Module 1.8.2

European Union Risk Management Plan (EU-RMP) for INCRUSE ELLIPTA/ROLUFTA ELLIPTA

RMP version to be assessed as part of this application	
RMP Version number	8.0
Data lock point for this RMP	22 December 2023
Date of final sign off	20 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 8.0
I	SI	Update to epidemiological data (updated to provide more recent epidemiological data; no substantial changes which can impact benefit/risk profile).
II	SV	Update to post-authorization exposure.
II	SVII	Proposed removal of risks and missing information: update to all sections in consideration of results of PASS 201038 and GVP module V Revision 2 guidelines. Relevant data from Study 201038 added where applicable.
III	III.2	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 INCRUSE/ ROLUFTA. Proposed removal of List of Important Potential Risks.
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)**
7.2	EMEA/H/C/WS1589	29 October 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
Pharmacotherapeutic group(s) (ATC Code)	Drugs for obstructive airway diseases, anticholinergics (ATC Code: R03BB07)
Marketing Authorization Holder/ Applicant	GlaxoSmithKline (Ireland) Limited
Medicinal products to which this RMP refers	2
Invented name(s) in the European Economic Area (EEA)	INCRUSE ELLIPTA, ROLUFTA ELLIPTA
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Umeclidinium bromide is a long-acting muscarinic receptor antagonist.
	Summary of mode of action: Inhaled anticholinergic bronchodilators or long-acting muscarinic receptor antagonists (LAMAs) function by blocking endogenous airway smooth muscle cholinergic tone.
	Important information about its composition: Contains lactose monohydrate (which contains milk proteins).
Reference to the Product Information	Please refer to the approved product information.
Indication(s) in the EEA	Current: INCRUSE ELLIPTA, ROLUFTA ELLIPTA is indicated for maintenance bronchodilator treatment to relieve symptoms associated with chronic obstructive pulmonary disease chronic obstructive pulmonary disease.

	Proposed: Not applicable
Dosage in the EEA	Current: The recommended dose is one inhalation of INCRUSE ELLIPTA / ROLUFTA ELLIPTA 62.5 micrograms once daily. INCRUSE ELLIPTA / ROLUFTA ELLIPTA should be administered once daily at the same time of the day each day.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Each single inhalation provides a delivered dose (the dose leaving the mouthpiece of the inhaler) of 65 micrograms umeclidinium bromide (equivalent to 55 micrograms of umeclidinium). This corresponds to a pre-dispensed dose of 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium.
	Proposed: 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
CNS	Central nervous System
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	SARS-CoV-virus
CV	Cardiovascular
CVD	Cardiovascular Disease
CPRD	Clinical Practice Research Datalink
CSR	Clinical Study Report
CYP	Cytochrome
DALYs	Disability-adjusted life-years
DM	Diabetes Mellitus
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EEA	European Economic Area
EMA	European Medicine Agency
EU	European Union
EXACT	Pulmonary Exacerbations of Chronic Disease Tool
EXT	Extension (population)
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 second
FOR	Formoterol
FVC	Forced Vital Capacity
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
MACE	Major Adverse Cardiac Events
mcg	micro grams
MDI	Metered Dose Inhaler
MedDRA	Medical Dictionary for Regulatory Activities
mMRC	Modified Medical Research Council Dyspnoea Scale
MI	Myocardial Infarction
NHANES	National Health and Nutrition Examination Survey
NOAEL	No Observed Adverse Effect Level
OATP	Organic Anion Transporting Polypeptide
OD	Once Daily
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
QD	Quaque Die (once daily)
QTc(F)	Corrected QT interval using Fridericia's formula
RCT	Randomized Control Trial
RMM	Risk Minimization 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	Standardized MedDRA Query
sNDA	Supplementary New Drug Application
SOC	System Organ Class
SGRQ	St George's Respiratory Questionnaire
SUMMIT	Study to Understand Mortality and Morbidity in COPD
aRMM	Additional Risk Minimization 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

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ROLUFTA
ELLIPTA

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PART II: SAFETY SPECIFICATION

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

SI.1 Indication (COPD)

INCRUSE ELLIPTA / ROLUFTA ELLIPTA is indicated as a maintenance bronchodilator treatment to relieve symptoms 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. 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 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. 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. On average, the one-year incidence rate of COPD has increased 30-40 per 100,000 since 2010 [IHME, 2020].

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 personalized approach based on the individualized assessment of symptoms and future risk of exacerbation is preferred [GOLD, 2024].

Bronchodilators, such as beta2-agonists and anti-muscarinics, 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 unfavorable to ICS use are recurrent pneumonia, history of mycobacterial infection, and eosinophils (<100 cells/μL). Oral corticosteroids or antibiotics may be added to the treatment regimen for moderate exacerbations. Treatment of severe exacerbations would additionally include considerations of increased short-acting bronchodilator dosage, oxygen therapy, or non-invasive mechanical ventilation. For all patients hospitalized 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]. 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 if eos ≥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; single inhalers adherence to treatment; eos=blood eosinophil count in cells per microliter; mMRC=modified Medical Research Council dyspnoea scale; 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. 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 started in 2018 3-year mortality increased with increasing exacerbations and dyspnea 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 COPD patients on average tend to simultaneously suffer an array of chronic diseases

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 prevalence 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. 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].

<table>
<tr><td></td><td>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].</td></tr>
<tr><td>Smoking-Related Co-morbidities: Lung Cancer</td><td>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].</td></tr>
<tr><td>Age-Related Co-morbidities: Diabetes, Cataracts, Glaucoma</td><td>Most COPD patients are above 65 years of age, and older age can be an independent risk factor for diseases.

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].</td></tr>
</table>

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; 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].

<table>
<tr><td></td><td>Pooled risk ratios from [Festic, 2016]:

<table><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></table></td></tr>
<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</td></tr>
</table>

	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 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 - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

KEY SAFETY FINDINGS FROM NON-CLINICAL 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. In single dose tolerability studies in the rodent, UMEC was well tolerated following oral, intravenous or subcutaneous administration. • 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. • 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	• In clinical trials, the incidence of symptoms associated with local irritancy (*e.g.* cough, nasopharnygitis, oropharyngeal pain) were reported following treatment with UMEC or placebo. The incidence of these events was similar between UMEC and placebo, and were not associated with any sequelae. • A diagnostic ultrasound of the gall bladder in two Phase IIb 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 did not result in an increased incidence of RUQ pain and/or gall bladder-

Key Safety findings (from non-clinical studies)	Relevance to human usage
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 with UMEC, 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 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. • There were no hepatotoxicity or nephrotoxicities identified following treatment with UMEC. <u>Genotoxicity</u>: • *In vitro* or *in vivo* genotoxicity studies indicate that UMEC does not represent a genotoxic hazard to humans. <u>Carcinogenicity</u>: • There were no treatment-related increases in tumor incidence following lifetime administration of UMEC by the inhalation route in either the rat or mouse. <u>Developmental Toxicity</u>: • 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.	related adverse events, and was not associated with abnormal findings for gall bladder length and width compared with placebo. In addition, in the clinical studies, the incidence of on-treatment adverse events in the gallbladder disorders AESI category which includes AEs of cholecystitis, acute cholecystitis, chronic cholecystitis and cholelithiasis, was low and similar following treatment with either UMEC or placebo. • As there are no studies in pregnant women, UMEC 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	• The effect of an eight-fold, supra-therapeutic dose of UMEC (500 mcg QD) on QT prolongation was investigated in a controlled, randomized, 10-day repeat dose, incomplete block crossover study in healthy volunteers.

