20 February 2014
EMA/175100/2014
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Incruse

International non-proprietary name: umeclidinium bromide

Procedure No. EMEA/H/C/002809/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Product information

Name of the medicinal product:	Incruse
Applicant:	Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS UNITED KINGDOM
Active substance:	UMECLIDINIUM BROMIDE
International Nonproprietary Name/Common Name:	UMECLIDINIUM BROMIDE
Pharmaco-therapeutic group (ATC Code):	R03BB07
Therapeutic indication(s):	Incruse is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).
Pharmaceutical form(s):	Inhalation powder, pre-dispensed
Strength(s):	55 µg
Route(s) of administration:	Inhalation use
Packaging:	Blister
Package size(s):	1 inhaler (7 doses), 1 inhaler (30 doses), 3 inhalers (3 x 30 doses) (multipack)

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List of abbreviations

AC	Active controlled
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
Ae	amount of drug excreted unchanged in urine
AE(s)	Adverse event(s)
Af Am	African American/African heritage
AMS	accelerator mass spectrometry
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ATS	American Thoracic Society
AUC(0-∞)	area under the concentration-time curve from time zero (predose) extrapolated to infinite time
AUC(0-t)	area under the concentration-time curve from time zero (predose) to last time of quantifiable concentration within a subject across all treatments
AUC(0-x)	area under the concentration-time curve from time zero (predose) to x hours postdose
AUC(0-τ)	area under the concentration-time curve over the dosing interval
BD	Bis in die (twice daily)
BDI	Baseline dyspnea index
Bf	Breathing frequency
BMI	Body mass index
CAT	COPD assessment test
CI	Confidence interval
CLcr	creatinine clearance
CLr	renal clearance
Cmax	maximum observed concentration
COA	cellobiose octaacetate
COPD	Chronic obstructive pulmonary disease
CRM	Cardiorespiratory measures
CSR(s)	Clinical Study Report(s)
CV	between-subject coefficient of variation
CYP	cytochrome P450

DB	Double blind
DD	Double dummy
DPI	Dry powder inhaler
ECG(s)	Electrocardiogram(s)
EDS	Exercise dyspnea scale
EET	Exercise endurance time
EMA	European Medicines Agency
Emax	maximum effect
EQ-50D	EuroQol-50D
ESWT	Endurance shuttle walk test
FDA	Food and Drug Administration
Fe	fraction of dose excreted unchanged in urine
FEV1	Forced expiratory volume in 1 second
FF	fluticasone furoate
FRC	Functional residual capacity
FTIH	First in humans
FVC	Forced vital capacity
GCP	Good clinical practice
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
HARP	Harmonization for Analysis and Reporting Program
HPLC-MS/MS	high pressure liquid chromatography with tandem mass spectrometric detection
HR	Hazard ratio
IC50	half maximal inhibitory concentration IH inhaled
ICS	Inhaled corticosteroid
IH	Inhalation
INN	international nonproprietary name
INVID	Investigator number
ISE	Integrated Summary of Efficacy
ISWT	Incremental shuttle walk test
ITT	Intent-to-treat
IV	intravenous

kg	Kilogram(s)
kr	Kenward-Roger
L	Liter
LABA	Long-acting beta agonist
LAMA	Long-acting muscarinic agonist
LLQ	lower limit of quantification
LS	Least squares
MACE	Major Adverse Cardiac Events
mcg	Microgram(s)
MgSt	magnesium stearate
mITT	Modified intent-to-treat
mMRC	Modified Medical Research Council
N	number of subjects who received a specific treatment
n	number of subjects with non-missing values (including not calculable where applicable)
n*	number of subjects for whom parameter could not be derived because of not quantifiable concentration
NA	not applicable
NDPI	Novel dry powder inhaler
NHANES	National Health and Nutrition Examination Survey
NQ	not quantifiable
OL	Open-label
OR	Odds ratio
PC	Placebo-controlled
PD	Pharmacodynamic
PG	Parallel group
P-gp	p-glycoprotein
PK	Pharmacokinetic
PLA	Placebo
PLB	Placebo
PM	poor metabolizer
PO	oral
QD	once-daily
QD	Quaque die (once-daily)

QTc(F)	QT interval corrected for heart rate using Fridericia's formula
R	Randomized
RAP	Reporting and Analysis Plan
Raw	Airway resistance
RER	Respiratory exchange ratio
s	Seconds
SCE	Summary of Clinical Efficacy
SD	standard deviation
SDAP	Summary document analysis plan
SE	Standard error
sGaw	Specific airway conductance
SGRQ	St George's Respiratory Questionnaire
SOBDA	Shortness of breath in daily activities
SpO2	Arterial oxygen saturation
t½	half-life
TDI	Transition dyspnea index
TFH	24-hour population
TIO	Tiotropium
tlast	time to last quantifiable plasma concentration
tmax	time of occurrence of Cmax
UMEC	umeclidinium bromide (GSK573719)
US	United States
USAN	United States adopted name
VCO2	Carbon dioxide production
Ve	Minute ventilation
VI	vilanterol (GW642444)
VO2	Oxygen uptake
Vt	Tidal volume
WHO	World Health Organization
WM	Weighted mean
XO	Crossover

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo Group Ltd submitted on 25 April 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Incruse, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 18 October 2012.

The applicant applied for the following indication:

Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that umeclidinium bromide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

The applicant requested the active substance umeclidinium bromide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 20/05/2010 and 23/09/2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Glaxo Operations (UK) Ltd. (trading as Glaxo Wellcome Operations)
Priory Street
Ware, Herts SG12 0DJ
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur:	**Concepcion Prieto Yerro**	**Co-Rapporteur:**	**Robert James Hemmings**

- The application was received by the EMA on 25 April 2013.
- The procedure started on 22 May 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 5 August 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 August 2013.
- During the PRAC meeting on 5 September 2013, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the meeting on 19 September 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 September 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 20 November 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 30 December 2013.
- During the PRAC meeting on 9 January 2014, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the CHMP meeting on 23 January 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 29 January 2014.
- During the PRAC meeting on 6 February 2014, the PRAC agreed on a PRAC RMP advice and assessment overview.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding issues to all CHMP members on 6 February 2014.
- During the meeting on 20 February 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Incruse.

2. Scientific discussion

2.1. Introduction

Problem statement

Chronic Obstructive Pulmonary Disease (COPD) is a common disease that accounts for 5% of deaths globally [World Health Organisation (WHO) 2012]. As a leading cause of morbidity and mortality worldwide, COPD produces a substantial, and growing, economic and social burden. COPD is characterised by persistent, usually progressive, airflow limitation associated with an enhanced inflammatory response in the airways and the lung. The goals of pharmacologic therapy in COPD are the reduction in symptoms and in the frequency and severity of exacerbations, and the improvement of health status and exercise tolerance. Bronchodilators, such as a long acting muscarinic antagonists (LAMA) and long-acting beta2 agonist beta2-agonists (LABA), are central for improving lung function and managing symptoms in COPD. In patients not adequately controlled with bronchodilators, the addition of a ICS (Inhaled corticosteroid) usually leads to reductions in the frequency of exacerbations, improves symptoms and quality of life and produces small improvements in lung function [GOLD, 2013].

About the product

The application concerns Incruse, Inhalation powder, pre-dispensed. The active ingredient is umeclidinium bromide, a novel long acting muscarinic antagonist (LAMA) that exerts bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic cholinergic receptors on airway smooth muscle.

Incruse is indicated for the treatment of COPD. The recommended posology is one inhalation of Incruse 55 micrograms delivered dose once daily.

Type of Application and aspects on development

This Marketing Authorisation Application is submitted in accordance to article Article 3(2)(a) of Regulation (EC) No 726/2004) (New active substance).

Umeclidinium bromide has been evaluated in a clinical development programme for the maintenance treatment of patients with COPD as a monotherapy (Incruse) and as umeclidinium bromide/vilanterol combination product (Anoro). This dossier only pertains to the development as monotherapy. Two relevant doses were tested in phase III (62.5 mcg and 125 mcg). The applicant states that the development program complied with regulatory guidelines. Advice on the development program was sought from regulatory authorities in the United States (US), European Union (EU), Japan and Canada. Though the advice received at the agency meetings was specific to UMEC/VI and positioning of the combination product, the program as designed included both the combination and monotherapy arms and some of the advice is equally applicable for UMEC monotherapy. The resultant Phase III clinical development program was consistent with guidance for the development of medicinal products for the treatment of patients with COPD in place at the time.

It should be noted that the data submitted in the application dossier referred to Incruse 62.5 µg as the finished medicinal product, which corresponds to the metered dose of the active substance. This was the basis used during the assessment of this application.

However in accordance with the “Guideline on Summary of Product Characteristics (SmPC) and QRD Recommendations on the expression of strength in the name of Centrally Authorised Human Medicinal Products” (as stated in Section 1 of the SmPC and in the name section of the Labelling and Package Leaflet), the CHMP agreed that the strength should refer to the delivered dose of the active substance and therefore the name of the medicinal product finally approved by the Committee was expressed as follows:

Incruse 55 micrograms, in all official approved documents (CHMP opinion/future EC decision and CHMP assessment report). Since 62.5 µg (metered dose) were the strengths referred to throughout the non-clinical and clinical development of this medicinal product and the data submitted in the application, this has been left unchanged in the sections of this assessment report relating to the non-clinical and clinical development.

GlaxoSmithKline (GSK) obtained scientific advice from the Committee for Medicinal Products for Human Use (CHMP) for UMEC/VI. CHMP agreed that the dose ranging studies were appropriately designed to support dose selection. CHMP agreed that the proposed Phase III clinical development program was sufficient to support the development of both the UMEC combination and monotherapy products. CHMP endorsed the inclusion of a broad patient population and agreed with forced expiratory volume in 1 second (FEV1) as a lung function measure while emphasizing the importance of measuring symptomatic benefit. Following CHMP advice, a symptomatic endpoint (Transition Dyspnea Index [TDI], which is accepted by CHMP) was specified as the key secondary endpoint for the analysis of the results of the placebo-controlled studies for the Marketing Authorization Application (MAA).

2.2. Quality aspects

2.2.1. Introduction

The finished product contains umeclidinium bromide as the active substance, the active moiety being umeclidinium. It is a pre-dispensed inhalation powder which is presented in a plastic inhaler. The inhaler contains a multi-dose blister strip, having either 7 or 30 doses. Each blister contains a pre-dispensed dose of 62.5 micrograms of umeclidinium (as bromide).

When actuated, the inhaler delivers the contents of a single blister of the blister strip. Each actuation provides a delivered dose of 55 micrograms of umeclidinium (as bromide). The inhaler is packaged in a sealed tray with a desiccant.

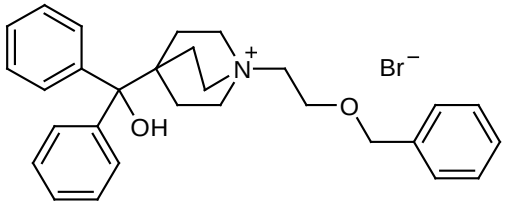
Other ingredients are lactose monohydrate and magnesium stearate.

2.2.2. Active Substance

Incruse contains umeclidinium bromide a novel long acting muscarinic antagonist.

Umeclidinium bromide

The chemical name of umeclidinium bromide (INN) is 1-[2-(Benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide and has the following structure:



Umeclidinium bromide (INN) is a white crystalline, non-hygroscopic powder that is practically insoluble in water and heptane, very slightly soluble in toluene and t-methyl butyl ether, slightly soluble in acetonitrile, ethanol and 2-propanol, soluble in methanol and freely soluble in dichloromethane and dimethyl sulfoxide.

The molecular structure has been fully characterised by elemental analysis, proton and carbon NMR, MS, IR, X-ray crystallography. Umeclidinium bromide has a non-chiral molecular structure. Polymorphism has been observed but the synthesis process consistently yields one polymorphic form.

Manufacture

Non-micronised active substance is supplied by one manufacturer. The starting materials and reagents are well defined and with acceptable specifications.

Umeclidinium bromide was developed using a 'quality by design' (QbD) approach which involved the identification of potential critical process parameters (CPPs) that might have an impact on the critical quality attributes (CQAs) of the drug substance. Ranges were set for those process parameters that were found to be critical. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed ranges.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Specification

The active substance specification includes tests for description (visual), identity and solid state form (IR), umeclidinium bromide content by HPLC), related impurities (HPLC), residual solvent (GC), water content (Karl Fischer titration), residue on ignition and particle size distribution (laser diffraction). The absence of a microbial limit test and heavy metals has been satisfactorily justified.

It has been demonstrated that the results for assay, related impurities, residual solvents, water content and residue on ignition tests are not affected by micronisation. Therefore, it was found acceptable to perform these tests on the non-micronised drug substance. The limits for impurities have been qualified for the inhalation route in safety assessment studies.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analyses data on eight production scale batches of micronised active substance and three batches of the non-micronised active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial batches of micronised active substance from the proposed manufacturer stored in the intended commercial package for 18 months under intermediate conditions at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH were submitted. Additionally, stability data for one batch of the non-micronised active substance under intermediate conditions at 30 ºC / 65% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided.

The following parameters were tested: description, content, drug-related impurities, water content, particle size distribution (for micronised umeclidinium bromide) and solid state form by XRPD (for micronised umeclidinium bromide). The analytical tests used are stability indicating.

Photostability testing following the ICH guideline Q1B was also performed. Stress testing was performed on one batch of micronised and on one batch of non-micronised umeclidinium bromide under 50°C/ambient humidity for 3 months, freeze/thaw conditions of -20°C and 30°C under 7 day cycles and under 40°C/75% RH for 3 months with storage in a low density polyethylene (LDPE) bag, maintained in an upright orientation.

Forced degradation studies were also conducted in the solid state (14 days at 80ºC under ambient and 75% relative humidity), and under exposure to UV/visible light; and in solution at 80 ºC and under acidic, basic and oxidative conditions, in order to identify potential degradation pathways.

All stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container and proposed storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The goal was to develop a dry powder inhaler that would deliver a long acting muscarinic antagonist (umeclidinium bromide) via the orally inhaled route of administration to the lungs, with acceptable chemical and physical stability. Umeclidinium bromide exhibits appropriate functional characteristics, is chemically and physically stable and is, therefore, suitable for formulation as a dry powder inhaler for oral inhalation. It was also found to exhibit no undesirable taste. The inhaler, a novel dry powder inhaler capable of delivering pre-metered doses form the blister strip, has been designed to provide up to thirty days therapy and it incorporates a counter which shows the number of doses remaining.

A quality by design (QbD) approach was adopted for product development.

The excipients used in Incruse are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards and additional in-house standards. There are no novel excipients used in the finished product formulation. The excipients are magnesium stearate and lactose monohydrate.

A novel inhalation device containing a blister strips has been developed to allow optimal inhalation of the active substance. Appropriate studies have been conducted in accordance with the EU 'Guideline on the pharmaceutical quality of inhalation and nasal drug products' (EMEA/CHMP/QWP/49313/2005 Corr) demonstrating the performance of the device. The blister strips are made of a formed silver coloured base foil laminate, sealed with a peelable lid foil laminate. Confirmation that the packaging materials comply with the current EU requirements has been provided.

The inhaler has a light grey body and a light green mouthpiece cover and a dose counter. It is packed in a foil tray which also contains a desiccant. Adequate information on the design and composition of the inhaler has been included in the product information.

Adventitious agents

Lactose monohydrate is of animal origin and magnesium stearate is of vegetable origin.

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Manufacture of the product

Incruse is manufactured by a manufacturing process that involves the following operations: umeclidinium blending, filling of the strip, and assembly of the inhaler and packing.

A 'quality by design' (QbD) approach was adopted for product development.

The data collected as part of process qualification indicate that the manufacturing process is robust and will consistently yield a product of acceptable quality. The process has been validated for twenty-six production-scale batches of inhalers manufactured at the applied site. The data collected indicate that the manufacturing process is robust and will consistently yield a product of intended quality. The manufacturing process is adequately described and critical steps are under control.

Product specification

The finished product release specifications include appropriate tests for appearance, identification umeclidinium (UV, HPLC), mean umeclidinium content, umeclidinium uniformity of delivered dose (HPLC), fine particle mass (by next generation impaction) and microbiological quality. The analytical methods have been adequately validated.

Batch analysis data have been presented for eleven production-scale batches. Results have been presented for eight batches in the 30-dose and three batches in the 7-dose presentations. The batches were all produced at the intended site of manufacture.

All batches for which results have been provided complied fully with the release specification presented above. The data confirm consistency and uniformity of manufacture and indicate that the process is capable of consistently producing a finished product that meets the predefined specifications and that the manufacturing process is under control.

Stability of the product

Stability data have been generated under long-term (25ºC/60%RH), intermediate (30ºC/75 %RH), and accelerated (40ºC/75%RH) conditions in line with the ICH guidelines. Up to 18 months primary stability data for umeclidinium inhalation powder are presented for three batches. These batches were produced at production-scale and assembled at the proposed commercial site using a representative commercial process. The primary pack (blister strip) is identical to the one intended for commercialisation, and the tray and inhaler used in the stability studies are representative of the commercial ones. The tests performed are the same as those performed at release and are considered to be stability indicating.

Three months in-use stability data for both initial and aged product are presented. Testing has been performed from the initial time point and after storage for 6 and 9 months at 25°C/60% RH. Following removal of the secondary packaging and desiccant packet, the inhaler was replaced on storage at 25°C/75% RH. The results of the stability studies demonstrate the chemical and physical stability of the finished product when stored for the proposed in-use storage period at 25°C/75% RH. No significant changes were observed in description, drug-related impurity, content of umeclidinium or particle size distribution. All results comply with the proposed commercial specification up to the proposed patient in-use period.

In addition, photostability and stress testing was performed: freeze/thaw studies, high temperature and UV-visible light exposure.

The shelf-life specifications include the same tests as for release with the exception of the following three additional tests: drug-related impurities (HPLC) and mean moisture content.

