone or in combination with an ICS to evaluate the risk of hospitalizations, intubations, or death.

Safety data was integrated and presented as follows:

- Integration of the four 24-week Primary Efficacy Studies (DB2113361, DB2113373, DB2113360, DB2113374)
- Safety Study (DB2113359)
- Integration of the two 12-week Exercise Studies (DB2114417 and DB2114418)
- All COPD studies grouping, an integration of DB2113361, DB2113373, DB2113360, DB2113374, DB2113359, DB2114417, DB2114418, HZC112206, HZC112207, HZC102871, HZC102970, AC4113589, B2C111045, AC4115408. (The date of this integration was 2012).
- 24-hour Holter data was integrated for UMEC/VI studies DB2113361/DB2113373, and FF/VI studies HZC122206/122207
- All COPD studies grouping, an integration for all UMEC/VI studies 201012, 201211, 201749, CTT116855, DB2113120, DB2113359, DB2113360, DB2113361, DB2113373, DB2113374, DB2114634, DB2114930, DB2114951, DB2116134, DB2116960, DB2116961, ZEP117115, DB2115362, 201317, 204990, DB2114417, DB2114418, DB2116132, DB2116133. (Updated August 2019).

Table 7 Summary of UMEC/VI Exposure - All COPD Studies grouping*

	UMEC/VI 62.5/25 N=7538	UMEC/VI 125/25 N=1653
Exposure (days)		
n	7538	1653
Mean	158.8	171.5
SD	115.55	95.27
Median	123.5	168.0
Min.	1	1
Max.	444	371
Total Subject-Years Exposure	3277.23	775.97
Range of exposure		

	UMEC/VI 62.5/25 N=7538	UMEC/VI 125/25 N=1653
n	7538	1653
≥1 day	7538 (100%)	1653 (100%)
>4 weeks	6912 (92%)	1578 (95%)
>8 weeks	6478 (86%)	1523 (92%)
>12 weeks	4898 (65%)	1435 (87%)
>16 weeks	3814 (51%)	1191 (72%)
>20 weeks	3718 (49%)	1165 (70%)
>24 weeks	2480 (33%)	660 (40%)
>28 weeks	1642 (22%)	286 (17%)
>32 weeks	1606 (21%)	278 (17%)
>36 weeks	1590 (21%)	276 (17%)
>40 weeks	1571 (21%)	262 (16%)
>44 weeks	1538 (20%)	260 (16%)
>48 weeks	1529 (20%)	258 (16%)
>52 weeks	987 (13%)	53 (3%)
Age		
n	7538	1653
<35 years	0	0
>=35 years to <65 years	3971 (53%)	886 (54%)
>=65 years to <75 years	2773 (37%)	599 (36%)
>=85 years	38 (<1%)	1 (<1%)
Gender		
n	7538	1653
Female	5088 (67%)	1162 (70%)
Male	2450 (33%)	491 (30%)
Ethnic or Racial Origin		
n	7538	1653
African American / American Heritage	182 (2%)	40 (2%)
American Indian or Alaskan Native	111 (1%)	23 (1%)
Asian – Central/South Asian Heritage	10 (<1%)	1 (<1%)
Asian – Japanese/East Asian Heritage/South East Asian Heritage	611 (8%)	400 (24%)
Mixed Asian Heritage	0	0
Native Hawaiian or Other Pacific islander	4 (<1%)	0
White	6559 (87%)	1177 (71%)
African American/African Heritage & American Indian or Alaska Native & White	0	0
African American/African Heritage & White	16 (<1%)	1 (<1%)
American Indian or Alaska Native & Asian	1 (<1%)	0
American Indian or Alaska Native & White	36 (<1%)	11 (<1%)
Asian & White	0	0
White - Mixed Race	2 (<1%)	0

	UMEC/VI 62.5/25 N=7538	UMEC/VI 125/25 N=1653
Native Hawaiian or Other Pacific Islander & White	0	0
Asian & Native Hawaiian or Other Pacific Islander & White	0	0
African American/African Heritage & American Indian or Alaskan Native	0	0
Mixed Race	6 (<1%)	0
Missing	0	0

* This is an integration for all studies with UMEC/VI treatment arms to show UMEC/VI exposure (updated August 2019).
UMEC=umeclidinium; VI=vilanterol

Table 8 Summary of UMEC/VI Exposure - Primary Efficacy Studies

	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Exposure (days)							
n	555	842	832	418	629	1034	423
Mean	136.6	150.1	147.6	146.7	144.5	145.3	149.5
SD	55.39	44.11	46.97	47.03	48.53	47.85	45.75
Median	167.0	168.0	168.0	168.0	167.0	168.0	167.0
Min.	1	1	1	1	1	1	1
Max.	192	177	179	179	183	206	176
Total subject-years exposure	207.52	345.92	336.27	167.88	248.89	411.20	173.09
Range of exposure							
n	555	842	832	418	629	1034	423
>=1 day	555 (100%)	842 (100%)	832 (100%)	418 (100%)	629 (100%)	1034 (100%)	423 (100%)
>4 weeks	495 (89%)	793 (94%)	782 (94%)	395 (94%)	585 (93%)	961 (93%)	395 (93%)
>8 weeks	468 (84%)	774 (92%)	747 (90%)	377 (90%)	558 (89%)	927 (90%)	382 (90%)
>12 weeks	452 (81%)	749 (89%)	729 (88%)	364 (87%)	538 (86%)	897 (87%)	374 (88%)
>16 weeks	415 (75%)	722 (86%)	698 (84%)	345 (83%)	509 (81%)	844 (82%)	365 (86%)
>20 weeks	405 (73%)	705 (84%)	684 (82%)	341 (82%)	498 (79%)	822 (79%)	359 (85%)
>24 weeks	169 (30%)	326 (39%)	281 (34%)	154 (37%)	200 (32%)	343 (33%)	116 (27%)
Gender							
n	555	842	832	418	629	1034	423
Female	185 (33%)	249 (30%)	269 (32%)	120 (29%)	211 (34%)	341 (33%)	130 (31%)

	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Male	370 (67%)	593 (70%)	563 (68%)	298 (71%)	418 (66%)	693 (67%)	293 (69%)
Age subgroup (years)							
n	555	842	832	418	629	1034	423
≤64	335 (60%)	453 (54%)	445 (32%)	217 (52%)	335 (53%)	592 (57%)	213 (50%)
65-74	170 (31%)	300 (36%)	309 (37%)	148 (35%)	232 (37%)	346 (33%)	160 (38%)
75-84	49 (9%)	85 (10%)	78 (9%)	50 (12%)	61 (10%)	93 (9%)	48 (11%)
≥85	1 (<1%)	4 (<1%)	0	3 (<1%)	1 (<1%)	3 (<1%)	2 (<1%)
Ethnic or Racial subgroup							
n	555	842	832	418	629	1034	423
African American / American Heritage	18 (3%)	30 (4%)	22 (3%)	14 (3%)	10 (2%)	19 (2%)	14 (3%)
American Indian or Alaskan Native	1 (<1%)	16 (2%)	22 (3%)	3 (<1%)	0	25 (2%)	20 (5%)
Asian	49 (9%)	73 (9%)	77 (9%)	35 (8%)	77 (12%)	76 (7%)	38 (9%)
Central/South Asian Heritage	0	1 (<1%)	1 (<1%)	0	0	2 (<1%)	0
Japanese/South East/East Asian Heritage	49 (9%)	72 (9%)	76 (9%)	35 (8%)	77 (12%)	74 (7%)	38 (9%)
Mixed Asian Heritage	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific islander	0	2 (<1%)	0	0	0	0	0
White	475 (86%)	694 (82%)	699 (84%)	354 (85%)	533 (85%)	902 (87%)	340 (80%)
African American/African Heritage & American Indian or Alaska Native & White	0	0	0	1 (<1%)	0	0	0
African American/African Heritage & White	2 (<1%)	0	1 (<1%)	1 (<1%)	0	2 (<1%)	1 (<1%)
American Indian or Alaska Native & Asian	0	0	0	0	0	1 (<1%)	0
American Indian or Alaska Native & White	10 (2%)	27 (3%)	11 (1%)	10 (2%)	8 (1%)	9 (<1%)	10 (2%)
Asian & White	0	0	0	0	1 (<1%)	0	0

Data Source: DB2_ISS Tables 1.03, 1.24 and 1.39
UMEC=umeclidinium; VI=vilanterol; TIO=tiotropium