Key Safety findings (from non-clinical studies)	Relevance to human usage
ion channel activities *in vitro* and as expected from the pharmacology of muscarinic antagonists, a number of cardiovascular 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.	Single dose oral moxifloxacin 400 mg (positive control) demonstrated assay sensitivity with mean increases in time-matched QTcF compared with placebo greater than 5 msec at 1, 2, 4, 8 and 12 hours after dosing. Upper 90% confidence limit exceeded 10 msec at 4 and 8 hours. • The estimated treatment difference from placebo of QTcF (msec) was negative at all time points post last dose on Day 10, and the upper limit of the 90% CI for the estimated treatment difference was less than 10 msec, indicating a lack of UMEC 500 mcg effect on QTcF compared with placebo which is eight times the proposed dose of UMEC. No categorical QTcF effects were observed for UMEC 500 mcg. • There were no clinically relevant changes from baseline in heart rate in the participants with COPD following treatment with UMEC 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).
<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 was found not to be a substrate of BCRP,	• There was no evidence of a clinically relevant increase in systemic exposure of UMEC in healthy human – CYP2D6 poor metabolizer participants at 8-fold higher dose (500 mcg) compared to healthy normal metabolizers. • A clinical study showed a moderate interaction with verapamil (an inhibitor of P-gp). • 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

Key Safety findings (from non-clinical studies)	Relevance to human usage
OATP1B1 or OATP1B3 transporters. UMEC 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. • The binding of UMEC to human liver microsomal protein was investigated *in vitro* with approximately 47% 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 may inhibit. The estimated K_i 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 C_{max}, 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.	healthy population of CYP450 isoenzyme 2D6 poor metabolizers (AC4110106). • 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 patients 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 7 L/h, suggesting no differential CLr for UMEC in COPD patients. • 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 patients 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 patients compared to COPD patients with normal 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

Key Safety findings (from non-clinical studies)	Relevance to human usage
	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). • 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.
Other toxicity-related information or data	
None	

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

SIII.1 Brief overview of development

Umeclidinium has been developed as a once-daily fixed dose LAMA oral inhalation product as a maintenance bronchodilator treatment in adult patients with chronic obstructive pulmonary disease (COPD).

The clinical development program was designed to support the registration of both UMEC monotherapy and UMEC/VI and included two doses of UMEC (62.5 mcg and 125 mcg) and UMEC/VI (62.5/25 mcg and 125/25 mcg). Therefore, where relevant, information for UMEC/VI is included for completeness.

SIII.2 Clinical Trial Exposure

Integrated safety information supporting the clinical development program included 8 completed clinical studies which contained an UMEC monotherapy arm (hereafter referred to as the 'all clinical studies' grouping) in COPD participants are used to support the global regulatory filing in patients with COPD.

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

	Number of Participants		
Study ID	Placebo N=1124	UMEC 62.5 N=576	UMEC 125 N=1087
Efficacy Studies			
AC4115408	68	69	69
DB2113361	275	N/A	407
DB2113373	280	418	N/A
DB2113374	N/A	N/A	222
Long-term Safety Study			
DB2113359	109	N/A	227
Exercise Studies			
DB2114417[a]	170	49	50
DB2114418[a]	151	40	41
Other			
AC4113589	71	N/A	71

Data Source: UMEC_ISS Table 1.01. UMEC=umeclidinium bromide; N/A = not applicable.
Note: All strengths are in micrograms (mcg)
a = Two-period, incomplete block design cross-over design study; participants are counted once under each treatment received.

Four Phase 3a studies with UMEC Inhalation Powder conducted over a 12- (AC4115408) or 24-week (DB2113361, DB2113373 and DB2113374) period are considered 'Efficacy Studies' for UMEC monotherapy in the COPD population.

Study AC4115408 was a 12-week, randomized, double-blind, placebo-controlled, parallel group study comparing UMEC to placebo.

- AC4115408 – UMEC 62.5 mcg, UMEC 125 mcg and placebo QD.
- This study provides safety data, including 12-lead ECG, vital signs and clinical chemistry and hematology assessments.

Studies DB2113361 and DB2113373 were 24-week, randomized double-blind, parallel-group studies comparing the combination of UMEC and the long-acting beta-agonist, vilanterol (VI) to its components and placebo, and UMEC to placebo.

- DB2113361 – UMEC 125 mcg, UMEC/VI 125/25 mcg, VI 25 mcg, and placebo QD.
- DB2113373 – UMEC 62.5 mcg, UMEC/VI 62.5/25 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.

Study DB2113374 was a 24-week, randomized, double-blind, parallel-group study, comparing UMEC/VI to UMEC and the LAMA, tiotropium (TIO). It should be noted that no powered safety comparison is being made between UMEC and TIO.

- DB2113374 – UMEC 125 mcg, UMEC/VI 125/25 mcg, UMEC/VI 62.5/25 mcg and TIO QD.
- This study provides safety data, including 12-lead ECG, vital signs and clinical chemistry and hematology assessments.

One 52-week safety study was conducted with UMEC/VI and UMEC:

- Study DB2113359 was designed to evaluate the safety and tolerability of UMEC 125 mcg and UMEC/VI 125/25 mcg compared with placebo administered once daily over 52-weeks.
- This study provides safety data including 12-lead ECG, 24-hour Holter monitoring, vital signs and clinical chemistry and hematology assessments.

Two exercise studies were conducted as part of the Phase 3a clinical development program:

- DB2114417 and DB2114418 were replicate two period, incomplete block design, cross-over exercise endurance studies, conducted to evaluate the effects of UMEC/VI and individual components in COPD patients over 12 weeks.

- Both studies evaluated UMEC 62.5 mcg, UMEC 125 mcg, UMEC/VI 62.5/25 mcg, UMEC/VI 125/25 mcg, VI 25 mcg and placebo QD.
- These studies provide safety data including 12-lead ECG, vital signs and clinical chemistry and hematology assessments.

One 28-day Phase 2b study was conducted with UMEC and placebo:

- Study AC4113589 was a randomized, double-blind, parallel-group, placebo-controlled study to evaluate the efficacy and safety of three doses of UMEC 125, 250 and 500 mcg QD.