Based on available stability data, the proposed shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on the development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner and adequate information has been provided on the design and testing of the inhalation device. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

The applicant has applied QbD principles in the development of the active substance and finished product and their manufacturing. Process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant has conducted a nonclinical toxicological evaluation to support the long-term clinical use of UMEC, with in vitro and in vivo pharmacodynamic studies, safety pharmacology, pharmacokinetics and general toxicity evaluation. Genotoxicity, reproductive toxicology and carcinogenic potential have also been evaluated, along with the potential for eye and dermal irritancy.

GLP aspects

All safety pharmacology studies, a number of pharmacokinetic studies and all pivotal general toxicity studies, genotoxicity, carcinogenicity and reproductive toxicity studies, including the toxicokinetic evaluation of each study, were conducted in compliance with Good Laboratory Practice regulations.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The *primary pharmacology* studies conducted with UMEC (GSK573719) showed that the product have an antagonist activity against all 5 human mAChRs in CHO cells with affinity values in the sub-nM range. In addition, saturation, association and dissociation binding studies showed that UMEC display a high affinity for receptor subtypes mAChR-3 and mAChR-2. 3H-UMEC associated faster and had a faster t½ with the mAChR-2 receptor compared with the mAChR-3 receptor. In studies conducted with mAChR-1, -2 and -3 it was shown that UMEC is a competitive inhibitor of the three receptor subtypes in vitro. Lastly, a study conducted with the human metabolites GSK1761002 (M33) and GSK339067 (M14) showed that M33 is a functional inhibitor of mAChR-1 and mAChR-3 in vitro, about ~10-fold less potent than UMEC, while GSK339067 has negligible pharmacological activity. GSK1761002A (M33) and GSK339067A (M14) were shown to have no direct stimulatory effect at any of the mAChR tested.

In vivo, UMEC was able to block the MCh-induced bronchoconstriction in a dose-dependent and sustained manner with UMEC producing 50% or greater inhibition for up to 72 hours when administered intranasally. In addition, UMEC dose-dependently blocked the bronchoconstriction in guinea pigs after intratracheal instillation, in a sustained and dose-dependent manner.

Studies were performed to investigate whether inhaled administration of the excipient magnesium stearate affected pulmonary function. Regarding the studies conducted in conscious rats and guinea pigs, acute inhaled exposure to a dry powder formulation of magnesium stearate for 60 minutes did not produce overt pharmacological effects.

Secondary pharmacodynamic studies

In vitro *secondary pharmacodynamics* studies were conducted with a battery of 50 receptors, ion channels, enzymes and transporters. UMEC showed affinity for the kappa opioid receptor, sigma receptor, Ca2+ channel, Na+ channel and dopamine transporter. In guinea pigs, UMEC did not consistently affect ACh-induced bradycardia. Considering the high selectivity of UMEC for the mAChRs and the low plasma concentrations (as a consequence of the low concentration of inhaled dose), it is unlikely that UMEC would interact in vivo with these receptor proteins. Furthermore, the neurobehavioral effects associated with activity at opioid and dopamine receptors have not been observed in preclinical safety studies.

As UMEC is a pan-active mAChR antagonist there is a potential for UMEC to have activity at extra-pulmonary muscarinic receptors (e.g., cardiac mAChR-2). However, based on local delivery to the lungs, the proposed low dose and the poor oral bioavailability of UMEC, the Applicant's conclusion that activity will likely be restricted to the airway is plausible. Available in vivo data support this as no effect on ACh-induced bradycardia was seen following intratracheal dosing of UMEC (0.25 or 2.5 mcg) in guinea pigs suggesting that there was little or no systemic exposure to M2 receptors on the myocardium of the heart. Based on these data the Applicant calculated that UMEC had a therapeutic window of at least 10 fold between the desired bronchodilatory effect (mAChR-3) and adverse cardiovascular effects (mAChR-2) such as bradycardia.

Safety pharmacology programme

The in vivo *safety pharmacology* study on central and peripheral effects in rats showed dilated pupils in few animals. A single inhaled dose of UMEC (215 or 2206 µg/kg) produced reversible increases in respiratory rate (18 to 45%) and concurrent decreases in tidal volume (3 to 17%) with no apparent effect on minute volume during the exposure. The Applicant considers that this finding could be related to the pharmacology of UMEC. As it is known that increasing bronchoconstriction generally causes a slower deeper breathing pattern, it would be reasonable to assume that bronchodilation could lead to a more rapid, shallow breathing pattern to optimize mechanical efficiency. Direct lung function was not measured during the repeat dose inhaled toxicity program on UMEC in both rats and dogs. However, given that the changes observed were minimal and reversible, an altered breathing pattern was only detected at high doses in the dog in dose ranging studies and is considered to be procedure-related and no histological changes in the lung indicative of altered lung compliance or airway obstruction were observed. The Applicant considers that the reversible minimal effect observed is not of concern for humans. As expected, changes in ventilatory parameters with UMEC are observed in clinical trials in COPD patients and are regarded as beneficial.

UMEC inhibited hERG channel tail current in vitro and, as expected from the pharmacology of muscarinic antagonists, caused a number of cardiovascular effects (increases in heart rate, prolongation of PR together with transient second degree AV block of Mobitz Type I

followed by a decrease of RR interval). In the general toxicology studies, treatment with UMEC caused tachycardia in dogs.

Pharmacodynamic drug interactions

No specific nonclinical pharmacodynamic drug interaction studies have been performed with UMEC. Based on the high selectivity of the UMEC to its native receptors, and the low plasma concentrations within the efficacious dose range (as a consequence of the low inhaled dose and its subsequent high rate of clearance from the bloodstream as well as the poor oral bioavailability), the potential for pharmacodynamic drug interactions is considered small. The use of LAMAs as human medicines is well documented and known potential drug interactions are described in the prescribing information. Considering the clinical data, no additional PD drug interactions studies are necessary

2.3.3. Pharmacokinetics

A comprehensive set of pharmacokinetic/toxicokinetic studies have been conducted with UMEC and the data presented is considered to adequately characterise the PK profile of UMEC. The PK parameters of UMEC were studied in the rat, dog and human. The PK after intravenous administration were similar across the species investigated including human, with a high clearance, indicating extrahepatic clearance routes such as direct renal secretion, and a large volume of distribution, indicating extensive distribution into tissues. Subcutaneous and intravenous administrations were considered appropriate surrogates for inhalation administration to achieve systemic exposure in safety pharmacology and preliminary embryofetal studies.

The Applicant included TK measurements of UMEC in most repeated dose inhalation toxicity studies in mice, rats, rabbits and dogs. Inter-animal and inter-study variability of systemic exposure was relatively high as is typical for inhalation administration, especially in the dog. Generally, systemic exposure to UMEC following inhalation administration to mice, rats, rabbits, dogs and humans increased with increasing dose in an approximately proportional manner. Cmax was usually detected immediately after the administration in all species, indicating rapid absorption across the lung.

The in vitro plasma protein binding of UMEC was moderate in animals and human. Protein binding data obtained using plasma from renally or hepatically impaired human subjects was slightly higher to that in plasma from healthy subjects. Blood cell association of UMEC was low in nonclinical species and human. Protein binding and blood cell association for UMEC were independent of concentration over the range investigated. In addition, UMEC was shown to be a substrate of human P-gp and of human organic cation transporter OCT1 and OCT2. These transporters are predominantly located in the liver and kidney, respectively. This data is contraindicative of distribution into tissues, and suggestive of the involvement of an active transport mechanism in the distribution of UMEC. However, further test on UMEC as a substrate for OATP1B1 and OATP1B3, as a possible hepatic uptake transporters, and BCRP and BSEP for their possible involvement in the biliary excretion should be considered and have been requested as further data to be provided post-authorisation.

Studies in rats showed that radioactivity was rapidly and widely distributed following intravenous administration. Tissue concentrations decreased with time and were generally below the limit of quantification by 10 days after dosing. Highest concentrations or radioactivity were observed in liver and kidneys, the organs associated with clearance of

UMEC. Some accumulation in the uveal tract and retina was detected. In addition, retention of UMEC in the lungs of mice was demonstrated for up to 24 hours following a single intranasal administration.

The metabolite profile of UMEC was evaluated in vitro and in vivo in several species, as well as in humans. The main routes of metabolism were oxidation followed by conjugation and O-dealkylation. All the metabolites in human were also observed in at least one species used for nonclinical toxicology testing. In addition, the production of metabolites in human liver microsomes was shown to be mediated primarily by CYP2D6, with CYP3A4 and CYP1A1 playing minor roles.

The elimination of 14C-UMEC was investigated following a single administration to mice, rats and dogs by oral and/or intravenous dosing. Following oral administration, the excretion of radioactivity was almost entirely via the faeces in rat and dog, which is consistent with humans and with the very low oral bioavailability observed in rat and dog.

On the other hand, elimination after i.v. administration to mice, rats and dogs was both via the faeces (49-66%) and urine (8-17%). Not all the dose was recovered in the excreta over the collection period, being some prolonged retention of radioactivity, with quantifiable amounts in the carcass of mice and rats, and radioactivity being present in excreta at the last collection time point in all species, including humans. However, the majority of the radioactivity was eliminated moderately rapid with over half the dose excreted within 24 hours in the rat and mouse, and 48 hours in the dog.

2.3.4. Toxicology

An adequate package of toxicity studies has been conducted with UMEC in relevant species. NOAELs were identified in each of the nonclinical species which provide good safety margins compared to the maximum proposed commercial dose of UMEC (55 µg/day delivered dose).

Single dose toxicity

No specific single dose toxicity studies were conducted with UMEC. Dose escalation in the 7 day dose range finding inhalation studies in the rat and the dog identified dose-limiting toxicity in the respiratory tract. In the in vivo genotoxicity micronucleus test, rats tolerated two intravenous doses of 10,000 or 20,000 mcg/kg (dose limited by solubility). Single oral doses up to 1,000,000 mcg/kg were well tolerated in the mouse. In the rat, a single dose of 50 mcg/kg and 60 mcg/kg was well tolerated using the intravenous and subcutaneous routes respectively.

Repeat dose toxicity

In repeat dose inhalation toxicity studies, the principal toxicities seen with UMEC were irritant effects in the respiratory tract and pharmacology-related cardiovascular effects, as well as a reduction in body weight gain.

According to the Applicant, the spectrum of microscopic changes observed in the upper respiratory tract of mice, rats and dogs are considered to be indicative of a local irritant effect to UMEC, which could have been exacerbated by the drying of the mucosa associated with the antimuscarinic pharmacological action of UMEC. This justification is considered acceptable. In addition, the NOAELs in the inhalation rodent studies were determined according to the severity of upper respiratory tract irritancy. The Applicant considers that these clinical observations are of little relevance to humans as the larynx is a particularly

sensitive area of the respiratory tract in rodents and the duration and method in which the rodents were dosed (nose-only inhalation for 60 minutes) is very different to the short oral inhalation method of administration in humans. In humans, local irritancy (e.g. cough, nasopharyngitis, oropharyngeal pain) were commonly reported during clinical trials across all treatment arms which included placebo. However, they were not associated with any sequelae.

On the other hand, tachycardia is a common effect of LAMAs, as well as alterations in ion channel activities in vitro and it is expected from the pharmacology of muscarinic antagonists.

Granuloma formation in the lung was observed in one dog study and was considered to be secondary to excessive antimuscarinic pharmacology. Gall bladder distension and myofibre degeneration detected in one 14-day dog study was not observed in pivotal studies in dogs, and available clinical data indicate no increased risk for gall bladder distension or clinical symptoms. The test article relationship of the arterial changes in the heart and lungs in the 39 week study in dogs could not be established; however, it was considered to be incidental or an exacerbation of an underlying idiopathic disease. Therefore, all these findings are considered of less importance and without clinical significance which is acceptable.

Genotoxicity

The study's results indicate that UMEC does not pose a genotoxicity risk to patients. An assessment of the route of synthesis for UMEC (as the bromide salt) has been conducted to determine whether any impurities might be present which are known or suspected DNA-reactive mutagens, and to assess the likelihood of any such impurities being present in final drug product. There were no impurities of mutagenic concern at a level that would exceed the threshold of toxicological concern (TTC) as defined by guidelines on the limits for genotoxic impurities.

Carcinogenicity

Administration of UMEC did not increase the incidence of neoplastic findings in mice or rats. An apparent increase in the incidence of two rare tumor types in rats was not considered treatment-related because it appeared only in one group/sex.

The non-neoplastic findings associated with administration of UMEC by inhalation for up to 104 weeks to mice and rats included upper respiratory tract irritancy, accumulations of eosinophilic inclusions, accumulation of alveolar macrophages and effects on the eye and Harderian glands.

Reproduction Toxicity

In reproductive and developmental toxicity studies in the rat and rabbit, UMEC had no effects on male or female mating performance or fertility at inhaled doses of up to 180 and 294 mcg/kg/day, respectively. In addition, no effects on embryofetal survival and development were seen in either the rat or rabbit following inhaled doses up to 278 and 306 mcg/kg/day, respectively or in the rabbit following subcutaneous doses up to 180 mcg/kg/day. In a rat pre-and post-natal study, slightly decreased pre-weaning pup body weights in litters was related to a decreased maternal body weight gain and food consumption. There were no other effects on pre-natal or post-natal development.

The male fertility study and the pre-and post-natal study in rats were conducted by subcutaneous administration; however, considering the high exposure observed by this route of administration, this is not considered an issue. Systemic exposure at the NOAEL in maternal rats was approximately 80 times the exposure in humans at the proposed commercial dose of 62.4 µg/kg/day.Based on the proposed indication and associated patient population, the lack of juvenile toxicity studies is acceptable. UMEC is being developed as a therapy for the treatment of Chronic Obstructive Pulmonary Disease which was added to the list of class waivers following an EMEA decision on 3rd December 2007.

Local Tolerance

UMEC was shown to be a non-sensitiser of the skin in a mouse local lymph node assay. When tested in a SkinEthic Reconstituted Human Epidermal model it was considered as a mild-moderate irritant. Similarly, in a SkinEthic Reconstituted Human Corneal model, UMEC was considered to be a mild-moderate ocular irritant.

Other toxicity studies

All specified impurities greater than the 0.15% threshold have been appropriately qualified in the 13 week study in mice, 26 week study in rats or 39 week study in dogs. In addition, none of the specified impurities are present at a level above 1.5 µg/day, the threshold of toxicological concern. Regarding the genotoxic impurities, none of them are at a level that would exceed the threshold of toxicological concern (>1.5 µg/day).

In vitro studies, UMEC showed no evidence of hemolysis in rat, dog or human blood.

Magnesium stearate

The repeated dose toxicity studies conducted with the excipient magnesium stearate at very high doses in rats and dogs did not show clinically relevant findings at the dose administered in the proposed commercial dose of UMEC. In addition, numerous toxicology studies, as well as pharmacodynamic and pharmacokinetic studies, have confirmed that magnesium stearate was not associated with any toxicological or local respiratory tract tolerance issues, did not affect the pharmacology or pharmacokinetics of the active substances and is therefore considered an acceptable inhalation formulation excipient for clinical use. Moreover, magnesium stearate use in general is well characterised and widely used as a pharmaceutical excipient in inhalation formulations for marketed respiratory medicines throughout the world.

2.3.5. Ecotoxicity/environmental risk assessment

Umeclidinium PEC surfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. Therefore umeclidinium is not expected to pose a risk to the environment. Some environmental fate and effects studies have been conducted with umeclidinium and the results and associated study reports have been provided in the non-clinical dossier.

Table 1. Summary of main study results

Substance (INN/Invented Name):umeclidinium bromide

CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.26	Not Potential PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.26	not B
	BCF		B/not B
Persistence	DT50 or ready biodegradability		P/not P
Toxicity	NOEC or CMR		T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	$3.2 \cdot 10^{-4}$	µg/L	Not > 0.01 threshold
Other concerns (e.g. chemical class)			No

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Freshwater Alga and Cyanobacteria, Growth Inhibition Test	OECD 201	NOEC	Inhibition of Yield (72 hr) EyC_{50}=0.21 NOEC= 0.0625 Growth Rate (72 hr) ErC_{50} = 0.42 NOEC = 0.125	mg/L	Species: *Pseudokirchneriella subcapitata*
Daphnia magna, Reproduction Test	OECD 211	NOEC	Immobilization (21 day) EC_{50} 8.5 (95% confidence	mg/L	

			limits of 5.0 – 14 mg freebase/l. LOEC = 10.00 NOEC = 3.20 Reproduction (21 day) EC_{50} > 10.00 LOEC = 10.00 mg/L NOEC = 3.20 mg/L		
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	Hatching LOEC > 10 NOEC (28 day) = 10 Larvae Mortality LOEC > 10 NOEC (28 day) = 10 Length & Weight LOEC > 10 NOEC (28 day) = 10	mg/L	Species: *Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	ND	µg/L	

2.3.6. Discussion on non-clinical aspects

A comprehensive non-clinical package has been conducted with umeclidinium bromide which has adequately characterised the pharmacology, pharmacokinetics and toxicology of umeclidinium bromide. Further information for UMEC on protein interaction should be considered and UMEC should be tested as a substrate for OATP1B1 and OATP1B3, as a possible hepatic uptake transporters, and BCRP and BSEP for their possible involvement in the biliary excretion. The applicant has agreed to provide the required data and this is captured in the risk management plan.

Umeclidinium was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in mice or rats at exposures ≥ 26 or ≥ 22-fold, times the human

clinical exposure of umeclidinium 55 micrograms delivered dose, based on AUC, respectively.

Umeclidinium was not teratogenic in rats or rabbits. In a pre- and post-natal study, subcutaneous administration of umeclidinium to rats resulted in lower maternal body weight gain and food consumption and slightly decreased pre-weaning pup body weights in dams given 180 micrograms/kg/day dose (approximately 80-times the human clinical exposure of umeclidinium 55 micrograms delivered dose, based on AUC).