Table 9 Summary of UMEC/VI Exposure - 12-month Safety Study

	Placebo N=109	UMEC 125 N=227	UMEC/VI 125/25 N=226
Exposure (days)			
n	109	227	226
Mean	269.4	269.0	285.3
SD	127.54	125.52	114.18
Median	357.0	357.0	357.5
Min.	1	1	1
Max.	372	375	371
Range of exposure			
n	109	227	226
>4 weeks	103 (94%)	215 (95%)	218 (96%)
>8 weeks	97 (89%)	204 (90%)	213 (94%)
>12 weeks	95 (87%)	202 (89%)	211 (93%)
>20 weeks	82 (75%)	172 (76%)	185 (82%)
>24 weeks	82 (75%)	170 (75%)	181 (80%)
>48 weeks	66 (61%)	133 (59%)	146 (65%)
Gender			
n	109	227	226
Female	36 (33%)	82 (36%)	70 (31%)
Male	73 (67%)	145 (64%)	156 (69%)
Ethnic or Racial subgroup			
n	109	227	226
African American/African Heritage	3 (3%)	13 (6%)	14 (6%)
American Indian or Alaska Native	0	0	0
Asian - Central/South Asian Heritage	0	0	0
Asian - East Asian Heritage	2 (2%)	0	1 (<1%)
Asian - Japanese Heritage	0	0	0
Asian - South East Asian Heritage	0	0	0
Asian - Mixed Race	0	0	0
Native Hawaiian or other Pacific Islander	0	0	0
White - Arabic/North African Heritage	0	0	0
White - White/Caucasian/European Heritage	104 (95%)	214 (94%)	211 (93%)
White - Mixed Race	0	0	0
Mixed Race	0	0	0

Data Source: DB2113359 Tables 5.11, 5.14 and 7.01
UMEC=umeclidinium; VI=vilanterol

Table 10 Summary of UMEC/VI Exposure - Exercise Studies

	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
Exposure (days)						
n	321	282	272	89	91	140
Mean	77.8	80.5	80.4	81.4	77.7	78.5

SD	20.17	16.23	16.50	12.73	21.07	19.39
Median	85.0	85.0	85.0	85.0	85.0	85.0
Min.	1	1	1	11	2	2
Max.	96	103	101	91	95	112
Total subject-years exposure						
	68.36	62.13	59.90	19.84	19.35	30.07
Range of exposure						
n	321	282	272	89	91	140
>=1 day	321 (100%)	282 (100%)	272 (100%)	89 (100%)	91 (100%)	140 (100%)
>4 weeks	302 (94%)	273 (97%)	262 (96%)	88 (99%)	85 (93%)	133 (95%)
>8 weeks	284 (88%)	260 (92%)	252 (93%)	83 (93%)	80 (88%)	123 (88%)
>12 weeks	199 (62%)	183 (65%)	189 (69%)	60 (67%)	57 (63%)	93 (66%)
Gender						
n	321	282	272	89	91	140
Female	141 (44%)	122 (43%)	131 (48%)	36 (40%)	43 (47%)	60 (43%)
Male	180 (56%)	160 (57%)	141 (52%)	53 (60%)	48 (53%)	80 (57%)
Age subgroup						
n	321	282	272	89	91	140
≤64	196 (61%)	182 (65%)	167 (61%)	59 (66%)	51 (56%)	93 (66%)
65-74	109 (34%)	83 (29%)	89 (33%)	26 (29%)	33 (36%)	39 (28%)
75-84	16 (5%)	17 (6%)	16 (6%)	4 (4%)	7 (8%)	8 (6%)
Race subgroups						
n	321	282	272	89	91	140
African American/African Heritage	9 (3%)	10 (4%)	4 (1%)	5 (6%)	1 (1%)	5 (4%)
American Indian or Alaskan Native	0	0	1 (<1%)	0	1 (1%)	0
Asian	0	1 (<1%)	0	1 (1%)	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
White	312 (97%)	269 (95%)	267 (98%)	83 (93%)	89 (98%)	134 (96%)
Mixed Race	0	2 (<1%)	0	0	0	1 (<1%)

Data Source: DB2_ISS Tables 1.04 and 1.22.
Includes studies DB2114417 and DB2114418
UMEC=umeclidinium; VI=vilanterol

Table 11 Summary of UMEC/VI exposure – Special Populations

Special population group	Persons	Person time
Pregnant women	0	0
Lactating women	0	0
Renal impairment – Severe[1]	9	-
Hepatic impairment – Moderate[2]	9	-

Data Source: DB2114636 Table 9.1; DB2114637 Table 9.1

1 - As defined by: ALT < 2xULN; alkaline phosphatase and bilirubin ≤ 1.5xULN (isolated bilirubin >1.5xULN is acceptable if bilirubin is fractionated and direct bilirubin <35%); Creatinine clearance < 30mL/min calculated by the Cockcroft-Gault equation using serum creatinine; participants with renal insufficiency must have stable renal function defined as ≤ 25% difference in creatinine clearance assessed on two occasions. Renal function will be based on estimated creatinine clearance calculated by the Cockcroft-Gault equation using serum creatinine obtained on two occasions separated by at least 4 weeks within the last 3 months (historic data is permitted for the first measurement).

2 - Known medical history of liver disease with or without a known history of alcohol abuse; Child-Pugh score of 7-9 points (moderate impairment). The components that contribute to the Child-Pugh score should be directly related to the underlying hepatic disease and not to non-hepatic disease; participants with no significant abnormality, apart from impaired hepatic function and related symptoms, or clinical examination. A participant with a clinical abnormality may be included only if the Investigator considers that the abnormality will not introduce additional risk factors and will not interfere with the study procedures. Hepatically impaired participants with other laboratory parameters outside the reference ranges will only be included if, in the opinion of the Investigator, the result is not clinically important and introduces no additional risk factors.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

The patient populations enrolled in the studies for the initial MAA for UMEC/VI and from study CTT116855 supporting the Type II variation, are representative of the target population approved for the SmPC.

SIV.1 Exclusion criteria in pivotal clinical studies within the development program

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Participants with a history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist or to any of the excipients (lactose monohydrate and magnesium stearate).	The excipient, lactose, can occasionally contain very small amounts of milk protein. There is a small risk that individuals who are allergic to milk proteins could have an allergic reaction. Allergy to anticholinergic/muscarinic receptor antagonists, beta2-agonists, or magnesium stearate is rare.	No	Hypersensitivity as a medical concept is well understood. Additional pharmacovigilance or additional risk minimization activities are not proposed for hypersensitivity. Hypersensitivity to any of the ingredients in the product is a contraindication in the product label.
Pregnant or lactating women or women of child bearing potential not using a reliable method of contraception. Women who became pregnant were required to withdraw from the study.	This is a standard safety - related exclusion criteria, as there have been no formal studies in the use in pregnancy in women, and pregnancy in participants with COPD is unlikely.	No	No pregnant or lactating women were included in the clinical development program. There is a gap in the scientific knowledge available on the safety profile of UMEC/VI in this patient group. Administration of UMEC/VI to pregnant or breastfeeding women should only be

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			considered if the expected benefit to the mother justifies the potential risk to the fetus or child.
Participants under 40 years of age.	Standard diagnosis of COPD is usually after the age of 40 years. Therefore, participants under the age of 40 years were excluded so as not to confound the determination of the efficacy profile of the study intervention (e.g. due to any participants having underlying asthma).	No	COPD is not common under the age of 40. In regards to an individual patient, if they meet the diagnostic criteria for COPD, then there is no reason to anticipate that a participants under the age of 40 would respond to treatment differently, or have any risks that were different from those over the age of 40, with COPD. This patient group does not represent a gap in scientific knowledge on the safety profile of UMEC/VI and is therefore not considered missing information.
Participants with a current diagnosis of asthma.	Participants with a current diagnosis of asthma were excluded to ensure the population studied had a clear diagnosis of COPD so as not to confound the determination of the efficacy profile of the study intervention in the COPD population.	No	UMEC/VI is not indicated in asthma. Treatment will be guided by established guidance and medical practice. For those with an established COPD diagnosis, requiring treatment, exclusion of those with concurrent asthma would not be appropriate. The safety profile in this population is not