Other supportive studies which contribute to the safety of UMEC are also referenced within the EU RMP, and include:

- AC4113073, a randomized, double-blind, placebo-controlled, three-way cross-over study to evaluate the safety, efficacy, and pharmacokinetics of UMEC administered once- and twice-daily in participants with COPD.
- AC4115321, a randomized, double-blind, placebo controlled, incomplete block, crossover, dose ranging study to evaluate the dose response of UMEC administered once or twice-daily over 7 days in patients with COPD.
- DB2114635, a randomized, placebo-controlled, incomplete block, four period crossovers, repeat dose study to evaluate the effect of the inhaled UMEC/VI combination and UMEC monotherapy on electrocardiographic parameters, with moxifloxacin as a positive control, in healthy participants.
- DB2114636, a single-blind, non-randomized pharmacokinetic and safety study of single dose of UMEC and UMEC/VI combination in healthy participants and in participants with severe renal impairment.
- DB2114637, an open-label, non-randomized, pharmacokinetic and safety study of single dose UMEC/VI combination and repeat doses of UMEC in healthy participants and in participants with moderate hepatic impairment.

Safety data was integrated and presented as follows:

- Integration of four Phase IIIa studies with UMEC Inhalation Powder conducted over 12-week (AC4115408) or 24-week (DB2113361, DB2113373 and DB2113374) treatment periods, hereafter referred to as ‘Efficacy Studies’.
- Long-term Safety Study (DB2113359)
- Integration of two 12-week exercise studies (DB2114417 and DB2114418)

- ‘All Clinical Studies’ grouping AC4115408, DB2113361, DB2113373, DB2113374, DB2113359, DB2114417, DB2114418, AC4113589. (The date of this integration was 2012).
- All COPD study grouping, an integration for all UMEC studies 200109, 200110, 200812, 201314, 201316, 201749, DB2113361, DB2113373, DB2113374, DB2113359, DB2114417, DB2114418, DB2116132, DB2116133, AC4113589. (The date of this integration was 2019).

Table 7 Duration of Exposure - All Clinical Studies

	Placebo		UMEC 62.5 mcg		UMEC 125 mcg		UMEC Combined[1]	
Duration of exposure	Persons	Person time[2]	Persons	Person time[2]	Persons	Person time[2]	Persons	Person time[2]
>=1 day	1124 (100%)	373.9	576 (100%)	202.4	1087 (100%)	454.4	1663 (100%)	656.7
>4 weeks	959 (85%)	365.8	548 (95%)	201.6	954 (88%)	447.3	1502 (90%)	648.9
>8 weeks	901 (80%)	359.4	522 (91%)	198.7	900 (83%)	441.5	1422 (86%)	640.2
>12 weeks	766 (68%)	329.8	450 (78%)	182.9	827 (76%)	425.6	1277 (77%)	608.5
>16 weeks	499 (44%)	265.5	345 (60%)	157.8	685 (63%)	390.5	1030 (62%)	548.3
>20 weeks	487 (43%)	261.3	341 (59%)	156.4	670 (62%)	385.4	1011 (61%)	541.8
>24 weeks	251 (22%)	154.1	154 (27%)	71.6	370 (34%)	249	524 (32%)	320.6
>28 weeks	78 (7%)	73.5	0	-	159 (15%)	150.5	159 (10%)	150.5
>32 weeks	74 (7%)	71.2	0	-	155 (14%)	148.2	155 (9%)	148.2
>36 weeks	73 (6%)	70.6	0	-	154 (14%)	147.6	154 (9%)	147.6
>40 weeks	68 (6%)	66.9	0	-	140 (13%)	137.2	140 (8%)	137.2
>44 weeks	66 (6%)	65.3	0	-	133 (12%)	131.7	133 (8%)	131.7
>48 weeks	66 (6%)	65.3	0	-	133 (12%)	131.7	133 (8%)	131.7
>52 weeks	19 (2%)	19.1	0	-	35 (3%)	35.2	35 (2%)	35.2
Total	-	373.9	-	202.4	-	454.4	-	656.7

Data Source: UMEC_ISS Table 99.01; UMEC – umeclidinium bromide

1 – Combined exposure of UMEC 62.5 mcg and 125 mcg doses; 2 - Person time is representative of exposure by patients-years

Table 8 Duration of Exposure – Dosage, Age group and Gender – All Clinical Studies

	Persons			Person time[1]		
Placebo						
	Male	Female	Total	Male	Female	Total
<=64 years	411	275	686	149.86	87.85	237.71
65-74 years	244	116	360	74.58	36.25	110.83
75-84 years	56	21	77	18.78	6.49	25.28
>=85 years	1	0	1	0.02	-	0.02
Total	712	412	1124	243.25	130.60	373.85
UMEC 62.5 mcg						
	Persons			Person time[1]		
	Male	Female	Total	Male	Female	Total
<=64 years	210	106	316	73.42	36.40	109.82
65-74 years	138	59	197	48.43	22.11	70.54
75-84 years	45	15	60	16.33	4.76	21.09
>=85 years	2	1	3	0.93	0.01	0.93
Total	395	181	576	139.10	63.28	202.38
UMEC 125 mcg						
	Persons			Person time[1]		
	Male	Female	Total	Male	Female	Total
<=64 years	353	263	616	154.51	109.74	264.25
65-74 years	261	110	371	106.64	44.61	151.25
75-84 years	72	25	97	28.33	9.10	37.43
>=85 years	3	0	3	1.43	-	1.43
Total	689	398	1087	290.90	163.45	454.36
Combined UMEC						
	Persons			Person time[1]		
	Male	Female	Total	Male	Female	Total
<=64 years	563	369	932	227.93	146.15	374.07
65-74 years	399	169	568	155.07	66.72	221.79
75-84 years	117	40	157	44.65	13.86	58.52
>=85 years	5	1	6	2.35	0.01	2.36
Total	1084	579	1663	430.00	226.74	656.74

Data Source: UMEC_ISS Table 99.02; UMEC – umeclidinium bromide

1 - Person time is representative of exposure by patient-years; 2 - Combined exposure of UMEC 62.5 mcg and 125 mcg doses

Table 9 Duration of Exposure – Race – All Clinical Studies

Placebo		
Race	Persons	Person time[1]
African American/African Heritage	32	11.55
American Indian or Alaskan Native	1	0.10
Asian	59	19.87
White	1020	337.69
Mixed Race	12	4.63
Total	1124	373.85
UMEC 62.5 mcg		
Race	Persons	Person time[1]
African American/African Heritage	20	6.69
American Indian or Alaskan Native	3	1.37
Asian	43	15.23
White	498	174.23
Mixed Race	12	4.87
Total	576	202.38
UMEC 125 mcg		
Race	Persons	Person time[1]
African American/African Heritage	30	12.24
American Indian or Alaskan Native	1	0.23
Asian	83	32.46
White	964	405.32
Mixed Race	9	4.10
Total	1087	454.36
UMEC Combined		
Race	Persons	Person time[1]
African American/African Heritage	50	18.93
American Indian or Alaskan Native	4	1.60
Asian	126	47.69
White	1462	579.55
Mixed Race	21	8.97
Total	1663	656.74