2.3.7. Conclusion on the non-clinical aspects

The overall non-clinical development programme of the umeclidinium was considered adequate to support the recommendation for a marketing authorisation for Incruse. The available non-clinical data and the environmental risk assessment did not raise any particular safety issue. The observed toxic effects are known class effects and primarily considered to be related to an exacerbated pharmacological activity of the product and indicative of its local irritant effects. The use of this class of compound in COPD is well established and the margins of safety between exposures at which effects were seen and exposures achieved at the clinical dose are considered adequate.

2.4. Clinical aspects

2.4.1. Introduction

The applicant applied for the following indication:

Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD)

The applicant received Scientific Advice from the CHMP on 20/05/2010 and 23/09/2010. The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

GCP

The Clinical trials were performed in accordance with GCP.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

A total of 21 clinical studies have been conducted supporting the clinical pharmacology of UMEC. Studies conducted with UMEC alone included administration by the inhaled (IH), intravenous, and oral (PO) routes.

Table 1. All Clinical Studies Referenced Herein by Treatment

Type of Study	Number of Studies	Studies
All Clinical Studies Contributing PK Data (21 studies total)		
UMEC	13	AC4105209, AC4105211, AC4110106, AC4106889, AC4108123, AC4112008, AC4113377, AC4115487, AC4112014, AC4113589, AC4115321, AC4113073, AC4115408
UMEC/VI [a]	8	DB2113208, DB2113950, DB2114635, DB2114636, DB2114637, DB2113120, DB2113361, DB2113373

a. UMEC treatment arm included in study; may include UMEC/VI or VI arms.

A total of 10 clinical studies have been conducted to investigate efficacy and safety of UMEC described in this application: 3 Phase IIb studies (AC4113073, AC4115321, and AC4113589) to support dose selection and dosing interval of UMEC in COPD subjects, as well as 7 Phase III studies that evaluated the efficacy and safety of UMEC in which a total of 2564 subjects were treated with UMEC monotherapy or Placebo. Of these 7 studies, 1 is a 12-week and 3 are 24-week Efficacy Studies, 2 are 12-week Exercise Endurance Studies, and 1 is a 52-week safety study that provides long-term data supportive of efficacy (DB2113359).

Table 2. Completed Clinical Studies Reported for this Integrated Summary of Efficacy

Study Number	Phase	Study Objective(s)	Study Design	Duration	Treatment Arms (mcg) (once-daily unless otherwise specified)	No. of Randomized (Completed) N(n)	Population	Integrated [a]
STUDIES SUPPORTING DOSING INTERVAL AND DOSE SELECTION								
Dose-Ranging and Dose-Interval Studies								
AC4113073	IIb	Dose response, dose interval	R, DB, DD, XO, PC Incomplete block	3 periods per subject, 14 days per period	Once-daily: UMEC 62.5 mcg UMEC 125 mcg UMEC 250 mcg UMEC 500 mcg UMEC 1000 mcg TIO 18 mcg OL PLA Twice-daily: UMEC 62.5 mcg UMEC 125 mcg UMEC 250 mcg PLA	 35(34) 34(33) 35(35) 38(37) 32(29) 35(34) 158(152) 34(32) 37(33) 34(32)	COPD	No
AC4115321	IIb	Dose ranging and dose interval	R, DB, XO, PC Incomplete block	3 periods per subject, 7 days per period	Once-daily: UMEC 15.6 mcg UMEC 31.25 mcg UMEC 62.5 mcg UMEC 125 mcg TIO 18 mcg OL PLA Twice-daily: UMEC 15.6 mcg UMEC 31.25 mcg	 60(58) 57(56) 59(59) 60(58) 56(56) 60(59) 56(55) 58(56)	COPD	No
AC4113589	IIb	Dose ranging	R, DB, PG, PC	28 days	UMEC 125 UMEC 250 UMEC 500 PLA	72 (65) 72(68) 72(64) 72(67)	COPD	No

12-Week and 24-Week Placebo-Controlled Efficacy Studies								
AC4115408	IIIa	Efficacy and safety	R, DB, PG, PC	12 weeks	UMEC 125 UMEC 62.5 PLA	69(56) 69(62) 68(50)	COPD	Yes[b]
DB2113361	IIIa	Safety, efficacy, and population PK	R, DB, PG, PC	24 weeks	UMEC 125 VI 25 UMEC/VI 125/25 PLA	408(312) 404(298) 403(325) 277(183)	COPD	
DB2113373	IIIa	Safety, efficacy, and population PK	R, DB, PG, PC	24 weeks	UMEC 62.5 VI 25 UMEC/VI 62.5/25 PLA	421(324) 421(318) 414(332) 280(204)	COPD	
24-Week Active Comparator Efficacy Study								
DB2113374	IIIa	Safety and efficacy	R, DB, DD, PG, AC	24 weeks	UMEC 125 UMEC/VI 125/25 UMEC/VI 62.5/25 TIO 18	222(165) 217(166) 218(163) 215(176)	COPD	
Exercise Studies								
DB2114417	IIIa	Exercise endurance and lung function	R, DB, PC, XO Incomplete block	12 weeks per period, 2 periods per subject	UMEC 125 UMEC 62.5 UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 PLA	50(19) 49(22) 144(59) 152(63) 76(30) 170(65)	COPD	Yes
DB2114418	IIIa	Exercise endurance and lung function	R, DB, PC, XO Incomplete block	12 weeks per period, 2 periods per subject	UMEC 125 UMEC 62.5 UMEC/VI 125/25 UMEC/VI 62.5/25 VI 25 PLA	41(14) 41(17) 128(51) 130(55) 64(25) 151(55)	COPD	
Long-Term Study								
DB2113359	IIIa	Long-term safety	R, DB, PG, PC	52 weeks	UMEC 125 UMEC/VI 125/25 PLA	227(133) 227(143) 109(66)	COPD	No

2.4.2. Pharmacokinetics

Absorption

The absorption, distribution, metabolism, and excretion (ADME) of UMEC were studied after oral and intravenous administration of radiolabeled drug (Study AC4112014). Supportive ADME data for intravenous UMEC and primary ADME data for inhaled UMEC were provided in Study AC4112008.

Study AC4112014 was a single-centre, open-label study in 6 healthy male subjects. Each subject participated in two separate dosing periods. In the first period, each subject received a 65 µg single dose of IV infusion containing 7.1 µCi (approximately 0.3 MBq) of [14C]-GSK573719. In the second period, each subject received a single 1000 µg oral dose containing 50 µCi (approximately 2 MBq) of [14C]-GSK573719. The two dosing periods were separated by a washout of at least 28 days. The duration of the study was approximately 11–12 weeks for each subject. Plasma concentrations of unchanged UMEC following single PO dose administration of [14C]-UMEC were all not quantifiable (NQ). Plasma total radioactivity pharmacokinetic parameter estimated following both IV and PO administrations of [14C]-GSK573719 are summarised in the table below.

Table 3. Summary of plasma ^{14}C- radioactivity pharmacokinetic parameters following both intravenous and oral administration of [^{14}C]-GSK573719

Parameter	Route	N	n	Geometric mean (CVb%)	95% Confidence interval
AUC(0–1) (ng.equiv.h/mL)	IV	6	6	0.529 (51.1)	0.319, 0.876
	PO	6	6	0.014 (45.0)	0.009, 0.022
AUC(0–∞) (ng equiv.h/mL)	IV	6	6	1.041 (90.9)	0.461, 2.350
	PO	6	6	0.796 (118.3)	0.298, 2.124
AUC(0–t) (ng equiv.h/mL)	IV	6	6	1.345 (29.0)	0.998, 1.812
	PO	6	6	0.970 (89.9)	0.433, 2.176
CL (L/h)	IV	6	5	46.5 (32.7)	31.3, 69.1
CL/F (L/h)	PO	6	5	988 (96.5)	360, 2705
Cmax (ng equiv/mL)	IV	6	6	1.39 (54.7)	0.81, 2.38
	PO	6	6	0.07 (126.1)	0.03, 0.20
tlast (h)[1]	IV	6	6	168.0 (96.0, 168.0)	NA
	PO	6	6	168.0 (96.0, 168.1)	NA
tmax (h)[1]	IV	6	6	0.5 (0.5, 0.5)	NA
	PO	6	6	4.0 (3.0, 4.0)	NA
Vss (L)	IV	6	5	1801 (50.1)	1000, 3243
	PO	6	5	66958 (81.2)	27670, 162030
F1 (%)	PO	6	4	5.4	1.81, 15.88
F2 (%)	PO	6	6	4.7	2.13, 10.31

Source Data: Table 10.4
1. Median (range).
NA = not applicable; F1 = oral bioavailability calculated based on AUC(0–∞); F2 = oral bioavailability calculated based on AUC(0–t).

Mean PO bioavailability estimates of plasma 14C-radioactivity following PO administrations of [14C]-UMEC calculated based on AUC(0-∞) were similar to those calculated based on AUC(0-t) and were approximately 5.4% (95% CI: 1.8%, 15.9%) and 4.7% (95% CI: 2.1%, 10.3%), respectively. Since PO bioavailability of unchanged UMEC was negligible, these data suggest that the majority of the dose was not absorbed and that there were low levels of metabolites in the systemic circulation. This was also supported by <1% total radioactivity in urine following PO administration. These data support very low absorption of radiolabelled drug with negligible absolute bioavailability of UMEC following PO dose.

Study AC4112008 (module 5.3.1.1) was a single-centre, open-label, sequential, cross-over study to evaluate examine the pharmacokinetics of three ascending single intravenous doses (20, 50 and 65 mcg), a single 1000 µg oral dose and a single 1000 µg inhaled dose of GSK573719 in 10 healthy male volunteers. This study is the primary study for defining biovailibility of inhaled UMEC.

Following a single inhaled dose administration, UMEC was rapidly absorbed with the Cmax values occurring at approximately 5 to 15 minutes postdose. Plasma concentrations declined rapidly following the occurrence of Cmax. Plasma concentrations of UMEC following single PO dose administration of UMEC were all non-quantifiable (NQ) (bioanalytical assay LLQ was 0.02 ng/mL). Therefore the maximal possible oral bioavailability was calculated as <1%. Selected plasma PK parameters of this study are summarized in the table below.

Table 4. Summary of Selected UMEC Pharmacokinetic Parameters Following a Single Dose Administration in Healthy Subjects (study AC4112008)

Parameter	Dose	N	n	Geometric Mean	95% CI	CV%
$AUC_{(0-\infty)}$ (h•ng/mL)	20 mcg IV	10	10	0.132	0.087, 0.201	64.3
	50 mcg IV	9	8	0.525	0.416, 0.661	28.2
	65 mcg IV	9	9	0.543	0.277, 1.067	108
	1000 mcg IH	9	9	1.33	1.08, 1.65	28.3
$AUC_{(0-t)}$ (h•ng/mL)	65 mcg IV	9	9	0.688	0.550, 0.860	29.7
	1000 mcg IH	9	9	0.615	0.525, 0.720	20.8
C_{max} (ng/mL)	20 mcg IV	10	10	0.377	0.305, 0.465	30.3
	50 mcg IV	9	8	1.14	0.99, 1.33	18.0
	65 mcg IV	9	9	1.55	1.22, 1.98	32.4
	1000 mcg IH	9	9	1.67	1.18, 2.35	47.2
t_{max} (h) [a]	20 mcg IV	10	10	0.48	0.33, 0.53	-
	50 mcg IV	9	8	0.48	0.48, 0.53	-
	65 mcg IV	9	9	0.48	0.33, 0.48	-
	1000 mcg IH	9	9	0.08	0.08, 0.25	-
F (%)	1000 mcg IH	9	8	12.82	9.04, 18.17	43.7

Data source: Study AC4112008; Table 11.2 and Table 11.3
N=number of subjects who received a specific treatment; n=the number of subjects with non-missing values (including not calculable where applicable)
Note: Each subject received treatment in the following order: IV Dose 1 (20 mcg), IV Dose 2 (50 mcg), IH dose (1000 mcg), IV Dose 3 (65 mcg).
a. Presented as median and range.

Absolute bioavailability of UMEC following inhaled administration was calculated using plasma data following 1000 mcg IH which averaged 12.8% (95% confidence interval [CI]: 9.0%, 18.2%). Results were similar for urine data, with F averaging 13.1% (95% CI: 10.5%, 16.3%). Absolute bioavailability of UMEC following PO administration using plasma data was reported as negligible (<1%) since all plasma concentrations of UMEC were NQ following PO administration. Assuming that drug not accounted for by inhaled bioavailability is swallowed (87%) and that the oral bioavailability for the swallowed portion of the dry powder dose is similar to that observed following oral solution administration; the highest possible contribution of the swallowed portion of the inhaled dose to the total systemic exposure would be approximately 7% for UMEC. Since it is unlikely that oral absorption for the dry powder would be as high as that for the solution, the contribution of the swallowed dose to total systemic exposure is considered to be negligible.

Bioequivalence

No bioequivalence studies were performed with UMEC since there were no changes to the formulation after the start of the Phase III studies.

Data from food-interaction studies

No study to investigate possible effects of food on the bioavailability of inhaled UMEC was conducted. The per oral (PO) bioavailability of UMEC is negligible (<1%). Even if co-administration with food were to affect the rate and/or extent of absorption of UMEC, it would not be expected to significantly impact the systemic exposure, compared with the fasted state, at the proposed clinical doses of UMEC. Therefore it is acceptable to the CHMP that no food effect study was performed.

Distribution

Following intravenous dosing, UMEC was rapidly and extensively distributed with an average last of 1 hour (Study AC4112014 described above). The average volume of distribution at steady state was 86.2 L, which is greater than the total body water for a 70 kg man (42 L). Blood cell association of UMEC was low in humans with a blood to plasma ratio ranging from 0.67 at 45 minutes post dose to 0.82 up to 24 hours post dose (Study AC4112014). In vitro plasma protein binding of UMEC in human plasma was moderate with an average value of 88.9% and was similar in plasma from males and females (Study 07DMW030 and Study QBR113236). Both plasma protein binding and blood cell binding for UMEC were independent of concentration (Study 07DMW030).

Elimination

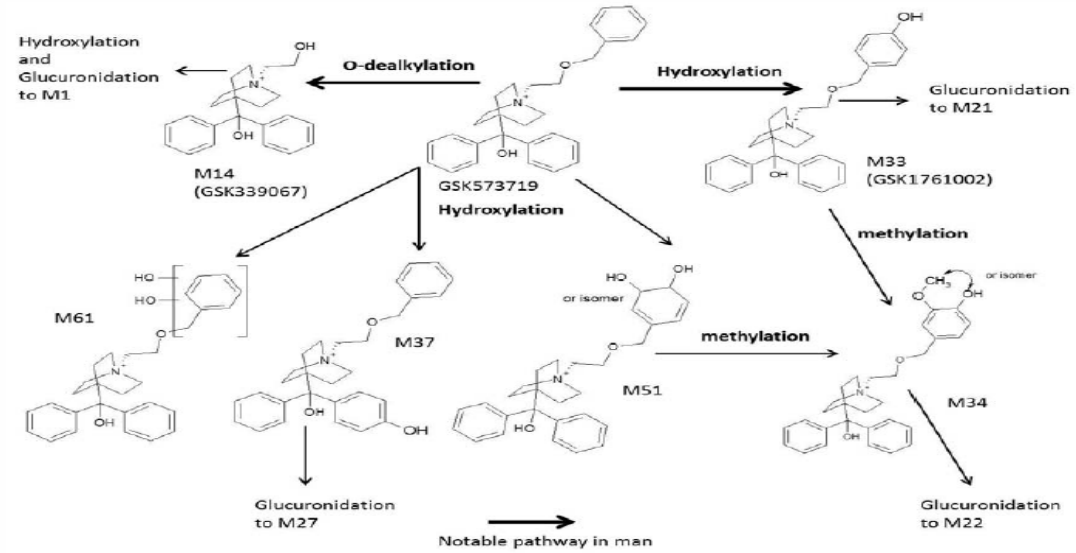
Excretion

The plasma clearance of UMEC is rapid and extensive and was reported to be around 151 litres/hour. After radiolabelled administration of IV UMEC, it is mainly excreted in faeces (58% of radiolabelled dose) and secondarily in urine (22% of the radiolabelled dose). This indicates secretion in to bile. Following oral administration of radiolabelled UMEC, 92% of the radiolabelled dose is excreted in the faeces and less than 1% is excreted in urine, suggesting negligible absorption following oral administration. The half-life of UMEC after inhalation was calculated to be 19 hours. In the radiolabelled studies of UMEC (after IV administration), recovery in the human ADME study is low with only 81% of the dose recovered. The guideline suggests that recovery should be greater than 90%, however it is accepted that this is a low dose compound. The applicant suggests that the low recovery in the human radiolabeled study is due to the low radioactive, and chemical, dose and therefore a greater contribution of non specific binding during analysis. This is considered a reasonable explanation.

Metabolism

The human metabolism of UMEC was investigated using fecal, urine, plasma, and bile samples collected following intravenous (65 mcg) and oral (1000 mcg) administration of (14C)-UMEC in Study AC4112014. Metabolic profiles were reported in a separate study (Study 11DMW019). The proposed metabolic pathway of UMEC in animals and humans is illustrated in Figure below.

Figure 1. Putative Metabolic Scheme for the Major Metabolites of UMEC in Animals and Humans



In vitro studies showed that umeclidinium bromide is principally metabolised by cytochrome P450 2D6 (CYP2D6) and is a substrate for the P-glycoprotein (P-gp) transporter. The primary metabolic routes for umeclidinium bromide are oxidative (hydroxylation, O-dealkylation) followed by conjugation (glucuronidation, etc), resulting in a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Systemic exposure to the metabolites is low. The information on the major elimination, including enzymes/transport proteins involved, is unclear. The applicant has agreed to provide the required data and this is captured in the risk management plan. Estimated submission is 1Q2015.