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			expected to be different to the target population. The product label will contain wording relating to warning against the use of UMEC/VI in asthma due to current lack of data in this patient population
Participants with other known respiratory disorders/procedures other than COPD, including and not limited to α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension and interstitial lung disease.	Participants with other known respiratory disorders or procedures were excluded to ensure the population studied had a clear diagnosis of COPD, so as not to put the safety of the participant at risk through participation, and to avoid confounding the efficacy or safety analysis if the disease/condition exacerbated during the study.	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. Some patients may have concurrent respiratory conditions. There is no reason to anticipate that such a participant would respond to treatment for COPD differently, and these patients are not expected to represent a group of patients in which the safety profile of UMEC/VI is expected to differ from the approved patient population and therefore is not considered as missing information
Participants with a chest X-ray or computed tomography (CT) scan that reveals evidence of clinically significant abnormalities not believed to be due to the presence of COPD.	It was important for the exclusion criteria to remove any uncertainty or identify any undiagnosed respiratory conditions so as not to put the safety of the participant at risk through participation, and to avoid	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. Some patients may have concurrent respiratory conditions. There is no reason to anticipate that such a participant would respond to treatment for their COPD differently, and these patients

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	confounding the efficacy or safety analysis if the disease/condition exacerbated during the study.		are not expected to represent a group of patients in which the safety profile of UMEC/VI is expected to differ from the approved patient population and therefore is not considered as missing information
Participant who had undergone lung volume reduction surgery within the 12 months prior to study start.	It was important for the exclusion criteria to ensure that patients enrolled in the UMEC/VI studies did not have lung function affected by other interventions, so as not to confound the efficacy or safety analysis.	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. It is important for COPD patients that may have undergone lung volume reduction surgery to adequately maintain control of their COPD. There is no reason to believe that this would represent a different population to those in the clinical studies. Therefore, the patient population is not considered as missing information.
Participants who used long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day.	It was important for the exclusion criteria to ensure that participants enrolled in the UMEC/VI studies could be assessed for changes in lung function caused by the investigational treatments, so as not to	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. It is important for COPD patients that used LTOT for longer than 12 hours a day to adequately maintain control of their COPD. There is no reason to believe that this would represent a different population to those in

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	confound the efficacy or safety analysis. Patients were not excluded if home oxygen was required for less than 12 hours a day.		the clinical studies. Therefore, the patient population is not considered as missing information.
Participants who had been hospitalized for COPD or pneumonia within 12 weeks prior to starting study.	Exclusion criteria prevented enrolment of participants with clinically significant conditions, so as not to confound the determination of the safety and efficacy profile of the study interventions if the disease/condition exacerbated during the study. It was important for this population to be clearly participants with COPD, who could be assessed for changes in lung function, and those recovering from respiratory infection may have improvements in lung function that were not a consequence of treatment with study drug.	No	Patients with COPD are at risk of pneumonia. In these patients it is important for their COPD to be adequately controlled, and there is no reason to believe that this would represent a different population to that in the clinical studies. Therefore, the patient population is not considered as missing information.
Participants with regular use (prescribed for use every day, not for as	It was important for this population to be assessed for changes in	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. This would include

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
needed use) of short-acting bronchodilators (e.g. albuterol/salbutamol) via nebulized therapy.	lung function due to investigational treatments. Those receiving regular nebulized therapies would be more difficult to assess, with respect to treatment response.		those who require nebulized short-acting bronchodilators. In these patients it is important for their COPD to be adequately controlled, and there is no reason to believe that this would represent a different population to those in the clinical studies. Therefore, the patient population is not considered as missing information.
Participants who had participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to study start.	It was important for this population to be assessed for changes in lung function due to investigational treatments. Those receiving pulmonary rehabilitation would be difficult to assess in respect to response to treatment.	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. This would include those who are undergoing pulmonary rehabilitation. In these patients it is important for their COPD to be adequately controlled, and there is no reason to believe that this would represent a different population to those in the clinical studies. Therefore, the patient population is not considered as missing information.
Participants with historical or current evidence of clinically significant[2] CV (including abnormal and significant ECG findings),	The study investigators had discretion on whether to exclude participants on the basis of whether the current condition was significant, defined as	No	COPD patients are at greater risk of CVD compared with age-matched and sex-matched individuals without COPD (Shi, 2021). In these patients it is important for their

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid) disease, clinical chemistry, hematological abnormalities that are uncontrolled and/or a previous history of cancer in remission for <5 years prior to starting the study.	any disease that would put the safety of the participant risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.		COPD to be adequately controlled, and there is no reason to believe that this would represent a different population to those in the clinical studies. Therefore, the patient population is not considered as missing information.
Participants with medical conditions such as of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the investigator, contraindicates study participation or use of an inhaled anticholinergic	Exclusion criteria prevented participants with clinically significant conditions, so as not to confound the determination of the safety and efficacy profile of the study interventions.	No	In UMEC/VI clinical studies, there were few events that suggested systemic anticholinergic effects, and few ocular events were reported. As patients with COPD often require a muscarinic antagonist to control their disease, it is not appropriate to contraindicate their use.
Participants with known or suspected history of alcohol or drug abuse within 2 years prior to study start.	Exclusion criteria prevented participants with clinically significant conditions, so as not to confound the determination of the safety and efficacy profile of the study interventions.	No	Patients will receive UMEC/VI if they have a diagnosis of COPD. This would include those who may have trouble complying with a prescribed treatment regimen. As they represent a proportion of patients with COPD the patient population is not

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			considered as missing information

SIV.2 Limitations to detect adverse reactions in clinical trial development program

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	The total number of participants exposed to UMEC/VI, UMEC and VI in studies of at least 4 weeks duration included in the initial clinical program is provided below: Treatment / N / PY Placebo / 1637 / 535 UMEC/VI 62.5/25 mcg / 1124 / 408 UMEC/VI 125/25 mcg / 1330 / 573 UMEC 62.5 mcg / 576 / 202 UMEC 125 mcg / 1087 / 454 VI 25 mcg / 2501 / 1271 PY – Patient years of exposure The total number of participants that received doses of UMEC/VI, UMEC and VI in these studies was 2454, 1663 and 2501, respectively. Additionally, the total number of participants that received an UMEC-containing or	The overall safety profile of UMEC/VI and individual components is consistent with that reported for licensed LAMA and LABAs and the COPD population. Although rare events may not have been observed during clinical studies, there is a large amount of established experience with both LABAs and LAMAs. Given that over 1,000 subjects have been exposed to UMEC 125 mcg, UMEC/VI 62.5/25 mcg and 125/25 mcg, then there is a >99% probability that very common (>1 in 10) and common (>1 in 100) AEs would have been observed during clinical studies (based on CIOMS and WHO criteria). Given that over 2,000 subjects have been exposed to VI, then there is >99% probability that very common (>1 in 10) and common (>1 in 100) AEs would have been observed and a >85% probability that uncommon (>1 in 1000) AEs would have been observed during clinical studies (based on CIOMS and WHO criteria).

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	VI-containing product was 4117 and 4955, respectively. Exposure and safety data from the IMPACT study (CTT116855) includes 2070 participants who were exposed to UMEC/VI, of which 1,529 (74%) participants had ≥ 48 weeks of treatment exposure. There is 95% confidence that uncommon (>1 in 1,000) AEs would have been observed from this study.	The safety profile for UMEC/VI is consistent with other dual combinations (LAMA/LABA) which are well known and understood in participants with COPD. Although rare events may not have been observed during the UMEC/VI clinical studies, post marketing exposure to UMEC/VI indicates the risk/benefit profile remains favorable.
Due to prolonged exposure	In the All COPD studies grouping (updated in August 2019), 1529 and 258 participants received once daily UMEC/VI 62.5/25 mcg and UMEC/VI 125/25 mcg. treatment for greater than 48 weeks.	There were no new safety signals identified during longer-term treatment with UMEC/VI, UMEC or VI. The AE profile of UMEC/VI in longer-term studies was similar to that observed in the 24-week Primary Efficacy Studies. The safety profile for UMEC/VI is consistent with other dual combinations (LAMA/LABA) which are well known and understood in participants with COPD. Although rare events may not have been observed during the UMEC/VI clinical studies, post marketing exposure to UMEC/VI indicates the risk/benefit profile remains favorable.
Due to cumulative effects	In the All COPD studies grouping that included UMEC/VI, over 6-month and 12-month study intervention periods, there was no evidence to suggest any cumulative adverse effects. There is a theoretical possibility of cumulative effects e.g. CV effects when LAMA and LABA are given	There were no new safety signals identified during longer-term treatment with UMEC/VI. The AE profile of UMEC/VI in longer-term studies was similar to that observed in the Primary Efficacy Studies. Based on data for UMEC/VI from clinical trials in which individual or combined components of FF, VI and UMEC have