Data Source: UMEC_ISS Table 99.03; UMEC – umeclidinium bromide

1 - Person time is representative of exposure by patient-years

Table 10 Summary of UMEC exposure – Special Populations

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

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 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 anticholinergics/muscarinic receptor antagonist 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 anticholinergics/muscarinic receptor antagonists 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 criterion, as there have been no formal studies in the use in pregnancy in women.	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 in this patient group. Administration of UMEC to pregnant or breastfeeding women should only be considered if the expected benefit to the mother justifies

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			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 40 years of age were excluded to ensure that participants with asthma were not included, so as not to confound the determination of the efficacy profile of the investigational products in the COPD population.	No	COPD is not common under the age of 40. In regard to an individual patient, if they meet the diagnostic criteria for COPD, then there is no reason to anticipate that a participant 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 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 investigational products in the COPD population.	No	UMEC is not indicated for 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

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			would not be appropriate. The safety profile in this population is not expected to be different to the target population. The product label will contain wording relating to warning against the use of UMEC 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 a-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 if they have a diagnosis of COPD. Some patients may have concurrent respiratory conditions, but it is still important for their COPD to be adequately controlled, therefore exclusion of those with such concurrent diseases would not be considered appropriate.
Participants with a chest X-ray or computed tomography (CT) scan that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD[i].	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 confounding the	No	Patients will receive UMEC if they have a diagnosis of COPD. Some patients may have concurrent respiratory conditions, but it is still important

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	efficacy or safety analysis if the disease/condition exacerbated during the study.		for their COPD to be adequately controlled.
Participants 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 participants enrolled in the UMEC 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 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.
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 studies could be assessed for changes in lung function caused by the investigational treatments, so as not to confound the efficacy or safety analysis. Patients were not excluded if home oxygen was required for less than 12-hours a day.	No	Patients will receive UMEC 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 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	No	Patients with COPD are at risk of pneumonia. In these patients, it is important for their COPD to be adequately controlled,

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
	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.		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 needed use) of short-acting bronchodilators (*e.g.* albuterol/salbutamol) via nebulized therapy.	It was important for this population to be assessed for changes in lung function due to investigational treatments. Those receiving regular nebulized therapies would be more difficult to assess, with regard to treatment response.	No	Patients will receive UMEC if they have a diagnosis of COPD. This would include 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	It was important for this population to be assessed	No	Patients will receive UMEC if they have a

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
phase of a pulmonary rehabilitation program within 4 weeks prior to study start.	for changes in lung function due to study interventions. Those newly receiving pulmonary rehabilitation would be difficult to assess, in regard to response to treatment. Participants who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.		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[1] cardiovascular (including abnormal and significant ECG findings), 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.	The study investigators had discretion on whether to exclude participants on the basis of whether the current condition was significant, defined as any disease that would put the safety of the participant at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.	No	COPD patients are at greater risk of CVD compared with age-matched and sex-matched individuals without COPD [Shi, 2021]. Consistent with the disease under study, the majority of COPD participants enrolled in the Efficacy Studies and the Long-term Safety Study had concurrent medical conditions at screening (77-94% across placebo and UMEC treatment groups), and across placebo and UMEC treatment groups 54-72% of participants reported a

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			cardiovascular risk factor at screening (*e.g.* hypertension, 44-60%; hyperlipidemia, 22-37%; diabetes, 11-28%) and 12-35% reported a concurrent cardiac disorder. 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.
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 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. The prescribing information will contain appropriate warning for use in patients with narrow-

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			angle glaucoma or urinary retention.
Participants with known or suspected history of alcohol or drug abuse within 2 years prior to study start.	Participants with known or suspected history of alcohol or drug abuse were excluded from the clinical trials due to concerns about being able to follow the study procedures. Exclusion criteria prevented participants with potentially serious compliance concerns from entering the study, so as not to confound the determination of the safety and efficacy profile of the investigational products.	No	Patients will receive UMEC 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, it is not appropriate to contraindicate their use.

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

<table>
<tr><th>Ability to detect adverse reactions</th><th>Limitation of trial program</th><th>Discussion of implications for target population</th></tr>
<tr><td>Which are rare</td><td>The total number of participants exposed to UMEC of at least 4 weeks duration is provided below:
<table><tr><th>Treatment</th><th>N</th><th>Patient-years</th></tr><tr><td>Placebo</td><td>1124</td><td>374</td></tr><tr><td>UMEC 62.5 mcg</td><td>576</td><td>202</td></tr><tr><td>UMEC 125mcg</td><td>1087</td><td>454</td></tr></table>Data source: UMEC_ISS Table 1.02

The total number of participants that received UMEC monotherapy at 62.5 mcg and 125 mcg strengths in these studies was 1663.</td><td>The overall safety profile of UMEC is consistent with that reported for licensed LAMAs and the COPD population.

Although rare events may not have been observed during clinical studies, there is a large amount of established experience with licensed LAMAs.

Given that 1663 participants have been exposed to UMEC monotherapy at 62.5 mcg and 125 mcg strengths, then there is a >99% probability that very common (>1 in 10) and common (>1 in 100) AEs would have been observed. There is a >80% probability that uncommon (>1 in 1000) AEs would have been observed during clinical studies (based on CIOMS and WHO criteria).</td></tr>
<tr><td>Due to prolonged exposure</td><td>In the All Clinical Studies grouping, 133 participants received once daily UMEC 125 mcg treatment for greater than 48-weeks.</td><td>There were no new safety signals identified during longer-term treatment with UMEC. The AE profile of UMEC in the Long-term Safety Study was similar to that observed in the Efficacy Studies.</td></tr>
<tr><td>Due to cumulative effects</td><td>In the All Clinical Studies grouping that included UMEC over 24-week and 52-week study treatment periods, there was no evidence to suggest any cumulative adverse effects.</td><td>There were no new safety signals identified during longer-term treatment with UMEC. The AE profile of UMEC in the Long-term Safety Study was similar to that observed in the Efficacy Studies.</td></tr>
<tr><td>Which have a long latency</td><td>In the All Clinical Studies grouping, 133 participants received once daily UMEC 125 mcg treatment for greater than 48-weeks.</td><td>There were no new safety signals identified with longer-term treatment with UMEC.</td></tr>
</table>

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

Table 11 Exposure of special populations included or not in clinical trial development program