Consequences of possible genetic polymorphism

Based on the results of in-vitro studies, the applicant has conducted appropriate clinical studies to address any potential efficacy/safety issues in patients with relevant genetic polymorphism to CYP2D6 (Study AC4110106). Plasma and urine PK data suggested no evidence of a difference in GSK573719 systemic exposure between healthy volunteers and CYP2D6 PM population. Following GSK573719 500 µg on Day 7, plasma AUC(0-τ) (hr*ng/mL) and Cmax (ng/mL) ratios (90% CI) between PM vs healthy volunteer were 1.03 (0.79, 1.34) and 0.80 (0.59, 1.08) respectively and urine Ae(0-24) (ng) ratio was 1.01 (0.82, 1.26) and similar ratios were observed following other single and repeat dose regimen. The proposed action (no dose adjustment is recommended) is supported by the results of the study.

Dose proportionality and time dependencies

The PK results show that systemic exposure is dose-proportional in the dose ranges tested. However given the large inter-subject variability for all parameters, this should be accepted with caution. In terms of the time dependency of PK, the accumulation looks consistent with what would be expected based on the half-life (AUC(0-inf)/AUC(0-tau). The applicant has explained that AUC(inf) could not be used in calculations of R because UMEC lambda z (which is required to calculate AUC(inf)) and t1/2 could not be accurately determined due to

one or more of the following reasons: limited sampling, a large number of NQ samples associated with low dose, and a flat elimination phase. Therefore, different derivable AUC0-t' (where t' is the latest time at which concentrations were quantified) following single dose and repeat dose were used to calculate R based on AUC. In conclusion, although observed data show high inter-study variability, dose strengths, and extent of sampling during the elimination phase, the results indicate that, on average, the accumulation appears consistent with that expected based on the calculated half-life.

Intra- and inter-individual variability

In the studies carried out in healthy subjects, a large inter-subject co-efficient of variation (%) for Cmax was seen: 39% (Study DB2114635); 46% (DB2113950) and 35% (AC4110106) for UMEC 500 mcg dose. For the UMEC 1000 mcg dose a CV of 64% is shown in study AC4110106. Similar results were obtained from the studies performed in patients with COPD. The large inter-subject variability for the estimation of the PK of UMEC may be due to the low systemic exposures and the variability in estimation near the limit of quantification.

Pharmacokinetics in target population

The most pertinent data on PK in COPD subjects was estimated by population pharmacokinetic modeling of data from Phase 3a clinical efficacy and safety studies. However, the PK profile of UMEC in subjects with COPD has also been established in one Phase I study, two Phase 2a, and three Phase 2b studies.

The table below compares UMEC systemic exposure in terms of steady state Cmax, AUC, and percent of UMEC dose excreted unchanged in urine over 24 hours between healthy subjects and subjects with COPD:

Table 5. Comparisin of UMEC Systemic Exposure in Healthy Subjects vs. Subjects with COPD following Repeat Dosing with UMEC

Study Number Duration (days)	DB2114635 (10)	DB2113950 (8)	DB2114637 (7)	AC4110106 (7)		AC4115321 (7)	AC4105211 (7)	AC4113073 (14)	AC4113589 (28)	AC4115408 (84)	DB2116975 (168)
	Healthy Subjects					Subjects in COPD					
C_{max} (pg/mL); Geometric Mean (%CVb)											
15.6 mcg QD						11 (114)					
31.25 mcg QD						20 (74)					
62.5 mcg QD						57 (63)		40 (54)		48 (131)	70 (NA)
125 mcg QD			283 (33)			111 (113)		100 (61)	114 (93)	123 (80)	139 (NA)
250 mcg QD							332 (58)	320 (60)	264 (102)		
500 mcg QD	1541 (39)	1183 (46)		1458 (35)				720 (41)	805 (93)		
1000 mcg QD				1756 (64)			2759 (61)	1600 (87)			
$AUC_{(0\text{-}15min)}$ for all studies expect AC4115321 and AC4105211, for which $AUC_{(0\text{-}t)}$ data are provided (pg*h/mL); Geometric Mean (%CVb)											
15.6 mcg QD						NA					
31.25 mcg QD						3.33 (87)					
62.5 mcg QD						10 (86)		10 (139)		7 (192)	
125 mcg QD			44 (30)			21 (108)		20 (128)	14 (150)	18 (174)	
250 mcg QD								50 (59)	33 (179)		
500 mcg QD	239 (36)	189 (39)						130 (45)	105 (210)		
1000 mcg QD								240 (91)			
Urine Excretion Fe24 (%); Arithmetic Mean											
15.6 mcg QD						2.3					
31.25 mcg QD						2.5					
62.5 mcg QD						2.4		2.4			
125 mcg QD			4.0			2.2		3.1			
250 mcg QD							2.3	2.6			
500 mcg QD		3.9		3.3				2.9			
1000 mcg QD				3.3			3.4	2.0			

Data Source: C_{max} and $AUC_{(0\text{-}15min)}$ data:: Study DB2114635, Table 11.2; Study DB2113950, Table 12.3; Study DB2114637, Table 10.2; Study AC4110106, Table 11.2; Study AC4115321, Table 9.03; Study AC4105211, Table 11.2; Study AC4113073, Table 8.03; Study AC4113589, Table 8.03; Study AC4115408 Table 9.03 and Study: DB2116975, 12.5, 12.6. Fe24 data:: Study DB2113950, Table 12.8, Study DB2114637, Table 10.9; Study AC4110106, Table 11.7, Study AC4115321, Table 9.09; Study AC4105211, Table 11.5 and Study AC4113703, Table 8.09.

Plasma data appear to show somewhat lower UMEC systemic exposure in subjects with COPD compared with healthy subjects at doses of 500 mcg and lower. At UMEC 1000 mcg, systemic exposure does not appear to be different between the 2 populations. The applicant argues this result is skewed due to the lack of steady state systemic exposure data in

healthy subjects at low doses since higher numbers of healthy subject studies used higher doses while a greater number of studies in subjects with COPD used lower doses. In subjects with COPD, studies with the NDPI assessed dose proportionality over the proposed therapeutic dose range in Study AC4115321 (proposed therapeutic and lower doses) and Study AC4113073 (proposed therapeutic and higher doses). The obtained values for Cmax at supra-therapeutic doses in the last one are in accordance with the expected dose-proportionality response. However, data from other studies (AC4105211 and AC4113589) are far from the expected values according a dose-proportionality response. The applicant argued that the higher Cmax in Study AC4105211at 1000 mcg QD could be attributed to the study differences and low subject numbers and is not a particular concern, which is agreed.

Special populations

Impaired renal function

Study DB2114636 was a single-blind, non-randomised, single-dose study to investigate the PK and safety of UMEC alone (125 mcg) and UMEC/VI (125/25 mcg) in subjects with severe renal impairment compared with healthy subjects. Nine subjects with severe renal impairment were enrolled with nine matched healthy control subjects. All subjects received a single dose of UMEC 125 mcg followed by a single dose of UMEC/VI 125/25 mcg, separated by a washout of at least 7 days. Table below shows the absorption pharmacokinetic results by renal function status.

Table 6. Summary of Results from Statistical Analysis of Derived UMEC Plasma PK Parameters (DB2114636)

Parameter	Group Comparison	Adjusted Geometric Mean	Ratio of Adjusted Geometric Mean	90% CI of Ratio
$AUC_{(0-2)}$ (h•pg/mL)	Severe renal impairment / healthy	59 / 66	0.90	0.64, 1.26
C_{max} (pg/mL)	Severe renal impairment / healthy	113 / 128	0.89	0.58, 1.35

Data Source: Study DB2114636, Table 10.3

There was no effect of renal impairment on urine $t_{1/2}$ (healthy subjects: 9.66 hours (95% CI 4.44, 20.99); severe renal impairment: 8.03 hours (95% CI: 6.49, 9.94).

In conclusion, there is no need for dose adjustment when UMEC is administered to patients with impaired renal function.

Impaired hepatic function

Study DB2114637 (Module 5.3.3.3) was an open-label, non-randomised study to investigate the PK and safety of single- and repeat-doses of UMEC alone (125 mcg) and a single dose of UMEC/VI (125/25 mcg) in subjects with moderate hepatic impairment compared with healthy subjects.

Hepatic impairment was classified using the Child-Pugh system –moderate: Child-Pugh B (7 to 9 points). Eligible subjects were males or females aged 18–70 years, inclusive, with a body weight ≥45 kg and a body mass index within the range 18– 33 kg/m^2. Healthy subjects had alanine aminotransferase (ALT), alkaline phosphatase and bilirubin ≤1.5 x upper limit of normal (ULN). Subjects with moderate hepatic impairment had a known medical history of liver disease with or without a known history of alcohol abuse; and a Child- Pugh score of 7–9 points. Nine subjects with moderate hepatic impairment were enrolled and 9 matched healthy control subjects. All subjects received a single dose of UMEC/VI 125/25 mcg, followed by a 7- to 14-day washout and a subsequent second treatment period with UMEC 125 mcg once-daily for 7 days.

Table 7. Summary of Results from Statistical Analysis of Derived UMEC Plasma PK Parameters (DB2114637)

Parameter	Group Comparison	Day	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of Ratio
$AUC_{(0-\tau)}$ (h*pg/mL)	Moderate Hepatic Impairment / Healthy	1	74 / 87	0.85	0.63, 1.15
		7	105 / 122	0.86	0.64, 1.17
$AUC_{(0-\tau)}$ (h*pg/mL) [a]	Moderate Hepatic Impairment / Healthy	7	438 / 482	0.91	0.72, 1.15
C_{max} (pg/mL)	Moderate Hepatic Impairment / Healthy	1	165 / 220	0.75	0.49, 1.14
		7	214 / 283	0.76	0.50, 1.15

Data Source: Study DB2114637, Table 10.3

a. As the dosing interval for UMEC is once-daily, $AUC_{(0-24)}$ corresponds to $AUC_{(0-\tau)}$.

Following single-dose administration, plasma UMEC exposure was average lower in subjects with moderate hepatic impairment.

Table 8. Summary of Results from Statistical Analysis of Derived UMEC Urine PK Parameters (DB2114637)

Parameter	Group Comparison	Day	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of Ratio
$Ae_{(0-24)}$ (ng)	Moderate Hepatic Impairment / Healthy	1	1833 / 2113	0.87	0.69, 1.09
	Moderate Hepatic Impairment / Healthy	7	4503 / 4903	0.92	0.73, 1.15

Data Source: Study DB2114637, Table 10.10

Following single-dose administration, plasma UMEC exposure was average lower in subjects with moderate hepatic impairment compared with healthy subjects.

In conclusion, administration of UMEC 125 mcg to subjects with moderate hepatic impairment led to exposures that were on average lower for both UMEC in the subjects with moderate hepatic impairment than in the healthy subjects. These observed effects on systemic exposure are not believed to be clinically relevant, and therefore no dose adjustment for UMEC is warranted in patients with moderate hepatic impairment. UMEC was

not studied in patients with severe hepatic impairment and this is adequately reflected in the SmPC.

Gender

Population PK analyses showed that gender is not a significant covariate in the PK of UMEC and hence dose adjustments are not warranted based on gender (Study DB2116975).

Race

UMEC dataset primarily consisted of Caucasian subjects (87%), but there were 78 (5%) Japanese subjects and 67 (4%) South East Asian subjects in the UMEC group. There were no racial differences in apparent clearance or apparent volume of distribution for UMEC (Study DB2116975).

Weight

In the population PK analyses, weight was found to be significant covariate of apparent inhaled clearance of UMEC, and weight was also a significant covariate of apparent volume of distribution. The analyses however demonstrated that the effect of weight on PK is marginal and no dose adjustment is warranted based on weight from the final PK model (Study DB2116975).

Elderly

In the population PK analyses, age was found to be significant covariate of apparent inhaled clearance of UMEC. The analyses however demonstrated that the effect of age on PK is marginal and no dose adjustment is warranted based on age from the final PK model.

Children

Not Applicable.

Pharmacokinetic interaction studies

Interactions

In vitro studies conducted using human recombinant cytochrome P450 (CYP) enzymes showed that UMEC was metabolized mainly by CYP2D6. In a clinical study conducted in both healthy extensive/normal and CYP2D6 poor metaboliser subjects, there was no clinically significant difference in the systemic exposure to UMEC following 7 days repeat dosing with 8 to 16-fold higher supra-therapeutic IH doses. No dose adjustment for use of CYP2D6 inhibitors concomitant with UMEC administration appears warranted. In vitro studies also indicated UMEC as a substrate of P-glycoprotein (P-gp). Separate pre-clinical studies in mdr1a/b knockout (P-gp knockout) mice indicated the potential for increased systemic exposure to UMEC with potent P-gp inhibitors. However, there was no evidence for UMEC inhibiting P-gp. Since P-gp is a relatively high capacity transporter, a P-gp based clinical interaction is unlikely due to the low inhalation dose. No dose adjustment is therefore warranted for UMEC administered concomitantly with P-gp inhibitors. UMEC is an in vitro inhibitor of CYP3A4 and CYP2D6 (IC50 values between 0.1 and 1 microM). At clinical doses, the highest anticipated Cmax in humans (<0.2 ng/mL or 0.5 nM) is at least 200-fold lower than the lowest IC50 value (0.1 microM) as a worst case for all CYPs and transporters investigated.

In vivo, the study DB2113950 (Module 5.3.3.4) was conducted to investigate the effect of verapamil on the PK of UMEC (administered as UMEC and as UMEC/VI combination). The

results did not show any significant effect on the PK of UMEC, except for a 40% increase in AUC of UMEC which is not considered significant. Results from this study support the position that no dose adjustment is recommended in patients using concomitant P-gp transporter inhibitors. Exposure relevant for safety evaluation

Exposure relevant for safety information

A total of 8498 PK observations from 1635 subjects contributed to the UMEC PK analyses (Study DB2116975). There was no apparent pharmacokinetic –pharmacodynamic relationship between maximum heart rate and model predicted UMEC Cmax at steady state.

2.4.3. Pharmacodynamics

Mechanism of action

Umeclidinium is an inhaled long-acting muscarinic antagonist (LAMA) that acts locally on airways to produce bronchodilation. The compound has activity across multiple muscarinic receptor subtypes. Umeclidinium competitively inhibits binding of acetylcholine with muscarinic receptors on airway smooth muscle. Umeclidinium demonstrates slow reversibility at the human M3 muscarinic receptor subtype in vitro and long duration of action in vivo when administered directly to the lungs in pre-clinical models.

Primary and Secondary pharmacology

Primary pharmacology

Five studies have been performed to demonstrate the therapeutic effect in healthy subjects and COPD subjects. Three dose-ranging studies have been performed.

The following table provides a summary of which PD endpoints related to therapeutic effect were assessed within each UMEC, study.

Table 9. Summary of UMEC Pulmonary Function PD Endpoints by Study

Study	SGaw	FEV1	FVC
Study AC4105209 (HS)	✓	✓	
Study AC4115487 (HS)	✓	✓	
Study DB2113208 (HS)		✓	
Study AC4108123 (COPD)	✓	✓	✓
Study AC4105211 (COPD)		✓	

Abbreviations: COPD=chronic obstructive pulmonary disease study; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; HS=healthy subject study; SGaw=specific airway conductance.

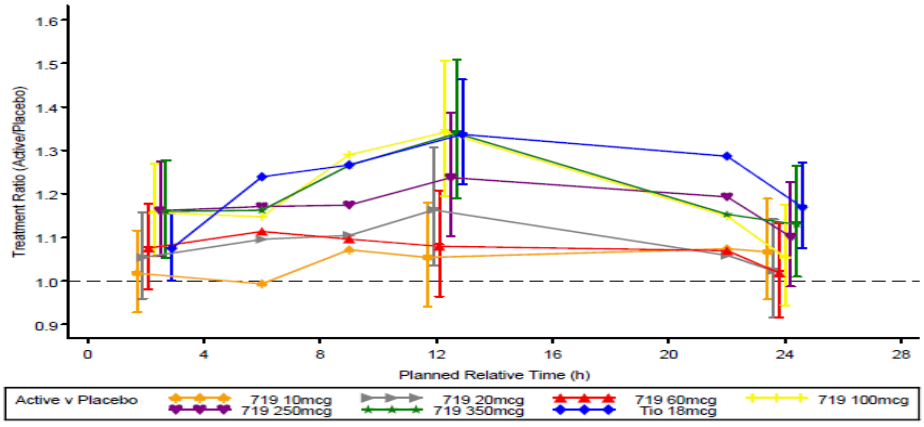
Study AC4105209

The Primary Study Objective is to investigate the safety and tolerability of single inhaled doses of UMEC in healthy male subjects. The key secondary objective was to investigate the bronchodilatory effect and duration of action of single inhaled doses of GSK573719 as measured by plethysmography (specific airways conductance [sGaw], airways resistance [Raw]) and spirometry forced expiratory volume in 1 second (FEV1) endpoints in healthy

male subjects. The treatment phase of the study included 2 interlocking cohorts (Cohorts I and II) of 10 healthy male subjects in each cohort.

Effective bronchodilatory activity was demonstrated for UMEC as indicated in the following figure.

Figure 2. PD-01. Plot of Treatment Ratios Relative to Placebo and 95% CIs from Analysis of sGaw (1/kPa*s) Data (AC4105209)

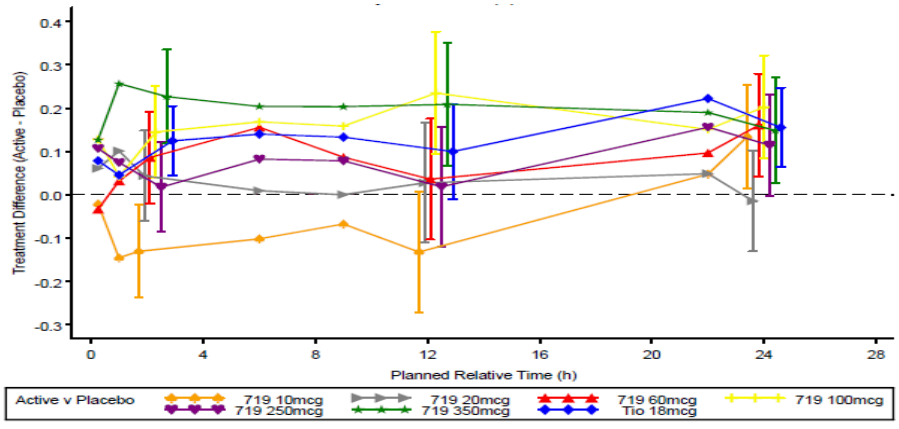


Higher sGaw (mid) values were observed at all time points for UMEC 350 mcg and tiotropium compared with placebo. At 12 hours, on average, values showed a 34% improvement over placebo and at 24 hours they showed a 13% and 17% improvement over placebo for UMEC 350 mcg and tiotropium, respectively.