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	together. In CTT116855 there was no evidence to suggest any cumulative adverse effects when comparing the incidence of AEs in the first 6 months with the incidence of AEs in the second 6 months.	been studied in patients with COPD, there is no evidence to suggest cumulative effects for AEs with UMEC/VI or individual components. In addition, the safety profile from post marketing exposure to UMEC/VI has not identified AEs suggestive of possible cumulative effects from UMEC/VI administration. The risk/benefit profile remains favorable
Which have a long latency	In the All COPD studies grouping (updated in August 2019), 1529 and 258 participants received once daily UMEC 62.5/25 mcg and UMEC/VI 125/25 mcg treatment for greater than 48 weeks.	There were no new safety signals identified with longer-term treatment with UMEC/VI. In addition, the safety profile from post marketing exposure to UMEC/VI has not identified AEs suggestive of possible cumulative effects from UMEC/VI administration. The overall safety profile of UMEC/VI is consistent with other dual combinations (LAMA/LABA) which are well known and understood in participants with COPD.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development program

Table 12 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure
Pregnant women	Not included in the clinical development program. There were no reports of pregnancy in the COPD clinical development program with UMEC/VI or the individual components. The prescribing information will contain an appropriate wording regarding use in pregnancy and lactation. In the completed FF/VI asthma clinical development program that includes VI which is a component of

Type of special population	**Exposure**
There is a low incidence of pregnancy in the COPD population due to their age.	UMEC/VI, 36 pregnancies have occurred. Of these, 29 had known outcomes; sixteen pregnancies resulted in live births (one set of twins), 9 were spontaneous abortions, 2 were stillbirths, and 2 were electively terminated. No pregnancies occurred in the completed COPD studies from the FF/VI COPD clinical development program. In addition, no significant information relating to UMEC/VI exposure during pregnancy or administration during lactation has been identified based on cumulative review from post marketing exposure to UMEC/VI.
Breastfeeding women	Not included in the clinical development program. There were no reports of pregnancy in the COPD clinical development program with UMEC/VI or the individual components. The prescribing information will contain an appropriate wording regarding use in pregnancy and lactation. In the completed FF/VI asthma clinical development program that includes VI which is a component of UMEC/VI, 36 pregnancies have occurred. Of these, 29 had known outcomes; sixteen pregnancies resulted in live births (one set of twins), 9 were spontaneous abortions, 2 were stillbirths, and 2 were electively terminated. No pregnancies occurred in the completed COPD studies from the FF/VI COPD clinical development program. In addition, no significant information relating to UMEC/VI exposure during pregnancy or administration during lactation has been identified based on cumulative review from post marketing exposure to UMEC/VI.
Patients with relevant comorbidities: • Patients with hepatic impairment	Patients with hepatic or renal impairment were not excluded from clinical trials unless they had a clinically significant impairment. Clinical pharmacology studies were performed with UMEC/VI, in severe renal (creatinine clearance <30mL/min) and moderate hepatic impaired (Child-Pugh score 7-9) participants. Patients with severe hepatic impairment were studied as part of FF/VI development program but not in the UMEC/VI development program. UMEC is mainly metabolized by the hepatic CYP2D6 pathway; no difference in systemic exposure of UMEC has been shown in poor versus extensive metabolisers (see Section Part II: Module SII). Given the overlap in component products and well characterized ADR profile for the COPD patient population a change in benefit risk profile in this specific population is not expected. No additional studies are planned to assess UMEC/VI in severe hepatic impairment. There is no limitation regarding these patient groups and appropriate wording will be provided in the prescribing information.

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>• Patients with renal impairment</td><td>No dose adjustment or maximum dose is required for patients with renal impairment.</td></tr>
<tr><td>• Patients with CV impairment</td><td>COPD patients are at greater risk of CVD compared with age-matched and sex-matched individuals without COPD (Shi, 2021). . In these patients it is important for their COPD to be adequately controlled, and there is no reason to believe that this would represent a different population to those in the clinical studies supporting the initial clinical development program.
The additional safety data provided by study CTT116855, which are supportive of the addition of key efficacy and safety findings to the SmPC, was intentionally designed to be as permissive as possible with regard to the inclusion of patients with significant comorbidities (e.g. CV) in order to allow an assessment of safety that is more representative of the targeted population than often seen in clinical trials. Most participants exposed to UMEC/VI had concurrent medical conditions in addition to COPD. The four most common current medical conditions are displayed in the table below, the majority of which were CV in nature
<table>
<tr><th>Study</th><th>116855 (ITT Population)</th></tr>
<tr><td>Participants on UMEC/VI (n)</td><td>2070</td></tr>
<tr><td colspan="2">Participants with current medical condition: n (%)</td></tr>
<tr><td>Any</td><td>1422 (69)</td></tr>
<tr><td>Hypertension</td><td>1079 (52)</td></tr>
<tr><td>Hypercholesterolemia</td><td>639 (41)</td></tr>
<tr><td>Coronary Artery Disease</td><td>200(10)</td></tr>
<tr><td>Diabetes Mellitus</td><td>306 (15)</td></tr>
</table>
CSR CTT116855 RAP Table 1.22, CSR CTT116853 RAP Table 1.19, CSR 200812 RAP Table 1.19
The population studied in clinical studies is considered representative of the target post marketing population.

Immunocompromised patients were not included in clinical development programme.

UMEC/VI is currently indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD. The majority of participants enrolled in the</td></tr>
</table>

<table>
<tr><th>Type of special population</th><th>Exposure</th></tr>
<tr><td>

- Immunocompromised patients
- Patients with a disease severity different from inclusion criteria in clinical trials

</td><td>clinical development programme had post-bronchodilator GOLD stage of either Stage II or III.

CTT116855 included patients who had at least one moderate/severe exacerbation in the 12 months prior to screening. The population studied is considered representative of the target post marketing population.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>Although the majority of patients in clinical studies supporting the initial clinical development programme were White, no ethnicities were excluded.

The clinical exposure of the UMEC/VI studies was substantial in the EU.

<table>
<tr><td colspan="7">N [Patient Years]</td></tr>
<tr><td colspan="7">Primary Efficacy Studies (DB2113361, DB2113373, DB2113360, DB2113374)</td></tr>
<tr><td></td><td>Placebo</td><td>UMEC/VI 62.5/25</td><td>UMEC/VI 125/25</td><td>UMEC 62.5</td><td>UMEC 125</td><td>VI 25</td></tr>
<tr><td>All regions</td><td>555 [208]</td><td>842 [346]</td><td>832 [336]</td><td>418 [168]</td><td>629 [249]</td><td>1034 [411]</td></tr>
<tr><td>EU</td><td>268 [100]</td><td>237 [102]</td><td>384 [158]</td><td>124 [51]</td><td>311 [124]</td><td>468 [185]</td></tr>
<tr><td colspan="7">12-month Safety Study (DB2113359)</td></tr>
<tr><td>All regions</td><td>109</td><td>-</td><td>226</td><td>-</td><td>227</td><td>-</td></tr>
<tr><td>Romania</td><td>28</td><td>-</td><td>56</td><td>-</td><td>61</td><td>-</td></tr>
<tr><td>Slovakia</td><td>4</td><td>-</td><td>5</td><td>-</td><td>11</td><td>-</td></tr>
</table>
Data Source: DB2_ISS Table 1.03, 1.12; DB2113359 Table 5.12

LAMAs and LABAs are prescribed internationally, there are no reported safety concerns based on racial and/or ethnic origins

Although the majority of patients exposed to UMEC/VI in CTT116855, were White (1628 participants cumulatively [79%]), no ethnicities were excluded. There is no evidence from this study to suggest that the safety profile in other ethnic groups is significantly different to the White population.</td></tr>
</table>

Type of special population	**Exposure**
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other • Pediatrics	Paediatric patients were not included in the clinical development programme. There is no relevant use of UMEC/VI in the paediatric population (under 18 years of age) in the indication for COPD.
• Elderly	Elderly patients were not excluded from UMEC/VI studies. The incidence of ADRs of special concern for the elderly (64 years of age, 65 to 74 years of age, or 75 to 84 years of age) were broadly similar across treatment groups and age groupings therein. Few patients were over 85 years in the UMEC/VI COPD studies (n=14), which is consistent with the prevalence of the disease in this age group. Consistent with the clinical development program for UMEC/VI, additional safety data obtained in CTT116855 for UMEC/VI in which 53% (1093/2070) patients were ≥ 65 years, showed no significance difference in their safety profile to warrant dose adjustment.
• Other relevant comorbidities	Participants with historical or current evidence of clinically significant CV, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid) disease, clinical chemistry or hematological abnormalities that are uncontrolled and/or a previous history of cancer in remission for <5 years prior to starting the study were excluded from UMEC/VI studies. Participants with concurrent medical conditions such as of narrow-angle glaucoma, prostatic hypertrophy or bladder neck obstruction that, in the opinion of the investigator, contraindicates study participation or use of an inhaled anticholinergic were excluded.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorization exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for UMEC/VI.