Type of special population	Exposure Total number of participants and person time
Pregnant women There is a low incidence of pregnancy in the COPD population due to their age.	Not included in the clinical development program. There are no or limited amount of data from the use of UMEC to assess the safety of UMEC in pregnant women; The incidence of pregnancy in the COPD population is low due to their age. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Umeclidinium should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus. During the clinical development program, per protocol, female participants of childbearing potential were required to have a urine pregnancy test conducted at Screening (Visit 1), during the study, and/or the Early Withdrawal Visit. Participants who became pregnant during the study were to discontinue study drug and were withdrawn from the study. No pregnancies occurred in any participants during a completed or ongoing study in the COPD clinical development program (safety data cut off 10 December 2012). In the ongoing asthma studies as described in Section 1.1.3.3 from the FF/UMEC asthma clinical development program (safety data cut-off 10 December 2012), 4 pregnancies have occurred. Two pregnancies occurred prior to administration of any study medication. Two pregnancies occurred while on blinded study medication; one pregnancy was ongoing and the other pregnancy had an outcome of abortion spontaneous while on blinded FF/UMEC, FF or FF/VI. No pregnancies occurred in the completed COPD studies from the UMEC COPD clinical development program. In addition, no significant information relating to UMEC exposure during pregnancy or administration during lactation has been identified based on cumulative review from post marketing exposure to UMEC.

Type of special population	Exposure Total number of participants and person time
Breastfeeding women In most cases, person time exposure data can be omitted for these populations	Not included in the clinical development program. In addition, no significant information relating to UMEC exposure during pregnancy or administration during lactation has been identified based on cumulative review from post marketing exposure to UMEC.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with CV impairment	Patients with hepatic or renal impairment were not excluded from the clinical studies unless they had significant impairment as determined by the investigator. Clinical pharmacology studies were performed in severe renal (creatinine clearance <30mL/min) and moderate hepatic impaired (Child-Pugh score 7-9) participants, so there is no limitation regarding these patient groups and appropriate wording will be provided in the prescribing information. No dosage adjustment is required in patients with mild or moderate hepatic impairment. UMEC has not been studied in patients with severe hepatic impairment and should be used with caution. Participants with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to UMEC (C_{max} and AUC), and no evidence of altered protein binding between participants with moderate hepatic impairment and healthy volunteers. UMEC has not been evaluated in patients with severe hepatic impairment." No dose adjustment or maximum dose is required for patients with renal impairment. 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. UMEC is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD. The majority of participants enrolled in the clinical

<table>
<tr><th>Type of special population</th><th>Exposure
Total number of participants and person time</th></tr>
<tr><td>• Immunocompromised patients

• Patients with a disease severity different from inclusion criteria in clinical trials</td><td>development program had post-bronchodilator GOLD stage of either Stage II or III.

Immunocompromised patients were not included in clinical development program.

UMEC is currently indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic COPD. The majority of participants enrolled in the clinical development program had post-bronchodilator GOLD stage of either Stage II or III.</td></tr>
<tr><td>Population with relevant different ethnic origin</td><td>All Phase 3 COPD clinical studies were conducted internationally and although the majority of patients were White, no ethnicities were excluded.

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

<table>
<tr><td></td><td colspan="3">N [Patient Years]</td></tr>
<tr><td colspan="4">Efficacy Studies
(AC4115408, DB2113361, DB2113373, DB2113374)</td></tr>
<tr><td></td><td>Placebo</td><td>UMEC
62.5</td><td>UMEC
125</td></tr>
<tr><td>All regions</td><td>623
[220]</td><td>487
[183]</td><td>698
[263]</td></tr>
<tr><td>EU</td><td>313
[109.2]</td><td>169
[61]</td><td>358
[133]</td></tr>
<tr><td colspan="4">Long-term Safety Study (DB2113359)</td></tr>
<tr><td>All regions</td><td>109</td><td>-</td><td>227</td></tr>
<tr><td>Romania</td><td>28</td><td>-</td><td>61</td></tr>
<tr><td>Slovakia</td><td>4</td><td>-</td><td>11</td></tr>
</table>
Data Source: UMEC_ISS Tables 1.03, 1.12; DB2113359 Table 5.12
UMEC – umeclidinium; EU – European Union

LAMAs are prescribed internationally and there are no reported safety concerns based on different racial or ethnic origins.</td></tr>
<tr><td>Subpopulations carrying relevant genetic polymorphisms</td><td>Not included in the clinical development program</td></tr>
<tr><td>Other
• Pediatrics

• Elderly</td><td>Pediatric patients were not included in the clinical development program. There is no relevant use of UMEC in the pediatric population (under 18 years of age) in the indication for COPD.

Elderly patients were not excluded from phase III COPD studies. Few patients were over 85 years in the clinical</td></tr>
</table>

Type of special population	Exposure Total number of participants and person time
• Other relevant comorbidities	studies, which is consistent with the prevalence of the disease in this age group. Adverse event experience by age categorization from the Efficacy and Exercise Studies. There were no remarkable differences in the pattern of incidence for any on-treatment AE across treatment groups (including placebo) for subjects ≤64 years of age, 65 to 74 years of age, or 75 to 84 years of age. The number of subjects ≥85 years of age (n=6 total) was small and therefore it is difficult to make conclusions on these data. The incidence of AEs of special concern for the elderly, including CNS (confusion/extrapyramidal) AEs, Events related to falling, Cardiovascular events, Cerebrovascular events, and Infections, were similar across treatment groups (including placebo) and age groupings therein (see Table 12 and Table 13). On-treatment AEs reported by 3% or more of participants on any treatment group and having an incidence greater than placebo by age categorization (in descending order) were: • ITT population: cough, URTI, back pain and hypertension • ≤64 years of age: cough, URTI, hypertension, toothache and COPD • 65 to 74 years of age: headache, nasopharyngitis, cough, arthralgia and diarrhea • 75 to 84 years of age: cough, URTI, back pain, pharyngitis and abdominal pain upper. Participants with historical or current evidence of clinically significant cardiovascular, 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 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.

Table 12 Summary of On-treatment AE Categories by Age Subgroup - Efficacy Studies

	Placebo N=623				UMEC 62.5 mcg N=487				UMEC 125 mcg N=698			
	≤64 yrs N=370	65-74 yrs N=200	75-84 yrs N=52	≥85 yrs N=1	≤64 yrs N=257	65-74 yrs N=171	75-84 yrs N=56	≥85 yrs N=3	≤64 yrs N=371	65-74 yrs N=256	75-84 yrs N=69	≥85 yrs N=2
Any AE	173 (47%)	89 (45%)	26 (50%)	0	126 (49%)	88 (51%)	28 (50%)	1 (33%)	204 (55%)	136 (53%)	35 (51%)	1 (50%)
Fatal AE	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0	0	0	0	1 (<1%)	1 (1%)	0
SAE	10 (3%)	13 (7%)	4 (8%)	0	15 (6%)	12 (7%)	1 (2%)	0	13 (4%)	22 (9%)	4 (6%)	0
AEs leading to permanent discontinuation	9 (2%)	14 (7%)	3 (6%)	0	17 (7%)	9 (5%)	6 (11%)	0	22 (6%)	16 (6%)	6 (9%)	0
CNS (confusion/extrapyramidal) AEs[1]	0	0	0	0	0	0	0	0	0	0	1 (1%)	0
Events related to falling[2]	9 (2%)	7 (4%)	1 (2%)	0	11 (4%)	7 (4%)	4 (7%)	0	11 (3%)	4 (2%)	3 (4%)	0
Cardiovascular events[3]	28 (8%)	9 (5%)	4 (8%)	0	20 (8%)	16 (9%)	7 (13%)	0	26 (7%)	20 (8%)	10 (14%)	0
Cerebrovascular events[4]	1 (<1%)	0	1 (2%)	0	0	1 (<1%)	0	0	1 (<1%)	0	0	0
Infections[5]	80 (22%)	36 (18%)	12 (23%)	0	59 (23%)	40 (23%)	16 (29%)	1 (33%)	76 (20%)	60 (23%)	13 (19%)	1 (50%)