For the UMEC 100 and 250 mcg groups, higher sGaw (mid) values were observed compared with placebo at all time points except 24 hours (although the 24-hour results for the UMEC 250 mcg were borderline to being significant). At 12 hours, improvements over placebo were 34% and 24% greater for the UMEC 100 and 250 mcg groups, respectively.

A display of FEV1 values over time in Study AC4105209 is presented in the plot.

Figure 3. PD-02. Plot of Treatment Differences Relative to Placebo and 95% CIs from Analysis of FEV1 (L) Data (AC4105209)



Abbreviations: FEV1=forced expiratory volume in one second; TIO=tiotropium.

Higher FEV1 values were observed compared with placebo, for UMEC 350 mcg at all time points except at 15 minutes, and at all time points except for 15 minutes and 1 hour for UMEC 100 mcg.

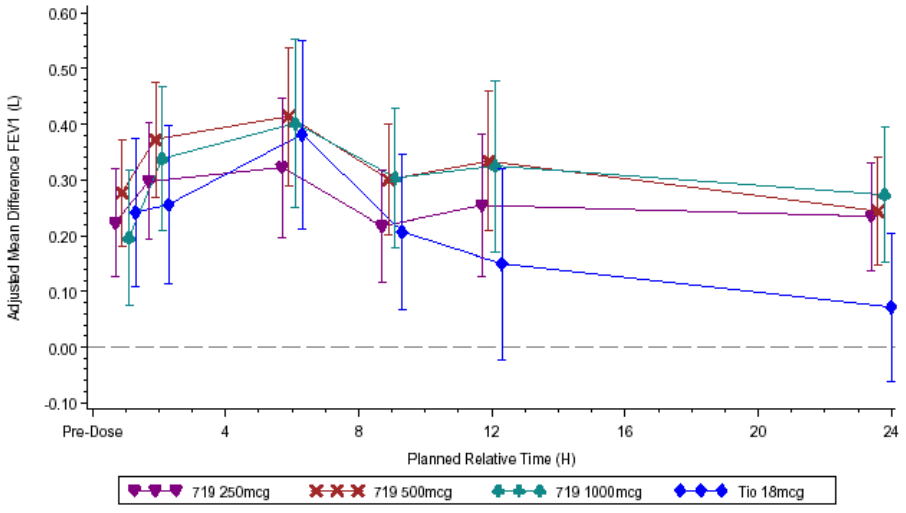
With regard to the comparison versus tiotropium, at most time points, the UMEC 100 and 350 mcg groups showed increases in FEV1 compared with tiotropium; however, these increases were not statistically significant (except at the 1-hour time point for the UMEC 350 mcg group).

Study AC4108123 (COPD)

Study AC4108123 was a multicenter, randomized, double-blind, placebo-controlled, double-dummy, dose-ascending, 4-way crossover, incomplete block study in ipratropium responsive subjects with COPD. Subjects were randomized to receive a single dose of 4 out of the 5 possible treatments (UMEC (250, 500, and 1000 mcg), tiotropium (18 mcg), or placebo). In subjects with COPD, values of sGaw were on average higher for all active treatment groups (UMEC 250, 500, and 1000 mcg, and tiotropium 18 mcg) compared with placebo over the 24-hour assessment period, with UMEC doses of 500 and 1000 mcg consistently showing the greatest differences relative to placebo. All 3 UMEC doses resulted in higher average sGaw values compared with tiotropium 18 mcg.

Trends in values of FEV1 were similar to those of sGaw; higher values were seen for all active treatment groups compared with placebo, with UMEC 500 and 1000 mcg showing the largest differences in adjusted means relative to placebo.

Figure 4. PD-04. Plot of Placebo Adjusted Mean Differences from Placebo and 95% CIs of FEV1 (AC4108123).



Abbreviations: FEV1=forced expiratory volume in one second

Dose-Effect Relationships for Subjects with COPD

The following dose-ranging studies have been performed: 1) AC 4113073 (FIIa); 2) AC 4115321 (FIIa); 3) AC 4116689 (combined Study AC4113073 and Study AC4115321).

Two Phase 2a dose ranging studies with UMEC were conducted in subjects with COPD (Study AC4113073 and Study AC4115321). Population model-based dose response analyses were performed for individual studies. In addition, an integrated model-based pooled analysis of the data from both studies was undertaken (AC 4116689). The rationale for the pooled analysis (combined Study AC4113073 and Study AC4115321) was due to the wide dose range of 15.6 mcg to 1000 mcg once-daily, similarity of both studies with respect to subject population, and crossover design. The primary endpoint was trough FEV1 at the end of the treatment phase. Model-based dose response evaluation was the primary analysis in Study AC4115321 and for the pooled analysis in Study AC4116689. A physiological maximum effect (Emax) model adequately characterized the dose-trough FEV1 response for UMEC over the once-daily dose range of 15.6 to 1000 mcg, with an estimated dose that would yield 50% of Emax (ED50) of 33 mcg (95% CI: 25 - 41) with a predicted maximum effect [Emax] for trough FEV1 of 187 ml [95% CI (170, 210]. The once-daily proposed UMEC doses of 62.5 mcg and 125 mcg have shown dose related increases in trough FEV1. There was no marked difference between the once-versus twice-daily regimen of the same total daily dose for UMEC. This translates into UMEC 33 mcg providing 50% of the maximum trough FEV1 effect compared with 30% for the 15.6 mcg dose, 46% for the 31.25 mcg dose, 63% for the 62.5 mcg dose and 77% for the 125 mcg UMEC dose. Based on simulation, the expected response at a certain dose adjusted for placebo is given in the below table. Further the results indicate no advantage of a twice-daily dosing interval over a once-daily dosing of UMEC.

Table 10. PD-02. Expected Response at a Certain Dose: Adjusted for Placebo (by Regimen) (AC4116689)

	Change from Baseline FEV_1 at Trough (mL) (End of treatment Period Dataset)	
UMEC dose	**Expected Response**	**90% Probability Response is Between**
15.6 mcg once-daily	96	(51 – 144)
31.25 mcg once-daily	100	(55 – 149)
15.6 mcg twice-daily	112	(60 – 160)
62.5 mcg once-daily	138	(103 – 172)
31.25 mcg twice-daily	111	(61 – 154)
125 mcg once-daily	159	(124 – 198)
62.5 mcg twice-daily	146	(92 – 204)
250 mcg once-daily	155	(103 – 204)
125 mcg twice-daily	151	(95 – 204)
500 mcg once-daily	156	(104 – 204)
250 mcg twice-daily	175	(111 - 239)
1000 mcg once-daily	164	(105 – 223)

Data Source: Study AC4116689, Table 6.05

Secondary pharmacology

Effects on QT interval, blood pressure and heart rate

Thorough QT study DB 2114635

It was a randomised, placebo-controlled, incomplete block, four period crossover, repeat dose study to evaluate the effect of the inhaled GSK573719/vilanterol combination and GSK573719 monotherapy on electrocardiographic parameters, with moxifloxacin as a positive control, in healthy subjects. At least 100 subjects were planned to be enrolled (at

least 50 of each gender) to ensure at least 83 evaluable subjects (i.e., subjects who complete all treatment periods). The actual number of subjects enrolled was 103 (48 female and 55 male), with 86 subjects completing the study. The study was conducted according to ICH recommendations. The effect of an eight-fold, supra-therapeutic dose of UMEC (500 mcg QD) on QT prolongation was investigated. Single-dose oral moxifloxacin 400 mg (positive control) demonstrated assay sensitivity with mean increases in time-matched QTc(F) compared with placebo greater than 5 msec at 1, 2, 4, 8 and 12 hours after dosing. The upper 90% CI exceeded 10 msec at 4 and 8 hours. The following results were found:

- Effects on QT interval: No categorical QTc (F) effects were observed in the UMEC 500 mcg group. The study was negative for UMEC 500 mcg and UMEC/VI 125/25 mcg in that the adjusted mean treatment difference did not exceed 5 msec, and the upper bound of the 90% CI for the estimated treatment difference did not exceed 10 msec at any time point out to 24 hours after dosing. At the supra-therapeutic dose of UMEC/VI (500/100), there was evidence of an effect on QTc during the first hour after dosing. The time-matched difference from placebo exceeded 5 msec at 10 min and 30 min post-dose. The 90% CI exceeded 10 msec only at the 30 min time point.

Table 30 **Results of Statistical Analysis of Mean Change from Baseline for QTc(F) on Day 10 (Manually Read ECGs) (All Subjects Population – DB2114635)**

	Adjusted Means (msec)					Treatment Difference (90% CI) (msec)			
Time Point	Pbo (A)	Moxi 400 mg (B)	UMEC 500 mcg (C)	UMEC/VI 125/25 mcg (D)	UMEC/VI 500/100 mcg (E)	B – A	C – A	D – A	E – A
Predose	0.6	-1.6	**-0.9**	-1.9	-1.6	-2.3 (-4.1,-0.4)	**-1.5 (-3.3, 0.3)**	-2.5 (-4.3,-0.7)	-2.2 (-4.1,-0.4)
5 mins	-1.9	-3.3	**-4.0**	-0.3	2.2	-1.4 (-3.8, 1.0)	**-2.1 (-4.4, 0.3)**	1.6 (-0.8, 3.9)	4.2 (1.8, 6.5)
10 mins	1.7	0.1	**-1.2**	6.0	8.2	-1.6 (-3.7, 0.5)	**-2.9 (-5.0,-0.9)**	4.3 (2.2, 6.4)	6.4 (4.3, 8.5)
30 mins	-1.6	3.2	**-2.4**	2.6	6.6	4.8 (2.8, 6.7)	**-0.8 (-2.8, 1.1)**	4.2 (2.3, 6.1)	8.2 (6.2, 10.2)
1 h	0.0	8.1	**-1.0**	-0.8	0.5	8.1 (6.2, 9.9)	**-1.0 (-2.9, 0.8)**	-0.8 (-2.6, 1.0)	0.5 (-1.4, 2.3)
2 h	0.5	8.2	**-1.6**	-1.1	-0.4	7.7 (6.0, 9.4)	**-2.1 (-3.8,-0.4)**	-1.5 (-3.2, 0.1)	-0.8 (-2.5, 0.9)
4 h	0.5	10.1	**-1.3**	-0.4	-0.1	9.7 (8.0, 11.3)	**-1.8 (-3.5,-0.1)**	-0.9 (-2.6, 0.8)	-0.6 (-2.3, 1.1)
8 h	-7.7	1.3	**-8.7**	-8.2	-8.0	9.0 (7.4, 10.5)	**-1.0 (-2.5, 0.6)**	-0.5 (-2.0, 1.1)	-0.4 (-1.9, 1.2)
12 h	-4.5	1.2	**-5.3**	-5.5	-4.3	5.7 (4.1, 7.3)	**-0.8 (-2.5, 0.8)**	-1.0 (-2.6, 0.6)	0.3 (-1.4, 1.9)
16 h	2.2	6.7	**0.3**	0.9	1.1	4.6 (2.9, 6.3)	**-1.8 (-3.6,-0.1)**	-1.2 (-3.0, 0.5)	-1.1 (-2.8, 0.6)
24 h	-2.9	1.8	**-4.0**	-4.1	-4.5	4.7 (3.1, 6.3)	**-1.1 (-2.7, 0.5)**	-1.2 (-2.8, 0.4)	-1.6 (-3.2, 0.0)

Data Source: Study DB2114635, Table 10.3
Abbreviations: Pbo=placebo; Moxi=moxifloxacin.

- Effects on blood pressure were evaluated for UMEC at 250 mcg, 500 mcg and 1000 mcg. For 250 and 500 mcg showed decrease. However UMEC at 1000 mcg showed an increase in systolic and diastolic BP of around 3 mmHg.

- Efects on heart rate: In the TQT study, heart rate for UMEC 500 mcg was similar to placebo. The maximum time matched change in heart rate for UMEC 500 mcg compared with placebo was 2.1 bpm at 8 hours post dose.

Study AC4108123:

Study AC4108123 was a randomised, double blind, placebo-controlled, double dummy, 4-way crossover, dose ascending study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of GSK573719 (250, 500 and 1000 µg) and tiotropium bromide (18 µg) via DPI in COPD patients.

For maximum and weighted mean (0–4 h) heart rate, treatment differences relative to placebo were close to 0 for the GSK573719 250 µg and 500 µg groups. Increases were observed for GSK573719 1000 µg, and decreases for tiotropium bromide 18 µg. For systolic blood pressure, the GSK573719 250 µg and 500 µg groups showed decreases in maximum and weighted mean (0–4 h) and GSK573719 1000 µg and tiotropium bromide 18 µg both showed increases. Maximum and weighted mean (0–4 h) diastolic blood pressure, in general, showed decreases relative to placebo, except for GSK573719 1000 mcg, where increases were seen. Generally, maximum and weighted mean (0–4 h) QTcB decreased relative to placebo in all treatment groups, apart from GSK573719 500 µg, which showed increases relative to placebo. Maximum (0-4 h) QTcF showed differences to placebo close to 0 for all treatment groups. Weighted mean (0-4 h) QTcF was close to 0 in the lower dose groups, however, a decrease was seen for GSK573719 1000 µg and an increase for tiotropium. For maximum heart rate from Holter monitoring (0–24 h), all treatments showed decreases relative to placebo. Mean and maximum heart rate from Holter monitoring (0–24 h) followed similar patterns, but point estimates were closer to zero for mean heart rate. Clinically significant findings on Holter ECG were noted in two subjects (9%) following GSK573719 250 µg, one subject (5%) following GSK573719 500 µg, one subject (8%) following GSK573719 1000 µg, one subject (13%) following tiotropium bromide 18 µg and no subject following placebo.

Relationship between plasma concentration and effect

Unlike the effect at the site of action (lungs) which cannot be modelled using systemic drug concentration as a surrogate of effect site concentration, cardiovascular effects show direct correlation with systemic drug concentration. Therefore, throughout clinical development of UMEC, heart rate (HR) was considered to be one of the most sensitive markers for systemic PD response. Concentration-QT analysis discussed before also explored the concentration-heart rate relationship in Study DB2114635. The analysis for UMEC indicated no obvious trends between UMEC C_{max} and change from baseline in heart rate. No relationship was observed between UMEC plasma concentrations and heart rate at doses up to 1000 mcg UMEC in subjects with COPD. Similarly, the relationship between plasma UMEC concentrations and changes in QTcF was modelled. Predicted mean QTcF changes at all time points were <5 msec and none of the 95% CIs showed upper 95% CI greater than 10 msec.

Pharmacodynamic interactions with other medicinal products or substances

PD drug-drug interaction studies with other drugs that may be co-administered have not been performed but inhaled umeclidinium bromide has been used concomitantly with other COPD medicinal products including short and long acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of drug interactions. This is appropriately reflected in the Product Information.

The co-administration of UMEC with other anticholinergic containing drugs has not been studied and therefore should not be recommended. As a PD interaction is likely to occur, this statement has been included in section 4.5 the SPC, in line with the SPC of other LAMA..

2.4.4. Discussion on clinical pharmacology

From the results of the PK studies, the absolute bioavailability in healthy volunteers after inhalation of 1000 mcg UMEC was around 13%. UMEC was rapidly absorbed with the Cmax

values occurring at approximately 5 to 15 minutes post dose declining rapidly after Cmax.The inhaled dose used for UMEC was near 10 times the proposed therapeutic dose. Despite using larger doses plasma UMEC concentrations were not quantifiable in all subjects. As for other drugs used in low doses by the inhaled route the applicability of these results to the lower therapeutic doses cannot be concluded with certainty but the applicant has used oral, IV and inhaled formulations as well as radio-labelled drug to characterise reasonably absorption, distribution, metabolism and excretion of UMEC in healthy subjects and the PK of metabolites.

The absolute bioavailability after oral administration (oral solution) was negligible (< 1%) for UMEC (1000mcg oral dose). Under this circumstances co-administration with food is not be expected to significantly impact the systemic exposure, compared with the fasted state, at the proposed clinical doses of UMEC and no food effect study is needed.

Results of clinical studies in patients with relevant genetic polymorphism to CYP2D6 Plasma and urine PK data suggested no evidence of a difference in UMEC systemic exposure between healthy volunteers and CYP2D6 PM population and therefore no dose adjustment is recommended in the product information.

In vitro (HLM) UMEC was primarily metabolised by CYP2D6. CYP3A4 and CYP1A1 were also involved but to a lesser degree. However, considering that no evidence of a difference was seen in exposure of UMEC in PM versus IM/URM CYP2D6 metabolizers indicate that CYP2D6 might be of only minor importance in the total elimination of UMEC. The need for additional studies to clarify major elimination pathways and enzymes/transport proteins involved has been captured in the risk management plan, and will be provided post-authorisation.

The PK results show that systemic exposure is dose-proportional in the dose ranges tested. In terms of the time dependency of PK, the accumulation looks consistent with what would be expected based on the half-life.

Study results in subjects with severe renal impairment and with moderate hepatic impairment didn't show clinically relevant differences in systemic exposure and no dosage adjustment is required. UMEC was not studied in patients with severe hepatic impairment and this information is reflected in the Product information.