SV.1.1 Method used to calculate exposure

One patient-year is calculated as 365 inhalations (one inhalation daily). In order to calculate patient-years of exposure, the cumulative unit dose powder sales estimated from IQVIA Health Prescribing Insights data is divided by 365.

Post-marketing cumulative exposure from launch (April 2014) to 31 March 2023 is estimated at 4 743 533 patient-years.

SV.1.2 Exposure

Based on IQVIA Health Prescribing Insights data, post-approval cumulative post-approval exposure during the time-period from launch (April 2014) to 31 March 2023 is estimated at 4 743 533 patient years.

On the basis of prescriptions written by general practitioners in office practice[1] (apart from Japan where hospital data are included) a greater number of prescriptions for COPD are written for males than females. The majority of prescriptions are written for elderly patients (≥65 years) with the greatest number of prescriptions written for patients aged between 65 and 74 years.

1 Data sourced from IQVIA's "Health Prescribing Insights data" . The prescribing insights covers office-based prescribing in over 11 key countries [including USA, Canada, Japan, France, Germany, United Kingdom (UK), Spain, Italy, Argentina, Mexico, Brazil], and it covers patient demographics as well as diagnosis specific prescribing information. Prescribing insight data may be limited to data from the last three years, and it does not include hospital-based doctors, with the exception of Japan, where hospital data is also covered. Medical audits reflect country prescribing practices and care should be taken when comparing countries or analysis on a regional or global basis. The data reflects prescriptions that are written. Information regarding prescriptions dispensed and refills are not included

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

GSK does not consider that there is a potential for misuse for illegal purposes with UMEC/VI considering the class and pharmacology. No instances of abuse of study medication were reported with UMEC/VI or of the individual components in clinical trials.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of safety concerns in the initial RMP submission

SVII 1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Proposed removal of Important potential risks and Missing Information

The safety concerns for UMEC/VI were reviewed in line with post-marketing experience with the drug, especially the results of PASS 201038, and definitions in GVP module V revision 2. UMEC/VI has been on the market for more than 10 years with an estimated post-marketing patient exposure of 4 743 533 patient-years.

As further described below, the risks initially listed in the EU RMP are no longer considered important and do not require any additional pharmacovigilance activities or additional risk minimization measures to characterize or mitigate them. Therefore, all the risks and the missing information are proposed for removal from the summary of safety concerns.

Important potential risk: Cardio- and Cerebrovascular Disorders

Background information

A large primary care population study in COPD patients with no history of cardiovascular disease found a 25% increase in the adjusted risk of major adverse cardiac events including myocardial infarction, stroke, or cardiovascular death (GOLD, 2024).

Patients with severe cardiovascular disease are at increased risk of future cardiovascular events. Congestive heart failure shares similar risk factors and common pathophysiological mechanisms with COPD (Hillas, 2015).The interaction and association between the two syndromes are still unclear, but some data suggest that in all COPD patients as well as COPD patients experiencing an exacerbation are at risk of CHF, however the prevalence of CHF appears to be higher in those exacerbating (up to 48% versus 3.8 to 16% of COPD patients with stable disease (Le Jemtel, 2007;Rutten, 2005).

Older age, a history of previous cardiac disease and worse lung function were predictive of increased risk of cardiovascular events in the COPD population [Calverley, 2010]. Certain comorbidities, including heart failure, ischemic heart disease and osteoporosis appear to be more frequent in COPD patients with higher symptomatology/breathlessness; however, there does not seem to be an association between COPD GOLD grade and comorbidities [Price, 2014b; Echave-Sustaeta, 2014; Miller, 2013]. One suggestion for this apparent lack of association with airflow limitation could be that COPD GOLD grade better represents morbidity rather than severity [Weinreich, 2015].

Particularly in those with a heavy smoking history, subjects with COPD have a high risk of cardiovascular associated morbidity and mortality [Stone, 2012]. In a recent systematic review of the literature assessing COPD and a number of CVD outcomes, COPD was shown to be associated with an increased risk of CVD, with the risk of CVD increasing with the severity of airflow limitation (reflected by the GOLD grade) [Müllerova, 2013].

Interpretation FEV_1 is an independent and generalisable predictor of mortality, cardiovascular disease, and respiratory hospitalisation, even across the clinically normal range (mild to moderate impairment) [Duong, 2019].

A number of large studies evaluating COPD therapy have suggested that good management may reduce long term cardiovascular risks and mortality (with an ICS/LABA [Calverley, 2010] or a LAMA [Celli, 2009]).

PASS 201038

Characterization of Cardio- and Cerebrovascular Disorders in patients treated with UMEC/VI was formally assessed in a PASS 201038, multinational, prospective, observational, nonrandomized study. The study addressed whether CV and cerebrovascular events differ for new users of UMEC/VI combination or UMEC compared with new users of tiotropium (TIO) in participants diagnosed with COPD. This study was completed in 2023 and the study report was issued in December 2023 and submitted to the EMA on 30 January 2024 through the procedure EMEA/H/C/PSR/S/0048.

Out of 6606 participants enrolled in the study, 6165 were included in the Full Analysis Set: 1246 participants were in the UMEC cohort, 2448 participants were in the UMEC/VI cohort, and 2471 were in the TIO cohort. The UMEC and TIO Propensity Score Matched (PSM) cohorts included 1114 participants per treatment, and the UMEC/VI and TIO PSM cohorts included 1404 participants per treatment. The proportion of participants discontinuing the study were similar across the cohorts at approximately 35%. The median (Q1-Q3) duration of exposure to the study medication among participants in the UMEC cohort was 945.5 (380.0, 1512.0) days, the median (Q1-Q3) duration of exposure among participants in the UMEC/VI cohort was 1105.0 (546.5, 1592.5) days, and among participants in the TIO cohort, the median (Q1-Q3) duration of exposure was 1154.0 (560.0, 1684.0) days.

<u>Primary outcomes</u>

UMEC and UMEC/VI both demonstrated non-inferiority to TIO. The adjusted hazard ratio (HR) (95% CI) for the composite outcome of myocardial infarction (MI), stroke, heart failure or

sudden cardiac death was 1.254 (0.830, 1.896) for UMEC vs. TIO cohorts, and 1.352 (0.952, 1.922) for UMEC/VI vs. TIO. Low rates of the composite endpoint were observed across all cohorts. The frequency and corresponding incidence rates (95% CI) were 37 (1.157 [0.814, 1.594] per 100 person-years), 89 (1.287 [1.034, 1.584] per 100 person-years), and 67 (0.924 [0.716, 1.174] per 100 person-years) events among the UMEC, UMEC/VI, and TIO cohorts, respectively.

This key finding shows that the risk of the composite endpoint of MI, stroke, heart failure, or sudden cardiac death was not higher among participants treated with UMEC or UMEC/VI than participants treated with TIO (this is based on the upper limit of the confidence interval being less than the pre-specified boundary of 2). It is important to note that the incidence rate of the composite endpoint was low across all cohorts.

Secondary outcomes

Incidence rates of the composite endpoint components: MI, stroke and heart failure ranged between 0.21 and 0.37 per 100 person-years across cohorts. The adjusted HR (95% CI) for MI was 1.754 (0.748, 4.115) for the UMEC vs TIO cohort and 2.195 (1.053, 4.575) for the UMEC/VI vs TIO cohort. The adjusted HR (95% CI) for stroke was 1.096 (0.458, 2.621) for the UMEC vs TIO cohort and 1.018 (0.470, 2.207) for the UMEC/VI vs TIO cohort. The adjusted HR (95% CI) for heart failure was 1.287 (0.654, 2.532) for the UMEC vs TIO and 0.832 (0.459, 1.509) for the UMEC/VI vs TIO cohorts.
For MI, an increased risk was found for the UMEC/VI cohort compared to the TIO cohort, but a thorough analysis of individual case safety reports did not suggest that any of the confirmed events were related to UMEC/VI.
The number of cases and incidence rates for MI, stroke, and heart failure were low across all cohorts in the study.

Safety outcomes

For the UMEC vs TIO analysis, the total number of participants with at least 1 stroke (any type) and the corresponding incidence rates (95% CI) were 7 (0.24 [0.097, 0.495] 100 person-years) in the UMEC PSM cohort, and 7 (0.21 [0.086, 0.439] per 100 person-years) in the TIO PSM cohort. For the UMEC/VI vs TIO analysis, the total number of participants with at least 1 stroke (any type) and the corresponding incidence rates (95% CI) were 10 (0.24 [0.117, 0.448] per 100 person-years) and 12 (0.30 [0.153, 0.517] per 100 person-years).