Data Source: UMEC_ISS Table 2.144; UMEC=umeclidinium bromide

Table 13 Summary of On-treatment AE Categories by Age Subgroup - Exercise Studies

	Placebo N=321				UMEC 62.5 mcg N=89				UMEC 125 mcg N=91			
	£64 yrs N=196	65-74 yrs N=109	75-84 yrs N=16	³85 yrs N=0	£64 yrs N=59	65-74 yrs N=26	75-84 yrs N=4	³85 yrs N=0	£64 yrs N=51	65-74 yrs N=33	75-84 yrs N=7	³85 yrs N=0
Any AE	58 (30%)	40 (37%)	7 (44%)	0	12 (20%)	6 (23%)	0	0	19 (37%)	14 (42%)	3 (43%)	0
Fatal AE	0	0	0	0	0	0	0	0	1 (2%)	0	0	0
SAE	5 (3%)	4 (4%)	1 (6%)	0	1 (2%)	0	0	0	1 (2%)	2 (6%)	1 (14%)	0
AEs leading to permanent discontinuation	6 (3%)	8 (7%)	3 (19%)	0	2 (3%)	0	0	0	1 (2%)	1 (3%)	1 (14%)	0
CNS (confusion/extrapyramidal) AEs[1]	0	0	0	0	0	0	0	0	0	0	0	0
Events related to falling[2]	4 (2%)	1 (<1%)	0	0	0	0	0	0	1 (2%)	0	0	0
Cardiovascular events[3]	3 (2%)	2 (2%)	3 (19%)	0	2 (3%)	0	0	0	1 (2%)	0	0	0
Cerebrovascular events[4]	0	1 (<1%)	1 (6%)	0	0	0	0	0	0	0	0	0
Infections[5]	23 (12%)	23 (21%)	0	0	4 (7%)	5 (19%)	0	0	6 (12%)	6 (18%)	1 (14%)	0

Data Source: UMEC_ISS Table 2.145; UMEC=umeclidinium bromide

1 - CNS (confusion/extrapyramidal) AEs - Deliria including confusion (HLGT); Dyskinesias and movement disorders NEC (HLT)

2 - Events related to falling AEs - Injuries NEC (HLGT); Gait disturbances (HLT); Cerebellar coordination and balance disturbances (HLT)

3 - Cardiovascular AEs - Conduction disorder (PT), ECG QT prolonged (PT), Long QT syndrome (PT), Cardiac arrhythmias (SMQ), Cardiac Failure (SMQ), Myocardial Infarction (SMQ), Other Ischemic Heart Disease (SMQ), Hypertension (SMQ), Sudden cardiac death (PT), Cardiac arrest (PT), Sudden death (PT), Cardio-respiratory arrest (PT), Cardiac death (PT), CNS hemorrhages and cerebrovascular conditions (SMQ)

4 - Cerebrovascular AEs - Hemorrhagic cerebrovascular conditions (SMQ); Ischemic cerebrovascular conditions (SMQ)

5 - Infection AEs – Infections and Infestations (SOC)

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.

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 estimates from IQVIA Health Prescribing Insights data is divided by 365.

Post-marketing cumulative exposure from launch (April 2014) to 30 September 2023 is estimated at 3 228 248 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 30 September 2023 is estimated to be 3 228 248 patient years [NB. IQVIA data can be up to 6 months in arrears from the PBRER/EU PSUR cut-off date].

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 prescription written for patients aged between 65 and 74 years.

[1] Data sourced from IQVIA's '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 considering its class and pharmacology. No instances of abuse of study medication were reported with UMEC 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 in updated RMP

Proposed removal of Important potential risks

The safety concerns for UMEC were reviewed in line with post-marketing experience with the drug, the results of PASS 201038 and definitions in GVP module V revision 2. UMEC has been on the market for more than 9 years with an estimated post-marketing patient exposure of 3 228 248 patient-years.

As further described below, the risks initially listed in the EU RMP are no longer considered to meet the definition of important and do not require any additional pharmacovigilance activities or additional risk minimization measures to characterize or mitigate them. Therefore, all the risks 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, patients 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 was formally assessed in PASS 201038, a 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 on 31 January 2023 and the study report was issued on 22 December 2023 and submitted to the EMA on 29 January 2024 as a Post Approval Measure procedure reference 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.

Primary outcomes

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 events 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 PAS Study 201038

The following data from the previous version of the Incruse Ellipta/Rolufta EU-RMP v. 7.2 supports the results from PAS Study 201038 were:

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

MACE analysis was conducted (both narrow and broad SMQ definition) for the following studies combined: AC4115408, DB2113361, DB2113373, DB2113374, DB2114417, DB2114418 and DB2113359.
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 AESI Subgroup (Myocardial Infarction SMQ and Other Ischemic Heart Disease SMQ) excluding fatalities,

- Stroke AESI Subgroup (Central Nervous System Hemorrhages and Cerebrovascular Conditions SMQ) excluding fatalities, and,

- Adjudicated cardiovascular deaths.

To investigate events relating specifically to myocardial infarction rather than other cardiac ischemic events, the narrow MACE definition included only the PTs of "myocardial ischemia" and "acute myocardial infarction" in place of the Cardiac Ischemia Special Interest AE (AESI) subgroup.

In the broad-definition MACE analysis (i.e., including non-fatal cardiac ischemia AESI), MACE events 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 subjects with events per 1000 subject-years of exposure compared with 45 and 31 subjects with events per 1000 subject-years of exposure for UMEC 62.5 mcg and UMEC 125 mcg treatment groups, respectively).

From the narrow-definition MACE analysis (i.e., using PTs of 'myocardial infarction' and 'acute myocardial infarction' rather than Cardiac Ischemia AESI subgroup excluding fatalities), the MACE incidences were low (<1%) in all treatment groups. The exposure-adjusted frequencies for subjects with any narrow-definition MACE were lower with both UMEC treatments (10 and 16 subjects with events per 1000 subject-years of exposure in the 62.5 mcg and 125 mcg treatment groups, respectively) compared with placebo (19 subjects with events per 1000 subject-years of exposure). The total number of narrow-definition MACE events was lower for both UMEC treatment groups (UMEC 62.5 mcg – 2 events; UMEC 125 mcg – 7 events) compared with placebo (8 events).