The population PK modelling ascertain the effects of different co-variates like age, weight, gender and race and none of these co-variates has a clinically significant impact on the PK. Therefore no dose-adjustments are required for these variates. Overall the characterisation of PK in relevant special populations is adequate and appropriate recommendations have been made based on the results.

UMEC is relatively potent inhibitor of CYP3A4 (IC50's=1.0 mcM) and is mainly metabolised through CYP2D6. However, as systemic concentrations are low interactions through systemic exposure are unlikely. The results of the interaction study with verapamil, a moderate CYP3A4 inhibitor and potent P-gp inhibitor did not show any significant effect on the PK of UMEC, except for a 40% increase in AUC of UMEC which is not considered significant. Therefore no dose adjustment is recommended in patients using concomitant P-gp transporter inhibitors.

Umeclidinium is an inhaled LAMA that acts locally on airways to produce bronchodilation which mechanism of action is similar to other anticholinergics in the class. The applicant has submitted five studies related to therapeutic effect in both, healthy and COPD subjects and 3 dose-ranging studies. Effective bronchodilatory activity has been demonstrated for UMEC.

The dose range is generally adequate to support the model that predicts the response for any particular dose.

Although no formal PD interaction studies with other drugs that may be co-administered have been performed, the potential for pharmacodynamic drug interactions is considered small. However, the co-administration of UMEC with other anticholinergic containing drugs has not been studied. As a PD interaction is likely to occur, appropriate statements were included in the product information, in line with other LAMAs.

Regarding secondary pharmacology, the effects of UMEC, on QT interval, blood potassium levels, heart rate, and blood pressure have been assessed. Thorough QT study (DB2114635) was negative for UMEC 500 mcg. Along with the recorded data, clinically significant effects on secondary pharmacology were not seen at the used concentrations.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology programme is deemed appropriate to investigate the PK and PD characteristics of UMEC for the proposed indication. All relevant information has been included in the Product information.

2.5. Clinical efficacy

2.5.1. Dose response studies

Three dose-finding studies (studies AC4113073, AC4115321 and AC4113589), all in COPD patients evaluated UMEC doses ranging from 15.6 mcg once daily to 1000 mcg once daily. All of them used change in trough FEV1 as the primary endpoint (see also chapter on primary pharmacology of this report).

Across these studies, doses of 62.5 and 125 mcg once-daily provided improvements in trough FEV1 at or near the level offered by higher doses. The additional increase in trough FEV1 with doses above 125 mcg was not considered to provide sufficient benefit to offset the increase in AEs.

The change in trough FEV1 as compared to placebo for 62.5 is available from 2 studies and the range of 0.124 -0.128 L is consistent across the studies. The change in trough FEV1 as compared to placebo for 125 mcg is in the range of 0.147-0.183. At doses higher than 125 mcg, it is seen that the response of trough FEV1 increases slightly (one study) or is decreased in comparison to 125 mcg, which suggest that the dose of 125 mcg is at the peak of the dose-response curve. Therefore, the selected doses of 62.5mcg and 125 mcg are considered acceptable by the CHMP.

Table 11. Summary of the Difference from Placebo for LS Mean Change from Baseline in Trough FEV1 (L) (95% CI) (Individual Study Results for AC4113589 ITT Population and AC4115321 and AC4113073 mITT Populations)

	Difference from Placebo for LS Mean Change from Baseline in Trough FEV_1 (L) (95% CI) by once daily UMEC dose (mcg) [a]						
Study	**15.6**	**31.25**	**62.5**	**125**	**250**	**500**	**1000**
AC4115321 at Day 8	0.113 (0.058, 0.168)	0.101 (0.045, 0.158)	0.124 (0.068, 0.179)	0.183 (0.127, 0.239)			
AC4113073 at Day 15			0.128 (0.060, 0.196)	0.147 (0.077, 0.216)	0.095 (0.027, 0.162)	0.140 (0.074, 0.205)	0.186 (0.113, 0.259)
AC4113589 at Day 29				0.159 (0.088, 0.229)	0.168 (0.099, 0.238)	0.150 (0.080, 0.220)	

Data Source: CSR AC4115321, Table 7.02; CSR AC4113073, Table 6.02; CSR AC4113589, Table 6.02
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; mITT=modified intent-to-treat; UMEC=umeclidinium bromide
Note: Number of subjects included in analysis is provided in data source tables.
a. Trough FEV_1 values are 24h after last scheduled dose for each study.

The applicant provided a dose response model incorporating data from the two crossover studies (Study AC4113073 and Study AC4115321) showing that doses of 62.5 and 125 mcg produce 63% and 77% of the maximal predicted response on trough FEV1 compared to 30% for the 15.6 mcg dose and 46% for the 31.25 mcg dose. The dose of 15.6 mcg (lowest dose tested) produced a clinically relevant and significant change of (0.113 L) as compared to placebo. In the dose response studies the lowest dose evaluated 15.6 mcg of UMEC also showed a clinically relevant effect on trough FEV1.

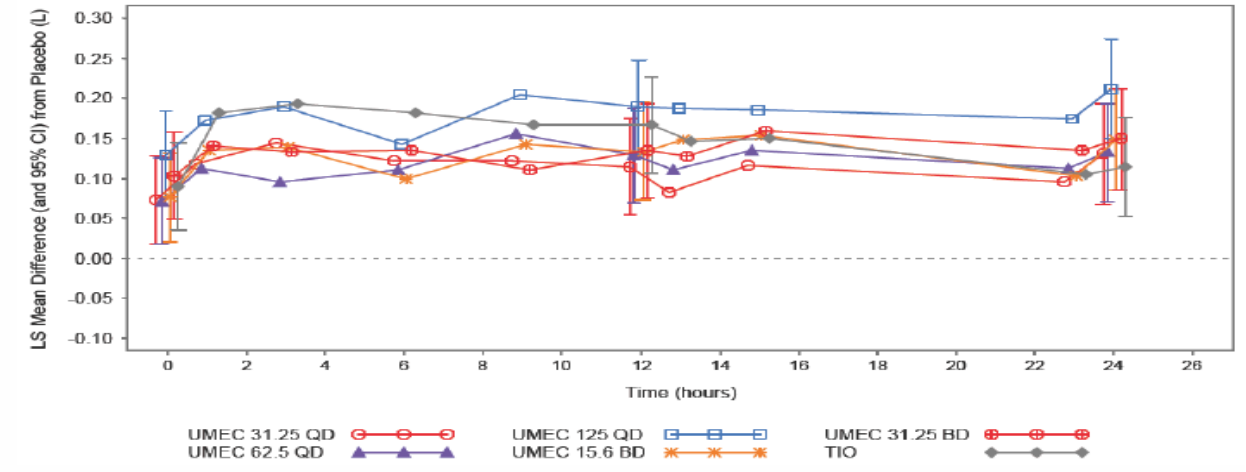
Evaluation of the dosing interval:

The evaluation of once- and twice-daily dosing was performed in the Phase IIb studies AC4115321 and AC4113073. In these studies, once-daily doses of UMEC were administered in the morning and twice-daily doses were administered in the morning and evening, approximately 12 hours apart. To maintain blinding, a double-dummy design was used where subjects using once-daily treatments took placebo in the evening.

In both studies, the 24-hour serial FEV1 response profiles with once-daily dosing showed consistent improvements in FEV1 relative to placebo over 24 hours and twice-daily dosing of UMEC at the same nominal dose did not provide greater benefit over once-daily dosing in the latter 12 hours of the dosing interval.

Data from study AC4115321 are displayed in Figure 5 below comparing 15.6 mcg BID and 31.25 mcg BID to 31.25 mcg OD and 62.5mcg OD. The BID regimen for the clinically relevant dose of 31.25 mcg BID performs only marginally better especially with differences between twice-daily and once-daily ranging between +24 ml and +15 ml for the low and high doses, respectively. This is not considered a significant difference and therefore the once-daily administration of UMEC is considered acceptable.

Figure 5. Differences (95% CI) from Placebo in LS Mean Change from Baseline in FEV_1 (L) Over Time at Day 7: UMEC Once-Daily (31.25, 62.5 and 125 mcg) and Twice-Daily (15.6 and 31.25 mcg) Doses and TIO (AC4115321 mITT Population)



Data Source: AC4115321 CSR, modified from Figure 7.12 and Figure 7.13 to include QD and BD doses in 1 figure.
Abbreviations: BD=twice-daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; mITT=modified intent-to-treat; QD=once-daily; TIO=tiotropium; UMEC=umeclidinium bromide
Note: Analysis performed using a mixed model with covariates of mean baseline, period baseline, treatment, period, time, time by period baseline interaction, time by mean baseline interaction and time by treatment interaction as fixed effects and subject as a random effect.

2.5.2. Main studies

In total there are 7 main clinical studies with UMEC in support of this application for the 62.5 mcg dose-strength (pre-dispensed dose of UMEC; the corresponding delivered dose is 55 mcg). These 7 clinical studies include:

- Three placebo-controlled studies: one 12-week study (AC4115408) and two 24-week studies (DB2113361 and DB2113373).
- One active controlled (tiotropium) 24-week study (DB2113374).
- Two supportive exercise 12-week studies (DB2114417 and DB2114418) and
- One 52-week extension study that provides long-term data supportive of efficacy (DB2113359).

Methods

Study Participants

The subjects included in the Efficacy Studies were selected to be representative of the intended broad COPD patient population suitable for treatment with a LAMA. Thus, inclusion criteria for these studies were:

- male and female subjects ≥40 years of age,
- clinical history of COPD (in accordance with the definition of the American Thoracic Society/European Respiratory Society [Celli, 2004]),
- a current or prior history of at least 10 pack-years of cigarette smoking (a major risk factor for COPD),
- airflow limitation, defined by a measured post-salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70, which is in accordance with the level of airflow limitation stated in the GOLD guidelines for COPD [GOLD, 2009; GOLD, 2010].
- Post-salbutamol FEV1 of ≤70% of predicted normal values ensuring that all subjects had at least moderate airflow limitation (GOLD II), and
- a modified Medical Research Council (mMRC) score ≥2 to demonstrate symptom burden.

ICS use at a stable dose throughout the duration of the treatment period was allowed in all studies as long as it was started at least 30 days prior to screening.

For the supportive Exercise Studies (DB2114417 and DB2114418), the patient population differed from the Efficacy Studies described above in that there was a lower limit of post-salbutamol FEV1 of ≥ 35% predicted due to safety concerns regarding the use of exercise in very severe COPD subjects (<30% FEV1 predicted) and an inclusion requirement of functional residual capacity (FRC) of ≥120% predicted in order to ensure patients had evidence of hyperinflation as hyperinflation is a significant limitation to exercise capacity. Unlike for the Efficacy Studies and the Long-term Safety study, participation in previous studies involving UMEC was not exclusionary since sufficient exposure was obtained in other studies and insignificant overlap was expected with the other study populations.

For the Long-term Safety study (DB2113359), the patient population differed from the Efficacy Studies described above in that there was a lower limit of post salbutamol FEV1 of

≥35% predicted due to safety concerns of having subjects with very severe airflow obstruction on placebo treatment for 52 weeks. In addition, there was an upper limit for post-salbutamol FEV1 of <80% predicted in line with similar studies of recently approved LAMAs. Subjects were also not required to have an mMRC ≥2 as this was primarily a safety study without any symptomatic endpoints.

Similar exclusion criteria for clinically significant medical conditions as determined by the investigator and other respiratory conditions including a current history of asthma which could confound assessment of efficacy or safety were applied across all studies. The inclusion and exclusion criteria for these studies were similar to those used in registration programs for other LAMAs [Center for Drug Evaluation and Research (CDER), Medical Reviews, aclidinium bromide, 25 May 2012].

Key withdrawal criteria in all studies except the Long-term Safety study included COPD exacerbation, as a recent COPD exacerbation could result in treatment with additional medications that may affect the study endpoints. In the Long-term Safety study, patients who had a COPD exacerbation were allowed to continue in the study at the discretion of the investigator.

Treatments

The treatments that were tested in each of the seven main studies are depicted in the table below.

The clinical development program evaluated 2 dosage strengths of UMEC and 2 dosage strengths of UMEC as part of the UMEC/VI combination (i.e., 62.5/25 mcg and 125/25 mcg) and was designed to support registration of both UMEC monotherapy and UMEC/VI.

Table E-04. Study drug doses for phase III studies

Study	PLA	UMEC 62.5 mcg	UMEC 125 mcg	TIO
AC4115408	✓	✓	✓	
DB2113361	✓		✓	
DB2113373	✓	✓		
DB2113374			✓	✓
DB2114417	✓	✓	✓	
DB2114418	✓	✓	✓	
DB2113359	✓		✓	

Abbreviations: PLA=placebo; TIO=tiotropium; UMEC=umeclidinium bromide

Objectives

Study AC4115408

The primary objective was to compare the efficacy and evaluate the safety of UMEC Inhalation Powder (62.5 mcg and 125 mcg) with placebo when administered once-daily via a Novel Dry Powder Inhaler (NDPI) over 12 weeks for treatment of subjects with Chronic Obstructive Pulmonary Disease (COPD).

Secondary objectives of this study were to evaluate the effects of UMEC (62.5 mcg and 125 mcg once-daily) compared with placebo on quality of life assessments and pharmacokinetic (PK) evaluation over 12 weeks in subjects with COPD.

Studies DB2113361, DB2113373 and DB2113374

The primary objective of these studies was to evaluate the efficacy and safety of UMEC/VI, UMEC and VI once daily for 24 weeks in subjects with COPD. While studies DB2113361 and DB2113371 were placebo controlled studies, the study DB2113373 was an active tiotropium controlled study.

The placebo controlled studies also had secondary objectives like pharmacokinetics and PK-PD analyses

Studies DB2114417 and DB2114418

The primary objectives of these studies was to evaluate the effect of UMEC/VI administered once-daily on exercise endurance time (EET) measured using the endurance shuttle walk test (ESWT) and trough FEV1 over 12 weeks in subjects with COPD.

The secondary objectives of these studies were to evaluate the effect of UMEC/VI, its components, and placebo administered once-daily on lung volumes and post-dose lung function over 12 weeks in subjects with COPD

Study DB2113359

The objective of this study was to evaluate the safety and tolerability of UMEC/VI 125/25 mcg and UMEC 125 mcg compared with placebo administered once-daily for 52 weeks in subjects with COPD

Outcomes/endpoints

Study AC4115408

Trough FEV1 on Day 85 was the primary endpoint and Weighted mean (WM) FEV1 over 0 to 6 hours postdose at Day 1, 28, and 84, as well as Serial FEV1 at 1, 3, 6, 23, and 24 hours post-dose at Day 1 and 84 were the two secondary endpoints.

Other endpoints included:

- Trough FEV1 at other time points
- Serial FEV1 at 1, 3 and 6 hours postdose at Day 28
- Serial, WM mean and trough forced vital capacity (FVC)
- Rescue salbutamol Use
- Transition dyspnea index (TDI) focal score
- Proportion of responders according to TDI
- Time to Onset on Day 1
- Proportion of subjects achieving an increase in FEV1 of ≥12 % and ≥ 200 mL above baseline at any time during 0 to 6 hours postdose on Day 1
- Proportion of subjects achieving an increase of ≥ 100mL above baseline in trough FEV1
- St. George's Respiratory Questionnaire (SGRQ).

Studies DB2113361, DB2113373 and DB2113374

Trough FEV1 on day 169 was the primary endpoint and TDI focal score at Day 168 was the key secondary symptomatic endpoint. A minimum clinically important difference for these two endpoints were pre-specified as an increase of 100 ml and +1 unit TDI score respectively as compared to the pre-treatment baseline.

Other endpoints included:

- 0-6h weighted mean FEV1
- Reduction in rescue salbutamol use
- St. George's Respiratory Questionnaire (SGRQ) excluding the exercise and long-term safety studies
- Time to first COPD exacerbation

Studies DB2114417 and DB2114418

Trough FEV1 and Exercise endurance time (EET) as measured by Exercise endurance shuttle walk test (ESWT) were the co-primary endpoints for the exercise studies. An improvement in EET of 45-85 seconds was considered a clinically significant improvement. In addition changes in lung volume measures like inspiratory capacity (IC), functional residual capacity (FRC) and residual volume (RV) were included as secondary endpoints. The sample size was calculated in order to provide at least 90% power for the comparisons of each UMEC/VI dose with placebo for each of the co-primary endpoints of Exercise Endurance Time (EET) and trough FEV1. For the UMEC versus placebo comparison, the power was 64% and 61% for EET and trough FEV1, respectively. In these two-period incomplete block crossover studies involving six treatments, there are 30 possible treatment sequences, and the power is affected by the treatment sequences which are used and the number of subjects who are randomized to each treatment. A SAS program was used to simulate data and calculate the theoretical power using various sequences and numbers of subjects assigned to each. The exercise studies were designed primarily for the comparison of UMEC/VI vs placebo and the strength of conclusions for UMEC vs placebo from these studies are much lower. However as no claims are being made based on the results of these studies and as these studies are not considered pivotal to establish efficacy of UMEC, this is acceptable.

Study DB2113359

Long-term safety study did not have any pre-specified efficacy endpoints. However as pre-specified safety endpoints included trough FEV1, rescue medication use and COPD exacerbations, these provide additional data supporting the long-term efficacy.

Sample size

The primary endpoint for the 12-week Efficacy Study (AC4115408) was trough FEV1, on Day 85 with 0-6 hr post-dose weighted mean and serial FEV1 as secondary endpoints. The sample size for this study was calculated in order to provide at least 90% power on the primary endpoint for the treatment comparison between each UMEC dose and placebo.

The primary endpoint for each 24-week Efficacy Study was trough FEV1 on Day 169, with 0-6 hr post-dose weighted mean FEV1 at Day 168 as a secondary endpoint. In the 24-

week, placebo-controlled studies, TDI score was included as the key symptomatic endpoint as required for the EMA. The sample size for these placebo-controlled studies was calculated in order to provide at least 90% power on the primary and secondary endpoints, including TDI, for the five primary treatment comparisons between UMEC/VI and placebo, UMEC and placebo, VI and placebo, UMEC/VI and VI, and UMEC/VI and UMEC.