Hospitalization for heart failure was uncommon in the study population and occurred in ≤2.0% of participants across all cohorts.

The incidence rate (95% CI) of SAEs was highest in the UMEC/VI cohort at 10.05 (9.266, 10.879) events per 100 person-years, followed by the UMEC cohort at 9.05 (7.973, 10.236) events per 100 person-years, then the TIO cohort at 7.61 (6.961, 8.313) events per 100 person-years. The incidence rate (95% CI) for drug-related AEs was highest in the UMEC cohort at 2.07 (1.569, 2.672) events per 100 person-years, followed by the UMEC/VI cohort at 1.40 (1.120, 1.734) events per 100 person-years, then the TIO cohort at 0.95 (0.725, 1.213) events per 100 person-years.

The incidence rate (95% CI) of serious CV or cerebrovascular AESIs was highest in the UMEC/VI cohort at 4.75 (4.219, 5.334) events per 100 person-years, followed by the UMEC cohort at 4.70 (3.936, 5.578) events per 100 person-years, and then the TIO cohort at 3.82 (3.357, 4.319) events per 100 person-years.

Conclusion

In summary, the abovementioned study findings demonstrate non-inferiority to TIO for both UMEC and UMEC/VI with regards to the risk of the composite endpoint (MI, stroke, heart failure, or sudden cardiac death). The incidence rates of the composite endpoint and individual endpoints were notably low across all cohorts, and CV mortality was also low across cohorts. There was no difference in risk of moderate/severe COPD exacerbation, consistent with previous observations. The overall benefit/risk profile for UMEC and UMEC/VI remains favorable. While certain SAEs and drug-related AEs incidence rates were numerically greater in the UMEC and UMEC/VI cohorts compared to the TIO cohort, differences were very small. The incidence and types of safety events collected in this study, across all cohorts, were similar to other studies in COPD. The study was not powered to detect difference for these outcomes (i.e., SAEs, drug-related AEs, and CV and cerebrovascular AESIs).

The conclusion is supported by a recent population-based cohort study also found no difference on risks of acute myocardial infarction (AMI), stroke, and major adverse CV events (MACE) among LAMA, LAMA/LABA, LABA/ICS and TIO users compared to LABA users [Rebordosa, 2022].

Data supporting PASS Study 201038

The following data from the previous version of the Anoro Ellipta/Laventair EU-RMP v. 9.0 supports the results from PASS Study 201038.

Major Adverse Cardiac Events (MACE) analysis conducted for a set of studies of UMEC/VI development program

Major Adverse Cardiac Events (MACE) analysis (both SMQ narrow and broad definition) was conducted for a set of studies (the 24-week Primary Efficacy Studies [DB2113361, DB2113373; DB2113360; DB2113374], the 12-month Safety Study [DB2113359], two 12-week exercise endurance studies [DB2114417, DB2114418], and a 12 week Phase 3 study [AC4115408]). The broad criteria were defined *a priori* as follows (and the groups of events meeting these criteria are referenced in the results as 'broad-definition MACE'):

- Cardiac Ischemia Special Interest AE Subgroup (Myocardial Infarction SMQ and Other Ischemic Heart Disease SMQ) excluding fatalities,
- Stroke Special Interest AE Subgroup (Central Nervous System Hemorrhages and Cerebrovascular Conditions SMQ) excluding fatalities, and,
- Adjudicated cardiovascular deaths.

The narrow MACE criteria were defined post-hoc and included only the specific PTs of 'myocardial ischemia' and 'acute myocardial infarction' instead of the Cardiac Ischemia Special

Interest AE subgroup. This narrow MACE definition includes only specific events associated with myocardial infarction rather than including other ischemic events.

In the broad-definition MACE analysis, the MACE incidences were low and similar across treatment groups (1%-2%) with a higher exposure-adjusted frequency in the placebo group than in the rest of the treatment groups (54 participants with events per 1000 subject-years of exposure compared with a range of 31-45 participants with events per 1000 subject-years of exposure in the other treatments). The broad-definition MACE incidence for any treatment group was largely driven by non-fatal cardiac ischemia AESIs.

From the narrow-definition MACE analysis (i.e., using PTs of 'myocardial ischemia' and 'acute myocardial infarction' rather than Cardiac Ischemia Special Interest AE Subgroup excluding fatalities), the MACE incidences were low (<1%) in all treatment groups.

PASS WWE117397

Although PASS WWE117397 was a retrospective longitudinal non-interventional observational cohort study aimed to characterize off-label use of UMEC/VI, through observing these participants, the study demonstrates the incidence of CV events was as expected for these drug classes, and no new safety signals were observed.

The stratification of the indications for LAMA/LABA in the PASS WWE117397 is provided in the Table 13.

Justification for removal of important potential risk of Cardio- and Cerebrovascular Disorders

- PASS 201038 findings presented in this RMP demonstrate non-inferiority in comparison to TIO for both UMEC and UMEC/VI with regards to the risk of the composite endpoint (MI, stroke, heart failure, or sudden cardiac death). The incidence rates of the composite endpoint and individual endpoints were notably low across all cohorts, and CV mortality was also low across cohorts
- Retrospective review of data for large cohort of COPD patients participating in PASS WWE117397 demonstrates the incidence of CV events was as expected for these drug classes.
- The risk is considered sufficiently characterized and no ongoing additional PV activities are considered necessary for the risk.
- GSK has been monitoring CV and cerebrovascular events, by means of routine pharmacovigilance processes and finding no cases influencing current benefit/risk profile of the product.
- There were no triggers to initiate signal evaluation regarding any aspect of this risk.
- The routine risk communication (product labelling) informs prescribers and patients of the potential for CV effects, such as cardiac arrhythmias e.g. atrial fibrillation and

tachycardia. This measure is considered appropriate and sufficient to minimize risk for patients using UMEC/VI without the need for further risk minimization measures.

Important potential risk: Asthma-related intubations, hospitalization and death

Background

LABA-containing compounds carry a class risk of asthma-related intubations, hospitalisation and deaths. An FDA meta-analysis of LABA vs. no LABA (60,954 patients in 110 trials) by age group on a composite endpoint of asthma-related deaths, intubations, and hospitalisations (asthma composite index) showed a statistically significant difference among age groups. The composite event incidence difference for all ages was 6.3 events per 1000 PY with LABAs compared with no LABA use. Among the 15,192 patients with concurrent ICS use, the incidence difference was 0.4 events per 1000 PY. The authors noted a trend of greater excess risk with LABA among the younger age groups [McMahon, 2011].

Treatment options for patients with asthma has been addressed by GOLD 2024 and GINA 2023.

There are extremely important differences in treatment recommendations for asthma and COPD. We no longer refer to asthma and COPD overlap (ACO), instead we emphasize that asthma and COPD are different disorders although may share some common treatable traits and clinical features (e.g., eosinophilia, some degree of reversibility). Asthma and COPD may co-exist in an individual patient. If a concurrent diagnosis of asthma is suspected, pharmacotherapy should primarily follow asthma guidelines. (GOLD 2024). Under these circumstances, the use of an ICS is mandatory. (GOLD 2024).

Use of long-acting muscarinic antagonists (LAMA) in asthma without concomitant ICS is associated with an increased risk of severe exacerbations. In particular treatment with long-acting bronchodilators alone (i.e. without ICS) is recommended for initial treatment in COPD but is contraindicated in asthma due to risk of severe exacerbations and death. Several studies have also shown that patients with diagnoses of both asthma and COPD are at increased risk of hospitalization or death if they are treated with LABA or LABA/LAMA compared with ICS-LABA (or ICS/LABA/LAMA). (GINA 2023)

There is no clinical experience of UMEC/VI in asthma.

Justification for removal of important potential risk of Asthma-related intubations, hospitalization and death

- GOLD 2024 and GINA 2023 clearly state that using LAMA/LABA without ICS is contraindicated in patients with asthma, and HCPs are made aware of this.

- GSK has been monitoring asthma-related intubations, hospitalization and death, by means of routine pharmacovigilance processes and finding no cases influencing current benefit/risk profile of the product.

- Study WWE117397 illustrated low off-label prescribing rates of UMEC/VI and UMEC compared to other LABD in a primary care UK setting. The stratification of the indications for LAMA/LABA in the PASS WWE117397 is provided in the Table 13.

- The risk of asthma-related intubations, hospitalization and death is considered sufficiently characterized, appropriately managed and adequately reflected in the UMEC/VI EU SmPC (Section 4.4). There were no triggers to initiate signal evaluation regarding any aspect of this risk.