PASS WWE117397

Post authorization safety study WWE117397 is a retrospective study with a cohort large patient with COPD who were new users of inhaled UMEC (3875 patients) and UMEC/VI combination (2224 patients), utilizing UK primary care and linked secondary care databases. Through observing these patients, the study demonstrates the incidence of cardiovascular events was as expected for these drug classes, and no new safety signals were observed.

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 without the need for further risk minimization measures.

Thus, the risk of Cardio- and Cerebrovascular Disorders is proposed to be removed from EU RMP. GSK will continue to monitor this event via routine pharmacovigilance activities.

Important potential risk: Lower Respiratory Tract Infection (incl. pneumonia)

Background information

Respiratory infections, including pneumonia and lower respiratory tract infections (LRTI) often occur in patients with COPD [Lineros, 2023]. Patients with COPD have an increased risk of such events, which can be serious, due to their chronic lung condition. The incidence of pneumonia, including pneumonia requiring hospitalization in the COPD population is dependent upon several patient characteristics, such as increasing age, COPD severity, low body mass index (<20), male gender, concurrent smoking, and the presence of co-morbid conditions [Williams, 2017].

LRTI and pneumonia are the inflammatory conditions of the tissues. Accumulating evidence suggests that LAMAs may modulate airway contractility and airway hyperresponsiveness not only by blocking muscarinic acetylcholine receptors (mAchRs) expressed on airway smooth muscle but also via anti-inflammatory mechanisms by blocking mAchRs expressed on inflammatory cells, submucosal glands, and epithelial cells, therefore LAMAs are the cornerstone for the treatment of COPD) [Calzetta, 2021].

PASS 201038

The study addressed whether the incidence rates of CV and cerebrovascular events differed for new users of UMEC/VI combination or UMEC compared with TIO in participants diagnosed with COPD., however for new users of UMEC/VI combination, UMEC or TIO, one of the secondary objectives was to quantify the incidence rate and frequency of serious pneumonia/ serious LRTI (composite endpoint).

In the UMEC PSM cohort, 29 (2.6%) participants had 1 serious pneumonia/serious LRTI event and 8 (0.7%) had ≥2 events. Similarly, in the TIO PSM cohort, 31 (2.8%) participants had 1 serious pneumonia/serious LRTI event and 3 (0.3%) participants that had ≥2 events. The incidence rates (95% CI) of serious pneumonia/serious LRTI were

1.29 (0.906, 1.773), and 1.05 (0.725, 1.462) per 100 person-years among the UMEC and TIO PSM cohorts, respectively. In the UMEC/VI PSM cohort, 60 (4.3%) participants had 1 serious pneumonia/serious LRTI event. In the TIO PSM cohort, 39 (2.8%) participants had 1 serious pneumonia/serious LRTI event. The incidence rates (95% CI) of serious pneumonia/serious LRTI were 1.79 (1.401, 2.255), and 1.10 (0.796, 1.471) events per 100 person-years among the UMEC/VI and TIO PSM cohorts, respectively.

The results revealed that serious pneumonia/serious LRTI events were uncommon (approximately 3% of participants) in the UMEC and TIO PSM and there was no evidence to suggest that the risks differed between cohorts.

Additionally, the results are supported by a nationwide cohort study used Korean National Health Insurance claim data from January 2002 to April 2016, where the risk of pneumonia associated with long-term ICS/LABA or LAMA treatment for COPD was compared and found that the overall risk of pneumonia was significantly higher in ICS/LABA treatment. The incidence rates of pneumonia and pneumonia-related hospitalization were higher in patients on ICS/LABA, especially in the youngest included age group (55 to < 75 years). This trend was even observed in COPD patients with COPD exacerbation history (no or one moderate exacerbation). The subgroups with higher pneumonia risk on ICS/LABA—compared to LAMA—were those with no history of pneumonia; treatment at a hospital-level medical institution with inpatient beds rather than a primary medical institution such as primary care, or a lower income class in the 4th quartile. Regarding comorbidities, pneumonia risk was higher when ICS/LABA was used in patients with chronic pulmonary diseases such as bronchiectasis and TB-destroyed lungs resulting in cough, sputum, and dyspnoea [Lee, 2023].

Data supporting PAS Study 201038

The incidence of AEs in the LRTI AESI category for the All Clinical Studies (AC4115408, DB2113361, DB2113373, DB2113374, DB2113359, DB2114417, DB2114418 and AC4113589 grouping at the proposed UMEC 62.5 mcg dose (<1%; 19.8/1000SY) was similar to placebo (<1%; 24.1/1000SY) compared with the UMEC 125 mcg dose (2%; 39.6/1000SY). The incidence of SAEs in the LRTI AESI category was comparable between UMEC 62.5 mcg (<1%; 9.9/1000SY) and placebo (<1%; 8.0/1000SY); with no SAEs reported in the UMEC 125 mcg treatment group (Table 14).

Table 14 Incidence and Exposure-Adjusted Frequency of Subjects with On-Treatment Pneumonia and LRTI AESI Events – All Clinical Studies (ITT population)

		Number (%) of Subjects [exposure adjusted frequency, subject years]		
AESI Group		Placebo N=1124 [374SY]	UMEC 62.5 N=576 [202SY]	UMEC 125 mcg N=1087 [454SY]
Pneumonia and LRTI Any event [a]	AE	13 (1) [34.8]	7 (1) [34.6]	33 (3) [72.6]
	SAE	7 (<1) [18.7]	3 (<1) [14.8]	8 (<1) [17.6]
	Fatal	1 (<1) [2.7]	0 [0]	1 (<1) [2.2]
Pneumonia AESI	AE	4 (<1) [10.7]	4 (<1) [19.8]	17 (2) [37.4]
	SAE	4 (<1) [10.7]	1 (<1) [4.9]	8 (<1) [17.6]
	Fatal	1 (<1) [2.7]	0 [0]	1 (<1) [2.2]
LRTI excluding pneumonia AESI	AE	9 (<1) [24.1]	4 (<1) [19.8]	18 (2) [39.6]
	SAE	3 (<1) [8.0]	2 (<1) [9.9]	0 [0]
	Fatal	0	0	0

Data Source: UMEC_ISS Tables 2.112, 2.116, 2.120, 2.124, 2.128, 2.132.

Abbreviations: AE=adverse event; AESI=adverse event of special interest; ITT=intent-to-treat; LRTI=lower respiratory tract infection; SAE=serious adverse event; SY=Subject years; UMEC=umeclidinium bromide.