The 24-week TIO study (DB2113374) evaluated UMEC 125 mcg once-daily for 24 weeks. No placebo arm was included in this study. TIO was a treatment arm, although no direct statistical comparisons between UMEC and TIO were performed. The co-primary endpoints in the Exercise Studies were EET at Week 12 and trough FEV1 at Week 12 and the sample size was calculated to provide at least 90% power on these two endpoints for the comparisons between UMEC/VI and placebo.

Randomisation

Generally the randomization code was generated by GSK using a validated computerized system RandALL version 2.5. Subjects were assigned to study treatment in accordance with the randomization schedule, using RAMOS, an interactive voice response system (IVRS). This is a telephone based system used by the investigator or designee. Once a randomization number was assigned to a subject it could not be reassigned to any other subject in the study.

The randomization ratio differed for the two 24-week placebo-controlled (3:2 actives: placebo) vs. the 12-week placebo-controlled and active comparator (1:1 actives: control) studies to allow for additional exposure to the active treatments for evaluation of safety in the two 24-week placebo-controlled studies.

In the exercise endurance studies, the subjects were randomized to receive a sequence of 2 of the 6 possible treatments. Subjects were randomized to 1 of 26 different sequences and the sequences were selected to optimize power for the comparisons between UMEC/VI and placebo.

For the long-term safety study, the randomization ratio was 2:2:1, again to ensure additional exposure to active treatments.

Blinding (masking)

All 7 main studies that support efficacy had a double-blind design. No problems of unblinding were found in the three placebo-controlled studies [one 12-week study (AC4115408) and two 24-week studies (DB2113361 and DB2113373)] or in the active controlled (tiotropium) 24-week study (DB2113374). A double-dummy design was used in DB2113374 because UMEC was delivered by an NDPI and the active comparator was delivered by Handihaler.

Statistical methods

Studies DB2113361 and DB2113373

These were 24-week randomised, placebo-controlled studies with COPD patients randomised in a ratio of 3:3:3:2 to one of the following treatments:

- UMEC/VI 125/25mcg, (DB2113361), UMEC/VI 62.5/25 mcg (DB2113373)

- UMEC 125mcg (DB2113361), UMEC 62.5 mcg (DB2113373)
- VI 25mcg,
- placebo

administered once daily by a novel dry powder inhaler. In study DB2113373 the number of subjects receiving each treatment (ITT poplation) was a follows:

Treatment	Number of Subjects Receiving Each Treatment (DB2113373 ITT Population)
UMEC/VI 62.5/25 mcg	413
UMEC 62.5 mcg	418
VI 25 mcg	421
Placebo	280

Abbreviations: ITT=Intent to Treat; UMEC=umeclidinium bromide; VI=vilanterol

Statistical methods for <u>Studies DB2113361 and DB2113373</u>

The details of the planned statistical methods were specified in the reporting and analysis plan (RAP) for the four main Phase III studies completed before the database freeze and the unblinding of the treatment codes of all four studies. No interim analyses were carried out.

The primary efficacy endpoint was the trough FEV1 on Day 169 defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168 after 24 weeks of treatment. The key secondary efficacy endpoints were the mean TDI focal score at Week 24 and the weighted mean FEV1 over 0 to 6 hours post dose at Week 24. For each study a number of additional secondary efficacy endpoints were specified.

The following efficacy analyses populations were defined for the primary and key secondary endpoints:

- Intent-to-treat (ITT) population comprising all subjects randomised who received at least one dose of study medication;
- Per protocol (PP) population comprising all subjects in the ITT population who were not identified as full protocol deviators; the PP population was used for confirmatory analyses of the primary and secondary efficacy endpoints irrespective of how many subjects were in the PP population.

For each test on each efficacy endpoint the null hypothesis was that there was no difference between treatments with the alternative hypothesis that there was a difference.

The following treatment comparisons were performed for the primary endpoint and the two key secondary endpoints:

- UMEC/VI versus placebo;
- UMEC versus placebo;
- VI versus placebo;
- UMEC/VI versus VI;
- UMEC/VI versus UMEC.

To account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure was applied using a hierarchy consisting of the five treatment comparisons described above performed in that order on the primary and then the secondary endpoints.

The primary endpoint was analysed for the ITT population using a mixed model repeated measures (MMRM) analysis including covariates of baseline FEV1, smoking status, day, centre group, treatment, day by baseline interaction and day by treatment interaction. The model used all available trough FEV1 values recorded on Days 2, 28, 56, 84, 112, 168 and 169. Two models were fitted, one with a response variable of trough FEV1 and another with a response variable of change from baseline in trough FEV1.

The least square (LS) means from the model for change from baseline in trough FEV1 for each treatment on Days 2, 28, 56, 84, 112, 168 and 169, along with the corresponding 95% confidence intervals (CIs), were plotted. The LS mean treatment differences, along with the corresponding 95% CIs, for change from baseline in trough FEV1 on Days 2, 28, 56, 84, 112, 168 and 169 were also plotted for the treatment comparisons of interest.

A thorough investigation of the patterns of missing data was planned. In addition sensitivity analyses using multiple imputation (MI) methods were conducted. Firstly, within each treatment arm a Bayesian multivariate normal model for the data (including the same covariates as for the primary MMRM analysis) was fitted using a Markov Chain Monte Carlo approach and quasi-independent samples drawn from the posterior distributions for the parameters of the multivariate normal distribution for each arm. Non-informative priors were used. This allowed all missing observations to be imputed, whether a subject had a monotone or non-monotone pattern of missingness. The following multiple imputation methods were used: the 'missing at random' (MAR) approach, the 'copy differences from control' (CDC) approach and the 'last mean carried forward' (LMCF) approach. For each imputation dataset, an analysis of covariance was carried out using Day 169 data, both actual and imputed, using the same covariates as in the primary analysis. Contrasts of interest were estimated, and then combined across imputations using standard MI rules.

A similar MMRM analysis was carried out for the key secondary endpoint, the TDI focal score on Day 168. An investigation of missing data and sensitivity analyses similar to those carried out on the primary endpoint was used. The second secondary endpoint was analysed using the same overall approach.

Study AC4115408

This was a 12-week randomised, placebo-controlled study in COPD patients randomised in a ratio of 1:1:1 to one of the following treatments:

- UMEC 62.5mcg
- UMEC 125mcg,
- placebo

administered once daily by a novel dry powder inhaler. A total of 69 subjects were randomised to each active treatment with 68 to placebo.

Statistical methods for Study AC4115408

This was a Phase III randomised, double-blind, placebo controlled study that compared the efficacy of 62.5 mcg and 125 mcg of UMEC to placebo after 12 weeks of treatment. The

primary endpoint was trough FEV1 as Day 85. 0-6 hours post-dose weighted mean and serial FEV1 were specified as secondary endpoints. TDI and SGRQ were defined amongst the other endpoints.

The following treatment comparisons were performed on trough FEV1 on Treatment Day 85: UMEC 125 mcg vs. placebo and UMEC 62.5 mcg vs. placebo. In order to account for multiplicity across treatment comparisons for the primary endpoint, a step-down closed testing procedure was applied, whereby inference for the comparison of UMEC 62.5 mcg with placebo was dependent on statistical significance having been achieved for the comparison of UMEC 125 mcg with placebo.

The primary endpoint of trough FEV1 on Day 85 was analyzed for the ITT population using a mixed model for repeated measures (MMRM) analysis including covariates of baseline FEV1, smoking status at screening, Day, center group, treatment, Day by baseline interaction, and Day by treatment interaction, where Day was nominal. The model used all available trough FEV1 values recorded on Days 2, 14, 28, 56, 84, and 85. Missing data were not directly imputed in this analysis; however, all non-missing data for a subject were used within the analysis to estimate the treatment effect for trough FEV1 on Day 85.

The analysis of 0 to 6 hour weighted mean FEV1 on Days 1 and Weeks 4 , 8 and 12 used the same methodology as that for the primary endpoint . Serial FEV1 at 1, 3, 6, 23, and 24 hours after dosing was analysed using a repeated measures model, with pre-defined variables, including baseline FEV1 fitted as covariates. Treatment, time and a time by treatment interaction term was included. This analysis was performed for Day 1 and Week 12 separately.

Study DB2113374

This was a 24-week randomised active-controlled study with COPD patients randomised in a ratio of 1:1:1:1 to the following treatments:

- UMEC/VI 125/25mcg,
- UMEC/VI 62.5/25mcg,
- UMEC 125mcg
- tiotropium 18mcg

administered once daily by a novel dry powder inhaler or, in the case of tiotropium, by the HandiHaler.

Statistical methods for Study DB2113374

The details of the planned statistical methods were specified in the reporting and analysis plan (RAP) for the four main Phase III studies completed before the database freeze and the unblinding of the treatment codes of all four studies. No interim analyses were carried out.

The primary efficacy endpoint was the trough FEV1 on Day 169 defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168 after 24 weeks of treatment. For each study a number of secondary efficacy endpoints were specified.

For the efficacy analyses, the ITT and PP populations were defined as for the placebo-controlled studies (DB2113361 and DB2113373). However serious GCP problems were identified at one investigator site for Study DB2113374 and so the ITT population used for

the primary analysis excluded patients from investigator site 040688. A sensitivity analysis was also conducted including these patients in the ITT population.

For Study DB2113374 the following treatment comparisons were performed for the primary endpoint and the key secondary endpoint, weighted mean FEV1 over 0 to 6 hours post dose at Week 24:

- UMEC/VI 125/25mcg versus tiotropium;
- UMEC/VI 125/25mcg versus UMEC.

A similar hierarchical procedure to that used for the placebo-controlled studies was specified with the comparisons above performed for the primary and secondary endpoints following by the same comparisons for the same endpoints for the lower dose of the combination.

The statistical methods used to analyse the primary endpoint were the same as for the placebo controlled-studies (DB2113361 and DB2113373). The same investigation of missing data and the same sensitivity analyses were used as in the placebo-controlled studies.

Studies DB2114417 and DB2114418

These were two Phase III randomised, double-blind, placebo-controlled, combination and component, two-period incomplete block design cross-over studies using UMEC and VI. A 10-12 day washout period between treatments was planned. The objective was to evaluate lung function and exercise endurance time after 12 weeks of once-daily administration of the following treatments:

- UMEC/VI 125/25mcg (A),
- UMEC/VI 62.5/25mcg (B),
- UMEC 125mcg (C),
- UMEC 62.5mcg (D),
- VI 25mcg (E),
- placebo (F),

delivered by the novel dry powder inhaler. In each study approximately 312 subjects with moderate/severe COPD were randomised in order to achieve 208 subjects completing both treatment periods.

Statistical methods for Studies DB2114417 and DB2114418

The details of the planned statistical methods were specified in the reporting and analysis plan (RAP) for these two Phase III studies completed before the database freeze and the unblinding of the treatment codes of all four studies. No interim analyses were carried out.

Subjects were randomised to one of 26 possible treatment sequences which were selected to optimise power for comparisons between UMEC/VI and placebo and therefore the number of subjects in each treatment was unbalanced.

Each study had two co-primary endpoints:

- exercise endurance time (EET) post-dose at Week 12 defined as the EET obtained 3 hours after dosing at Week 12;

- clinic visit trough (pre-bronchodilator and pre-dose) FEV1 at Week 12.

The following efficacy analyses populations were defined for the co-primary endpoints:

- Intent-to-treat (ITT) population comprising all subjects randomised who received at least one dose of study medication in either treatment period;
- Per protocol (PP) population comprising all subjects in the ITT population who were not identified as full protocol deviators. In addition subjects with deviations considered to affect trough FEV1 or EET in one or more treatment periods had those periods excluded from the PP analyses.

For each test on each efficacy endpoint the null hypothesis was that there was no difference between treatments with the alternative hypothesis that there was a difference.

The following treatment comparisons were designated primary:

- post-dose EET: UMEC/VI 125/25 mcg versus placebo;
- trough FEV1: UMEC/VI 125/25 mcg verses placebo;
- post-dose EET: UMEC/VI 62.5/25 mcg versus placebo;
- trough FEV1: UMEC/VI 62.5/25 mcg verses placebo.

These four treatment comparisons, in this order, comprised a pre-defined hierarchy of testing in a step-down procedure in order to account for multiple testing.

The co-primary endpoint of 3-hour post-dose EET at Week 12 was analysed for the ITT population using an MMRM analysis, including covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, centre group, visit by period walking speed interaction, visit by mean walking speed interaction, and visit by treatment interaction. The response variable was change from baseline in 3-hour post-dose EET.

The co-primary endpoint of trough FEV1 at Week 12 was analysed for the ITT population using an MMRM analysis, including covariates of period baseline, mean baseline, period, treatment, visit, smoking status, centre group, visit by period baseline interaction, and visit by mean baseline interaction, and visit by treatment interaction.

The analyses were repeated for the PP population and additional pre-defined sensitivity analyses were carried out using the 'missing at random' (MAR) approach and the 'copy differences from control' (CDC) approach.

Multiplicity:

To account for multiplicity across treatment comparisons and endpoints in each study, a step-down closed testing procedure was applied whereby inference for a test in the pre-defined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy.

In the 12-week, placebo-controlled study, the hierarchy consisted of the comparison of UMEC 125 mcg with placebo performed on the primary endpoint (trough FEV1) followed by the comparison of UMEC 62.5 mcg with placebo performed on the primary endpoint.

In the 24-week, placebo-controlled studies, the testing hierarchy consisted of the five primary treatment comparisons (UMEC/VI, UMEC and VI vs. placebo, UMEC/VI vs. VI and UMEC/VI vs. UMEC) for the primary endpoint (trough FEV1), the same comparisons for the

key symptomatic endpoint of TDI, and the same comparisons for the secondary endpoint of 0-6 hr weighted mean FEV1.

In the Exercise Studies, the hierarchy consisted of the comparison of UMEC/VI 125/25 mcg with placebo performed on the co-primary endpoints (EET and trough FEV1) followed by the comparison of UMEC/VI 62.5/25 mcg with placebo performed on the co-primary endpoints. These studies also included UMEC comparisons which were not included in the hierarchy. If all primary treatment comparisons of UMEC/VI vs placebo in the pre-defined testing hierarchy achieved statistical significance, inference was drawn from all other treatment comparisons on the co-primary and other endpoints, so in this case any comparison of UMEC vs. placebo with $p<0.05$ is considered statistically significant.

If at any point in the hierarchy a comparison did not demonstrate statistical significance, all further statistical analyses pre-specified in the hierarchy were fully described but are not strictly inferential. If statistical significance was demonstrated for all comparisons pre-specified in the testing hierarchy, then inference is drawn from all defined treatment comparisons on all other efficacy endpoints, without adjustment for multiplicity.

For the studies including UMEC/VI and UMEC, a non-statistically significant result for a UMEC/VI comparison will affect inference to be drawn from subsequent UMEC comparisons.

Data integration:

Integration was performed for the four Efficacy Studies as the designs were very similar. Two sets of integration were performed:

- a 12-week integration of Study AC4115408 and the first 12 weeks from Studies DB2113361, DB2113363 and DB2113374 (Note that the primary efficacy endpoint for study AC4115408 was trough FEV1 on Day 85, but this time point was not assessed in the 24-week studies. The trough FEV1 at Day 84, which was collected in all studies, has been integrated.),
- a 24-week integration of Studies DB2113361, DB2113363 and DB2113374. A separate integration was performed for the two Exercise Studies as the designs were identical. The Efficacy and Exercise Studies were not integrated together due to differences in design and patient population.

Efficacy data from the Long-term Safety study were not integrated with the data from other studies as the study was of a different duration and had a different objective.

In addition, a post-hoc Integration was undertaken to further explore the efficacy of the 62.5 mcg and 125 mcg dose from the three 12-week studies that included both doses of UMEC. This Post-hoc Integration included data from AC4115408 and the first treatment period only of two Exercise Studies (DB2114417 and DB2114418). The treatment comparisons performed for each endpoint in the integrated data were of each dose of UMEC and placebo. No adjustment for multiplicity was made in the integrated analysis. Analyses were performed on the intent-to-treat (ITT) population, defined as all randomized subjects who received at least one dose of study medication. In individual studies, a supportive Per Protocol analysis was also performed and gave similar results to the ITT analysis. Individual study analyses were defined in the study protocol with further details finalized prior to breaking the blind on the study, and all were adjusted for covariates of geographical region, smoking status and baseline (if appropriate). The impact of missing data was explored in the individual studies (AC4115408, DB2113361, DB2113373, DB2113374) using multiple imputation methods (Missing at Random, Copy Difference from Control and Last Mean

Carried Forward) to impute data missing following withdrawal from the study. In each case, the results from analysis of the imputed dataset were very similar to those from the primary mixed model repeated measures analysis.

Although the 24-week, placebo-controlled studies did not use co-primary endpoints (as recommended in CHMP guidance), the level of statistical evidence provided using the closed testing hierarchy is not very different. Considering just treatment comparisons for the trough FEV1 and TDI endpoints, there are a total of five significance tests (UMEC/VI vs. placebo, UMEC vs. placebo, VI vs. placebo, UMEC/VI vs. VI, and UMEC/VI vs. UMEC) for each endpoint. If the endpoints were considered co-primary, all ten tests would be required to be statistically significant to claim a positive study and to progress to drawing inference on further endpoints. By having a single primary endpoint of trough FEV1 and introducing the hierarchy, the progression has not been changed (for regulatory agencies which include TDI in the hierarchy, inferences should not be drawn on further endpoints unless all 10 tests are statistically significant), but a positive study can be claimed if statistical significance is achieved only on comparisons on the trough endpoint.

No statistical adjustments of the FEV1 values were made to account for use of rescue salbutamol during the studies. The precautions were taken in the conduct of the study such that a key lung function measure could not be taken within 4 hours of rescue medication use. This is acceptable.