Thus, the risk of asthma-related intubations, hospitalization and death is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Missing information: Off-label use in asthma (including pediatric use)

Background

There is no clinical experience of UMEC/VI in asthma.

Long-acting beta2-agonists are not recommended as monotherapy in asthma, as they do not influence airway inflammation and are potentially associated with a risk of asthma-related deaths [Bateman, 2008; Sears, 2009; Nelson, 2006].

Diseases frequently co-occurring with COPD include cardiovascular disease (CVD), anxiety and depression, pulmonary hypertension, metabolic syndrome, diabetes, osteoporosis, asthma, lung cancer and gastro-esophageal reflux disease [Van der Molen, 2010; Smith, 2014].

COPD does not affect children and is uncommon under the age of 40. COPD patients on average tend to simultaneously suffer an array of chronic diseases [Vanfleteren, 2013]

Characterization of off-label use of UMEC/VI was formally assessed in a retrospective longitudinal non-interventional observational cohort study (WWE117397). Based on a new prescription (index prescription date) that includes UMEC/VI, patients were identified utilizing electronic medical records database from two UK Primary Care EMR databases: Clinical Practice Research Datalink GOLD (CPRD GOLD) and The Health Improvement Network (THIN). Study WWE117397 study was completed, and the study report was issued in December 2019. This study has illustrated low off-label prescribing rates of UMEC/VI and UMEC compared to other LABD in a primary care UK setting. There were 69 (3.1%) new users of UMEC/VI with an asthma diagnosis, of whom 39 (1.8% of all UMEC/VI users) were not taking concomitant ICS at the index date, suggesting possible off-label use. For UMEC/VI users, concomitant ICS use was lower in the subgroup of patients without a diagnosis of COPD or asthma compared with patients with either diagnosis. (Requena, 2021).

Diagnosis and possible off-label prescribing in the primary care cohort is presented in Table 13.

Table 13 Diagnosis and Possible Off-Label Prescribing in the Primary Care Cohort (N=34,516)

Index Therapy	All new users	COPD	Asthma	Other (Not COPD or Asthma)	Possible Off - Label Prescribing
All, n (%)[1]	18 908	31 000	4876 (12.5)	3032 (7.8)	6385 (16.4)[2]
UMEC, n (%)	3875	(79.7)	130 (3.4)	141 (3.6)	271 (7.0)[3]
UMEC/VI, n (%)	2224	3604 (93.0)	69 (3.1)	126 (5.7)	195 (8.8)[3]
Other LABD, n (%)	32 809	2029 (91.2)	4677 (14.3)	2765 (8.4)	5919 (18.0)[2]
Other LAMA, n(%)	24 125	25 367	2327 (9.6)	2143 (8.9)	3980 (16.5)[2]
Other LABA, n (%)	6218	(77.3)	2278 (36.6)	482 (7.8)	1727 (27.8)[2]
Other LABA/LAMA, n(%)	2466	19 655 (81.5)	72 (2.9)	140 (5.7)	212 (8.6)[3]
		3458 (55.6)			
		2254 (91.4)			

Patients can qualify for cohort entry, disease or medication group more than once, which is reflected in the higher number new users than patients in the study; efined as all patients without a diagnosis code of COPD at any time, with the exception of a) patients with a diagnosis of asthma prescribed index TIO 2.5 µg, (other LAMA), if they entered the study on or after September 13, 2014, with a concurrent prescription for ICS/LABA; patients with a diagnosis of asthma prescribed an index other LABA and were receiving concomitant ICS at index date; defined as patients without a diagnosis of COPD only.

Source: [Requena, 2021]

Justification for removal of important potential risk of missing information of off-label use in asthma (including pediatric use)

- The GOLD 2024 and GINA 2023 guidelines mentioned in the previous paragraph clearly state that using LAMA/LABA without ICS is contraindicated in patients with asthma, and HCPs are made aware of this.
- Study WWE117397 illustrated low off-label prescribing rates of UMEC/VI and UMEC compared to other LABD in a primary care UK setting (Table 13).
- GSK has been monitoring off-label use in asthma (including pediatric use), by means of routine pharmacovigilance processes and finding no cases influencing current benefit/risk profile of the product.
- The missing information of the off-label use in asthma (incl. pediatric use) is considered sufficiently characterized, appropriately managed, and adequately reflected in the UMEC/VI EU SmPC (Section 4.4).
- There were no triggers to initiate signal evaluation regarding any aspect of this safety concern.

Thus, the missing information of off label use in asthma (incl. pediatric use) is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1 Presentation of important identified risks and important potential risks

There are no important identified/potential risks associated with UMEC/VI.

SVII.3.2 Presentation of the missing information

There is no missing information associated with UMEC/VI.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 14 Summary of safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

No routine PV activities beyond adverse reaction reporting and signal detection activities are required.

III.2 Additional pharmacovigilance activities

No additional PV activities beyond adverse reaction reporting and signal detection activities are required.

III.3 Summary Table of additional Pharmacovigilance activities

There are no on-going or planned additional pharmacovigilance activities for UMEC/VI.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OFTHE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Not applicable.

V.2. Additional Risk Minimisation Measures

Not applicable.

V.3 Summary of risk minimisation measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for ANORO ELLIPTA

This is a summary of the risk management plan (RMP) for ANORO ELLIPTA. The RMP details important risks of ANORO ELLIPTA, how these risks can be minimized, and how more information will be obtained about ANORO ELLIPTA risks and uncertainties (missing information).

ANORO ELLIPTA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ANORO ELLIPTA should be used.

This summary of the RMP for ANORO ELLIPTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of ANORO ELLIPTA's RMP.

I. The medicine and what it is used for

ANORO ELLIPTA is authorized for maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD) (see SmPC for the full indication). It contains Umeclidinium bromide/Vilanterol as the active substance and it is given by inhalation route.

Further information about the evaluation of ANORO ELLIPTA's benefits can be found in ANORO ELLIPTA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/anoro-ellipta-previously-anoro

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of ANORO ELLIPTA, together with measures to minimize such risks and the proposed studies for learning more about ANORO ELLIPTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of ANORO ELLIPTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of ANORO ELLIPTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of ANORO ELLIPTA.

II.C.2 Other studies in post-authorization development plan

There are no studies required for ANORO ELLIPTA.

Summary of risk management plan for LAVENTAIR ELLIPTA

This is a summary of the risk management plan (RMP) for LAVENTAIR ELLIPTA. The RMP details important risks of LAVENTAIR ELLIPTA, how these risks can be minimized, and how more information will be obtained about LAVENTAIR ELLIPTA risks and uncertainties (missing information).

LAVENTAIR ELLIPTA 's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how LAVENTAIR ELLIPTA should be used.

This summary of the RMP for LAVENTAIR ELLIPTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of LAVENTAIR ELLIPTA's RMP.

I. The medicine and what it is used for

LAVENTAIR ELLIPTA is authorized for maintenance bronchodilator treatment to relieve symptoms in adult patients with Chronic Obstructive Pulmonary Disease (COPD) (see SmPC for the full indication). It contains Umeclidinium bromide/Vilanterol as the active substance and it is given by inhalation route.

Further information about the evaluation of LAVENTAIR ELLIPTA's benefits can be found in LAVENTAIR ELLIPTA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: link to product's EPAR summary landing page on the EMA webpage.

https://www.ema.europa.eu/en/medicines/human/EPAR/laventair-ellipta-previously-laventair

II. Risks associated with the medicine and activities to minimize or further characterize the risks

Important risks of LAVENTAIR ELLIPTA, together with measures to minimize such risks and the proposed studies for learning more about LAVENTAIR ELLIPTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;

- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of LAVENTAIR ELLIPTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LAVENTAIR ELLIPTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

There are no studies which are conditions of the marketing authorization or specific obligation of LAVENTAIR ELLIPTA.

II.C.2 Other studies in post-authorization development plan

There are no studies required for LAVENTAIR ELLIPTA.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

Not applicable until further notice.