[ ] - Numbers represent the number of subjects with an event per 1000 subject-years of exposure. Note: Exposure-adjusted frequency is calculated as (1000 * number of subjects with AE) divided by (total duration of exposure in days / 365.25).

a. The total number of subjects with at least one on-treatment event reported in the Pneumonia and/or the LRTI subgroups.

b. The total number of on-treatment Pneumonia and LRTI adverse events reported.

Justification for removal of important potential risk of Lower Respiratory Tract Infection (incl. pneumonia)

- Review of data for COPD patients participating in clinical studies for UMEC 62.5 mcg demonstrates the incidence of LRTI (incl. pneumonia) events were similar to placebo.
- PASS 201038 findings presented in this RMP demonstrate there was no evidence to suggest that the risks differed between UMEC and TIO cohorts.
- GSK has been monitoring LRTI (incl. pneumonia) 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.

Thus, the risk of LRTI (incl. pneumonia) 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.

SVII.3.2 Presentation of the missing information

None.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 2 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.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

None.

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

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Not applicable.

V.2. Additional Risk Minimization Measures

Not applicable.

V.3 Summary of risk minimization measures

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for INCRUSE ELLIPTA

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

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

This summary of the RMP for INCRUSE 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 INCRUSE ELLIPTA's RMP.

I. The medicine and what it is used for

INCRUSE 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 as the active substance and it is given by inhalation route.

Further information about the evaluation of INCRUSE ELLIPTA’s benefits can be found in INCRUSE 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/incruse-ellipta-previously-incruse

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

Important risks of INCRUSE ELLIPTA, together with measures to minimize such risks and the proposed studies for learning more about INCRUSE 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 the case of INCRUSE ELLIPTA, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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 INCRUSE 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 INCRUSE 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 INCRUSE ELLIPTA.

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

There are no studies required for INCRUSE ELLIPTA.

Summary of risk management plan for ROLUFTA ELLIPTA

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

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

This summary of the RMP for ROLUFTA 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 ROLUFTA ELLIPTA's RMP.[ii]

I. The medicine and what it is used for

ROLUFTA 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 as the active substance and it is given by inhalation route.

Further information about the evaluation of ROLUFTA ELLIPTA’s benefits can be found in ROLUFTA 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/rolufta-ellipta

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

Important risks of ROLUFTA ELLIPTA, together with measures to minimize such risks and the proposed studies for learning more about ROLUFTA 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 the case of ROLUFTA ELLIPTA, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

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 ROLUFTA 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 ROLUFTA 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 ROLUFTA ELLIPTA.

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

There are no studies required for ROLUFTA ELLIPTA.

PART VII: ANNEXES

LIST OF ANNEXES

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ANNEX 1 EUDRAVIGILANCE INTERFACE

Not applicable until further notice.

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

Table 3 Completed Studies

Study	Summary of objectives	Safety concerns addressed	Reference to Protocol /Milestones
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 Distributed Network (Study WWE 117397) Category 3	• Drug utilization 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
Post-authorisation Safety (PAS) 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
8.0	Ongoing	Category 1 study (201038) This study has now completed and 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 Lower Respiratory Tract Infections (incl. pneumonia)(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.
7.2	29 Oct 2020 EMEA/H/C/WS1589	Category 1 study (201038): Study title amended to align with the primary study objective. The primary and secondary objectives were updated to include the composite endpoint and be in line with the approved version 4 protocol. 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.
7.1	Not approved. Superseded by Version 7.2.	Category 1 study (201038): Study title amended to align with the primary study objective. The primary and secondary objectives were updated 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. 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 'paradoxical bronchospasm' as an important potential risk. Proposed removal of missing information for: pregnancy and lactation; safety in long term use; safety in severe hepatic impairment. History of removal of potential risks from previous RMP versions in consideration of update within new EU-RMP template for INCRUSE/ ROLUFTA: glaucoma and bladder outflow obstruction/urinary retention included.
7.0	27/10/2016 Procedure number EMEA/H/C/PSUSA/00010263/201604	Removal of the following: Important Potential Risk(s): • Narrow angle glaucoma • Urinary retention • Change of tradename from ESPANDA to ROLUFTA • Update to reporting date of category 3 PASS, WWE117397 (formerly WEUSKOP6679, to Q4 2019 • As per PRAC recommendations, the risks of narrow angle glaucoma and Urinary retention were removed from the EU RMP. • The tradename of the duplicate MAA was changed at the request of the Applicant. The report date was aligned with that for ANORO/LAVENTAIR as requested by PRAC.
6.1	29th September 2016	Addition of the following: • Addition of duplicate trade name: ESPANDA Addition of ESPANDA as a second trade name due to a duplicate application.
6.0	February 2015	Inclusion of results from completed *in vitro* drug interaction studies, which were a required additional pharmacovigilance activity following regulatory review of the submission. The results from these *in vitro* substrate evaluation and microsomal binding studies indicate that there should not be any clinically meaningful increase in UMEC systemic exposure due to a drug-drug interaction.
5.0	February 2014	LTRI (including pneumonia) has been moved from a primary objective to secondary objective in the summary of study 201038.

		These changes were included in the EU RMP following the Pharmacovigilance Risk Assessment Committee (PRAC) review.
4.0	February 2014	The potential risk of 'Lower respiratory tract infection (including pneumonia)' has been included at the request of the PRAC. These changes were included in the EU RMP following PRAC assessment review.
3.0	January 2014	The prospective cohort post-authorization safety study has been: • Reclassified as a Category 1 study and denoted as study 201038 • Updated to include 'pneumonia and lower respiratory tract infection' as a secondary objective • Updated sample size calculation for the study population The retrospective PAS study number has been: • Denoted as study WWE117397 (formerly WEUSKOP6679). • Updated to include 'pneumonia and lower respiratory tract infection' as a secondary objective. Safety in long-term use has been included to the 'Summary table of risk minimization measures'. Regulatory review of the submission has highlighted additional in vitro drug interaction investigations which should be completed, and these have been included as missing information. These changes were included in the EU RMP following the CHMP review, and at the request of the PRAC.
2.0	October 2013	Addition of the following: Important Potential Risk(s): • Paradoxical bronchospasm • Narrow angle glaucoma • Bladder outflow obstruction and urinary retention Missing Information: • Safety in long-term use • Safety in severe hepatic impairment Non-clinical information relating to OCT1 and OCT2. Discussion of information relating to minimization of potential for medication errors. Timings for the proposed post-authorization safety observational cohort study have been updated to reflect the inclusion of mortality as a safety endpoint.

		ACCESS study has been moved from category 3 to category 4, as this study is not a pharmacovigilance activity for the post approval use of UMEC. These changes were included in the UMEC EU RMP following the CHMP review, and at the request of the PRAC. Additional changes to the UMEC EU RMP have been included following the CHMP/PRAC D180 review of the UMEC/VI EU RMP.

[i] Significant is defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the clinical study.