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 15 Completed Studies

Study	Summary of objectives	Safety concerns addressed	Reference to Protocol /Milestones
Regulatory review of the UMEC/VI submission highlighted additional required in vitro drug interaction investigations Category 3	Additional investigations to provide information to address: • binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations • providing data for VI as a substrate of OATP1B1 and 1B3 • providing data for UMEC as a substrate for BCRP and BSEP • providing further clarification for the lack of effect of UMEC in CYP 2D6 poor metaboliser, possibly through studies in microsomes and hepatocytes • provide data for UMEC as a substrate of OATP1B1 and 1B3	A series of post authorisation *in vitro* studies were conducted to determine the potential for drug-drug interactions	Final study report submitted 6 March 2015 EMEA/H/C/WS0723/G
Post-authorisation Safety Electronic Medical Records Database Cohort Study of New Users of Inhaled UMEC/VI or New Users of Inhaled UMEC in the Primary Care Setting: UK EMR	• Drug utilisation review of new users of UMEC/VI or UMEC, or Other LABD. • Quantify the disease burden of COPD and estimate the incidence of cardiovascular events of interest among new users of UMEC/VI and new users of UMEC.	Cardio- and Cerebrovascular Disorders Off-label use	Final study report submitted Q4 2019 during procedure EMEA/H/C/WS1761

Distributed Network (Study WWE 117397) Category 3			
Post-Authorisation Safety (PASS) Observational Cohort to quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD patients using Inhaled UMEC/VI Combination or Inhaled UMEC versus Tiotropium. (Study 201038) Category 1.	• To demonstrate non-inferiority of UMEC/VI combination and UMEC to tiotropium for risk of the composite endpoint of MI, stroke, heart failure or sudden cardiac death based on an analysis of time to first event for new users of UMEC/VI combination, UMEC or tiotropium. • To quantify the incidence rate and frequency of the composite endpoint of MI, stroke, heart failure or sudden cardiac death after the start of exposure to UMEC/VI combination or UMEC in the licensed indication, or to tiotropium in the post marketing setting over a minimum of 24 months follow up.	Cardiovascular and cerebrovascular events Safety in long term use	Reference to full protocol Final study report submitted Q1 2024 during procedure EMEA/H/C/PSR/S/0048

ANNEX 3 PROTOCOLS FOR PROPOSED, ON-GOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

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Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP:

Not applicable.

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP:

Not applicable.

Part C: Previously agreed protocols for on-going studies and final protocols not reviewed by the competent authority

Not applicable.

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

None.

ANNEX 5 PROTOCOLS FOR PROPOSED AND ON-GOING STUDIES IN RMP PART IV

Not applicable.

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not applicable.

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

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ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Version	Approval date Procedure	Change
10.0	Ongoing	Category 1 study (201038) This study has now completed and removed as a pharmacovigilance activity. This is reflected throughout the EU RMP. Part II: Module SI: Update of epidemiological data Part II: Module SVII:II: Proposed deletion of Important Potential Risks of Cardio- and Cerebrovascular disorders (supported by results of PASS 201038) and Asthma- related intubation hospitalization and death, and Missing Information of Off label use in asthma (both supported by GVP module V revision II guidelines). Part III, V, VI and annexes II and III: Updated in line with proposed removal of safety concerns Annex 8: Update of literature references
9.0	15/10/2020 Procedure number: EMEA/H/C/WS/1850	Category 1 study (201038): The primary and secondary objectives were updated throughout to include the composite endpoint. The sample size for the study was updated. Category 3 study (WWE117397): This study has now completed and this is reflected throughout the EU RMP. Part II: Module SVII: SVII.2 As part of procedure number EMEA/H/C/WS1586 approved on 03 October 2019, PRAC approved the removal of the important identified risks of paradoxical bronchospasm and hypersensitivity: the important potential risks of narrow angle glaucoma and bladder outflow obstruction and urinary retention; and the missing information Safety in pregnancy and lactation, Safety in long-term use and Safety in severe hepatic impairment. Part VI Summary of the risk management plan for ANORO ELLIPTA: Sections II.C, II.C.1 and II.C.2 added.

Version	Approval date Procedure	Change
8.1	03/10/2019 Procedure number EMEA/H/C/WS1586	Part II: Module SIII - Clinical trial exposure section updated to include integrated data in Table 4. Removed references to the ongoing procedure EMEA/H/C/WS1501 at the request of the PRAC. Part II: Module SIV: SIV.2 Limitations to detect adverse reactions in clinical trial development programs has been revised to remove sentences that contain inferences for which the assessment is still ongoing Part II: Module SIV: SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programs. Table 11has been amended to align the correct text for patients with hepatic impairment. Part II: Module SVII: SVII.3.1 Presentation of important identified risks and important potential risks. The potential risk asthma-related intubations, hospitalization and death has been updated with the outcome of the procedure.
8.0	Not approved. Superseded by Version 8.1 EMEA/H/C/WS1586	Update to EU-RMP template based on publication of GVP Module V Rev.2 on 30 March 2017 Safety In consideration of GVP module Revision 2 guidelines: Proposed removal of 'hypersensitivity' as an important identified risk. Proposed removal of missing information for: pregnancy and lactation; safety in long term use; safety in severe hepatic impairment. History of removal of identified risks from previous RMP versions in consideration of update within new EU-RMP template for ANORO ELLIPTA /LAVENTAIR ELLIPTA: paradoxical bronchospasm, glaucoma and bladder outflow obstruction/urinary retention included.
7.1	26/01/2017 procedure number EMEA/H/C/WS1031	Safety concern As per PRAC recommendations the identified risks of Glaucoma and Bladder Outflow obstruction/urinary retention were removed.

Version	Approval date Procedure	Change
7.0	Not approved. Superseded by Version 7.1 EMEA/H/C/WS1031	Safety concern Hypersensitivity was added as an identified risk following a signal evaluation and the outcome of the assessment that was reported in PSUR 2015N242481 (ref: EMA/PRAC/12673/2016 Corr. 2). Paradoxical bronchospasm was upgraded from a potential to an identified risk following a signal evaluation and the outcome of the assessment that was reported in PSUR 2017N342954.] Pharmacovigilance plan Notification of availability of study results on request for a category 4 study included in the RMP (Annex 9): A study Assessment of Comorbidities in COPD in European Symptomatic Subjects from primary care (HZC115058 - ACCESS study). Prior to availability of Anoro ELLIPTA /Laventair ELLIPTA, this non-interventional observation study was conducted assessing the co-morbidities in patients with or without COPD. Therefore, the results of HZC115058 are not relevant to the safety of Anoro/Laventair. The study was included in the initially submitted RMP because the data were to be used to provide a historical control for PASS study 201038. However, during EMA assessment it was agreed to have an active control arm (tiotropium) within study 201038.
6.0	25 June 2015 EMEA/H/C/WS0723/G	Pharmacovigilance plan The results from completed *in vitro* drug-drug interaction studies were reported. These studies were a required additional pharmacovigilance activity following regulatory review of the UMEC/VI submission. The data indicated that there should not be a clinically meaningful increase in either UMEC or VI systemic exposure due to drug-drug interaction.

Version	Approval date Procedure	Change
5.0	08 May 2014 EMEA/H/C/2751 and EMEA/H/C/3754	Pharmacovigilance plan Category 1 study (201038): Study title amended to align with the primary study objective. The incidence of 'pneumonia' and 'lower respiratory tract infection' were included as secondary objective. The sample size for the study was updated. Category 3 study (WWE117397): The secondary objective was updated to include 'pneumonia' and lower respiratory tract infection'. Inclusion of an additional i*n vitro* investigation to provide data for UMEC as a substrate of OATP1B1 and 1B3. Annex 3 updated To reflect approvals across territories
4.0	Version not approved. Superseded by Version 5. EMEA/H/C/002751 (initial MAA)	Safety Safety in long term use included in the Summary table of risk minimization measures Pharmacovigilance plan Prospective cohort post-authorization safety study (201038) re-classified as a Category 1 study. Study identifier for retrospective post authorization safety study changed to WWE117397 (formerly WEUSKOP6679). Additional *in vitro* drug-drug interaction investigations requested following regulatory (CHMP) review and at the request of the PRAC and identified as missing information.
3.0	Version not approved. Superseded by Version 4. EMEA/H/C/002751 (initial MAA)	Pharmacovigilance plan Addition of nonclinical information relating to OCT1 and OCT2. Additional *in vitro* drug-drug interaction investigations requested following regulatory (CHMP) review and at the request of the PRAC and identified as missing information. Timings for the proposed post-authorization safety observational cohort study (201038) updated to reflect the inclusion of mortality as a safety endpoint. ACCESS study re-categorized from category 3 to category 4 post authorization safety study.

Version	Approval date Procedure	Change
2.0	Version not approved. Superseded by Version 3. EMEA/H/C/002751 (initial MAA)	Safety concerns Potential risks added following regulatory (CHMP) review and at the request of the PRAC: paradoxical bronchospasm; narrow angle glaucoma; bladder outflow obstruction and urinary retention. Missing information added following regulatory (CHMP) review and at the request of the PRAC: Safety in long tern use; safety in severe hepatic impairment.