Analysis populations:

All integrated analyses for the 12- and 24-week Efficacy Studies and the Exercise Studies used the ITT Population from the individual studies. The ITT Population is defined as all subjects who were randomized to treatment and received at least one dose of study medication in the treatment period. Randomized subjects were assumed to have received study medication unless definitive evidence to the contrary existed. Outcomes were reported according to the randomized treatment allocation.

Results

Participant flow

Number of Subjects in the ITT Population

12-Week Integration: The table blow summarizes the number of subjects receiving UMEC or placebo in the ITT population for each study and for the integrated 12-week data set for Studies AC4115408, DB2113361, DB2113373, and DB2113374.

Table 12. Summary of Integrated Subject Populations (12-Week Integration, ITT Population)

Population	Placebo N=623	UMEC 62.5 mcg N=487	UMEC 125 mcg N=698	Total N=1808
All studies	623	487	698	1808
AC4115408	68	69	69	206
DB2113361	275	0	407	682
DB2113373	280	418	0	698
DB2113374	0	0	222	222

Data source: Table 3.01
Abbreviations: ITT=intent to treat; N=number of subjects; UMEC=umeclidinium bromide.

24-Week Integration: The table below summarizes the number of subjects receiving UMEC or placebo in the ITT population for each study and for the 24-week integrated data set for Studies DB2113361, DB2113373, and DB2113374.

Table 13. Summary of Integrated Subject Populations (24-Week Integration, ITT Population)

Population	Placebo N=555	UMEC 62.5 mcg N=418	UMEC 125 mcg N=629	Total N=1602
All Studies	555	418	629	1602
DB2113361	275	0	407	682
DB2113373	280	418	0	698
DB2113374	0	0	222	222

Data source: Table 3.02
Abbreviations: ITT=intent to treat; N=number of subjects; UMEC=umeclidinium bromide.

Exercise Integration: The table below summarizes the number of subjects receiving UMEC and/or placebo in the ITT population for each study and for the integrated data set for the Exercise Studies.

Table 14. Summary of Integrated Subject Populations (Exercise Integration, ITT Population)

Population	Placebo N=321	UMEC 62.5 mcg N=89	UMEC 125 mcg N=91	Total N=420
All studies	321	89	91	420
DB2114417	170	49	50	223
DB2114418	151	40	41	197

Data source: Table 3.03
Abbreviations: ITT=intent to treat; N=number of subjects; UMEC=umeclidinium bromide
Note: Subjects are counted once under each treatment received and once in the Total column.

Subject Disposition

12-Week Integration: A total of 1808 subjects from the UMEC 62.5 mcg, UMEC 125 mcg, and placebo treatment groups were included in the ITT population for the 12-Week Integration (see table below). The majority of subjects completed the studies (75%). Overall, the most common primary reason for withdrawal was lack of efficacy (10%). Withdrawals due to exacerbations were 11% for the placebo group compared with 5% for UMEC 62.5 mcg and 7% for UMEC 125 mcg treatment groups. Withdrawals due to AEs were 4% in the placebo group compared with 7% for the UMEC 62.5 mcg and 6% for UMEC 125 mcg treatment groups.

Table 15. Overall Subject Disposition (12-Week Integration, ITT Population)

	Number (%) of Subjects			
	Placebo N=623	UMEC 62.5 mcg N=487	UMEC 125 mcg N=698	Total N=1808
Completion Status				
Completed [a]	437 (70)	386 (79)	533 (76)	1356 (75)
Withdrawn	186 (30)	101 (21)	165 (24)	452 (25)
Primary Reason/Subreason for Withdrawal [b]				
Adverse event	26 (4)	35 (7)	44 (6)	105 (6)
Lack of efficacy	89 (14)	25 (5)	64 (9)	178 (10)
Exacerbation	66 (11)	23 (5)	48 (7)	137 (8)
Protocol deviation	8 (1)	7 (1)	4 (<1)	19 (1)
Subject reached protocol-defined stopping criteria	31 (5)	13 (3)	27 (4)	71 (4)
ECG abnormality	22 (4)	7 (1)	19 (3)	48 (3)
Lab. abnormality	0	2 (<1)	0	2 (<1)
Holter monitoring abnormality	9 (1)	4 (<1)	8 (1)	21 (1)
Study closed/terminated	0	0	0	0
Lost to follow-up	1 (<1)	0	3 (<1)	4 (<1)
Withdrew consent	31 (5)	21 (4)	23 (3)	75 (4)
Subject relocated	3 (<1)	2 (<1)	1 (<1)	6 (<1)
Frequency of visits	5 (<1)	2 (<1)	0	7 (<1)
Burden of procedures	7 (1)	4 (<1)	4 (<1)	15 (<1)
Other	9 (1)	10 (2)	15 (2)	34 (2)

Data source: Table 3.04.
Abbreviations: ECG=Electrocardiogram; ITT=intent to treat; Lab=Laboratory; N=number of subjects; UMEC=umeclidinium bromide.
a. Subjects are considered to have completed the treatment period if they attend the last clinic visit and did not withdraw at the visit.
b. Subjects only record one primary reason for withdrawal and are not required to indicate sub-reasons. However, subjects could select more than 1 sub-reason if appropriate.
Note: Subjects that were counted as withdrawals in the three 24-Week studies may have completed 12 weeks of treatment.

24-Week Integration: A total of 1602 subjects from the UMEC 62.5 mcg, UMEC 125 mcg, and placebo treatment groups were included in the ITT population for the 24-Week Integration (see table below). The majority of subjects completed the studies (74%). Overall, the most common primary reason for withdrawal was lack of efficacy (10%). Withdrawals due to exacerbations were 11% for the placebo group compared with 4% for UMEC 62.5 mcg, 7% for UMEC 125 mcg treatment groups. Withdrawals due to AEs were 5% in the placebo group compared with 8% in the UMEC 62.5 mcg and 7% in the UMEC 125 mcg treatment groups.

Table 16. Overall Subject Disposition (24-Week Integration, ITT Population)

	Number (%) of Subjects			
	Placebo N=555	UMEC 62.5 mcg N=418	UMEC 125 mcg N=629	Total N=1602
Completion Status				
Completed [a]	387 (70)	324 (78)	477 (76)	1188 (74)
Withdrawn	168 (30)	94 (22)	152 (24)	414 (26)
Primary Reason/Subreason for withdrawal [b]				
Adverse event	26 (5)	34 (8)	41 (7)	101 (6)
Lack of efficacy	81 (15)	20 (5)	60 (10)	161 (10)
Exacerbation	60 (11)	18 (4)	46 (7)	124 (8)
Protocol deviation	8 (1)	7 (2)	4 (<1)	19 (1)
Subject reached protocol-defined stopping criteria	25 (5)	13 (3)	22 (3)	60 (4)
ECG abnormality	16 (3)	7 (2)	14 (2)	37 (2)
Lab. abnormality	0	2 (<1)	0	2 (<1)
Holter monitoring abnormality	9 (2)	4 (<1)	8 (1)	21 (1)
Study closed/terminated	0	0	0	0
Lost to follow-up	1 (<1)	0	2 (<1)	3 (<1)
Withdrew consent	27 (5)	20 (5)	23 (4)	70 (4)
Subject relocated	3 (<1)	2 (<1)	1 (<1)	6 (<1)
Frequency of visits	5 (<1)	1 (<1)	0	6 (<1)
Burden of procedures	4 (<1)	4 (<1)	4 (<1)	12 (<1)
Other	8 (1)	10 (2)	15 (2)	33 (2)

Data source: Table 3.05
Abbreviations: ECG=Electrocardiogram; ITT=intent to treat; Lab=Laboratory; N=number of subjects; UMEC=umeclidinium bromide.
a. Subjects are considered to have completed the treatment period if they attend the last clinic visit and did not withdraw at the visit.
b. Subjects only record one primary reason for withdrawal and are not required to indicate sub-reasons. However, subjects could select more than 1 sub-reason if appropriate.

Exercise Integration: A total of 420 subjects receiving UMEC 62.5, UMEC 125 mcg and/or placebo treatment were included in the ITT population for the Exercise Integration. Overall, the most common primary reason for withdrawal was lack of efficacy (10%). Withdrawals due to exacerbations were 6% for subjects on placebo compared with 2% for subjects on UMEC 62.5 mcg and 8% for subjects on UMEC 125 mcg treatment. Withdrawals due to AEs were 5% for subjects on placebo compared with 3% for subjects on UMEC 62.5 mcg and 3% for subjects on UMEC 125 mcg.

Study DB2113359

The subject disposition in this long-term study is depicted in the table below:

Table 7 Overall Subject Disposition (DB2113359 ITT Population)

	Number (%) of Subjects			
	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226	Total N=562
Completion Status				
Completed [a]	66 (61)	133 (59)	143 (63)	342 (61)
Withdrawn	43 (39)	94 (41)	83 (37)	220 (39)
Primary reason/subreason [b] for withdrawal				
Adverse event	13 (12)	21 (9)	17 (8)	51 (9)
Lack of efficacy	9 (8)	3 (1)	1 (<1)	13 (2)
COPD exacerbations	4 (4)	1 (<1)	1 (<1)	6 (1)
Protocol deviations	2 (2)	6 (3)	6 (3)	14 (2)
Subject reached protocol-defined stopping criteria	8 (7)	37 (16)	36 (16)	81 (14)
ECG abnormality	0	12 (5)	13 (6)	25 (4)
Holter abnormality	8 (7)	26 (11)	26 (12)	60 (11)
Lab abnormality	0	1 (<1)	0	1 (<1)
Study closed/terminated	2 (2)	4 (2)	3 (1)	9 (2)
Lost to follow-up	1 (<1)	7 (3)	5 (2)	13 (2)
Withdrew consent	8 (7)	16 (7)	15 (7)	39 (7)
Subject relocated	1 (<1)	3 (1)	3 (1)	7 (1)
Frequency of visits	1 (<1)	2 (<1)	0	3 (<1)
Burden of procedures	0	3 (1)	3 (1)	6 (1)
Other	6 (6)	9 (4)	9 (4)	24 (4)

Data Source: Table 5.03

Abbreviations: COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; UMEC=umeclidinium bromide; VI=vilanterol

Note: The subject reported withdrawn for a lab abnormality did not have a laboratory value that met the liver chemistry stopping criteria. The subject was reported as withdrawn from the study due to protocol-defined stopping criteria for a lab abnormality "as determined by the investigator". The lab abnormality was not specified and was not reported as an AE.

a. Subjects were considered to have completed if they completed the last clinic visit excluding follow-up (Visit 7) and did not withdraw at the visit.

b. Subjects only recorded 1 primary reason for withdrawal. Subjects were not required to indicate a subreason for all primary reasons, however, if they did, they could have marked more than 1, if appropriate.

Recruitment

Study code	Initiation date	Completion Date	Date of Report	Countries outside EU
AC4115408	16 Jul 2011	13 Feb 2012	July 2012 – amended report – Nov 2012	US and Japan
DB2113361	22 Mar 2011	19 Apr 2012	Sep 2012	Ukraine, Phillipines, Japan, USA
DB2113373	30 Mar 2011	05 Apr 2012	Nov 2012	Russia, Chile, South Africa, Mexico, Thailand, Japan, USA and Canada
DB2113374	21 Mar 2011	10 Apr 2012	Nov 2012	Argentina, Australia, Chile, South Korea, Mexico, South Africa, United States, Canada
DB2114417	16 Mar 2011	14 Jun 2012	Oct 2012	Russian Federation, United States
DB2114418	16 Mar 2011	16 Jul 2012	Oct 2012	Ukraine, United States, Canada, South Africa
DB2113359	27 Jan 2011	23 Jul 2012	Nov 2012	Chile, South Africa, Russia, USA

All studies were multi-centre studies conducted across many countries all over the world. All studies included study centres from Europe. Generally the 6 month studies have been completed in a year and the long-term study in 18 months. All these studies have begun in early 2011 and have been completed by mid-2012, which suggest they were well-managed and well-run.

Conduct of the studies

Study AC4115408

There were no protocol amendments to the original protocol.

Study DB2113374

There was one amendment to modify the statistical testing hierarchy.

Study DB2113361

There were two amendments and one was essentially in line with the amendments for study DB2113374. The other amendment re-classified SOBDA score as an 'other' endpoint from 'secondary'

Study DB2113373

There were two amendment and these were in line with the amendments for study DB2113361

Study DB2114417

There was one amendment which clarified the timings of assessments and procedure, the ECG inclusion and exclusion criteria and permitted medications.

Study DB2114418

There was one amendment which was essentially in line with the above amendment for study DB2114417.

Study DB2113359

There was one amendment which included clarification of timepoints for study visits and clarification of ECG withdrawal criteria and permitted medications

Significant deviations from GCP for investigator site 040688 were identified by GSK during the conduct of the clinical development program, which affects 28 patients included in the phase IIb study AC4115321 and 10 patients recruited into the study DB2113359 (long-term safety). Sensitivity analyses of efficacy data with and without these subjects were conducted for Study AC4115321. Results of the analyses with and without these subjects were generally consistent and are included in the AC4115321 Clinical Study Report (CSR). No sensitivity analyses were performed on the safety data or in the safety study (DB2113359).

Baseline data

12-Week Integration: Demographic characteristics of subjects in the 12-Week Integration were generally similar across all treatment groups (see table below). Overall, the majority of subjects were White (85%) and male (67%); the mean age was 63.2 years. Six percent of the population were Hispanic or Latino. The mean BMI of 26.58 kg/m2 indicated that subjects tended to be slightly overweight.

Table 17. Summary of Demographic Characteristics (12-Week Integration, ITT Population)

Demographic Characteristics	Placebo N=623	UMEC 62.5 mcg N=487	UMEC 125 mcg N=698	Total N=1808
Age (years), n	623	487	698	1808
Mean	62.3	63.8	63.7	63.2
SD	8.77	9.22	8.40	8.78
Min, Max	40, 86	40, 93	40, 86	40, 93
Sex, n	623	487	698	1808
Female, n (%)	211 (34)	145 (30)	238 (34)	594 (33)
Male, n (%)	412 (66)	342 (70)	460 (66)	1214 (67)
Ethnicity, n	623	487	698	1808
Hispanic or Latino, n (%)	26 (4)	37 (8)	42 (6)	105 (6)
Not Hispanic or Latino, n (%)	597 (96)	450 (92%)	656 (94)	1703 (94)
Race, n	623	487	698	1808
African American/African heritage, n (%)	19 (3)	15 (3)	12 (2)	46 (3)
American Indian or Alaska native, n (%)	1 (<1)	3 (<1)	0	4 (<1)
Asian, n (%)	57 (9)	42 (9)	83 (12)	182 (10)
Central/South Asian heritage, n (%)	0	0	0	0
Japanese/East Asian heritage/ Southeast Asian heritage, n (%)	57 (9)	42 (9)	83 (12)	182 (10)
Native Hawaiian or other Pacific Islander, n (%)	0	0	0	0
White, n (%)	534 (86)	415 (85)	594 (85)	1543 (85)
African American/African heritage and American Indian or Alaska native andand White, n (%)	0	1 (<1)	0	1 (<1)
African American/African heritage and White, n (%)	2 (<1)	1 (<1)	0	3 (<1)
American Indian or Alaska native and White, n (%)	10 (2)	10 (2)	8 (1)	28 (2)
Asian and White, n (%)	0	0	1 (<1)	1 (<1)
Height (cm), n	623	487	698	1808
Mean	168.7	168.9	169.1	168.9
SD	9.05	9.36	8.82	9.04
Min, Max	139, 190	138, 200	142, 198	138, 200
Weight (kg)	623	487	698	1808
Mean	76.78	76.34	75.63	76.22
SD	19.449	19.591	18.457	19.107
Min, Max	34.0, 170.0	34.0, 169.0	33.8, 160.1	33.8, 170.0
Body mass index (kg/m²), n	623	487	698	1808
Mean	26.84	26.62	26.32	26.58
SD	5.959	5.891	5.696	5.841
Min, Max	12.3, 50.7	12.5, 53.9	14.4, 56.7	12.3, 56.7

Data source: Table 3.11 and Table 3.14.
Abbreviations: ITT=intent to treat; Max=maxiumum; Min=minimum; N=number of subjects; SD=standard deviation; UMEC=umeclidinium bromide

***24-Week Integration**:* Demographic characteristics of subjects in the 24-Week Integration were generally similar across all treatment groups (see table below). Overall, the majority of subjects were White (85%) and male (68%); the mean age was 63.2 years. Seven percent of subjects were Hispanic or Latino. The mean BMI of 26.53 kg/m2 indicated that subjects tended to be slightly overweight.

Table 18. Summary of Demographic Characteristics (24-Week Integration, ITT Population)

Demographic Characteristics	Placebo N=555	UMEC 62.5 mcg N=418	UMEC 125 mcg N=629	Total N=1602
Age (years) , n	555	418	629	1602
Mean	62.2	64.0	63.6	63.2
SD	8.79	9.16	8.45	8.78
Min, Max	40, 86	40, 93	40, 86	40, 93
Sex, n	555	418	629	1602
Female, (%)	185 (33)	120 (29)	211 (34)	516 (32)
Male, n (%)	370 (67)	298 (71)	418 (66)	1086 (68)
Ethnicity, n	555	418	629	1602
Hispanic or Latino, n (%)	26 (5)	37 (9)	42 (7)	105 (7)
Not Hispanic or Latino, n (%)	529 (95)	381 (91)	587 (93)	1497 (93)
Race, n	555	418	629	1602
African American/African heritage, n (%)	18 (3)	14 (3)	10 (2)	42 (3)
American Indian or Alaska native, n (%)	1 (<1)	3 (<1)	0	4 (<1)
Asian, n (%)	49 (9)	35 (8)	77 (12)	161 (10)
Central/South Asian heritage, n (%)	0	0	0	0
Japanese/East Asian heritage/ Southeast Asian heritage, n (%)	49 (9)	35 (8)	77 (12)	161 (10)
Native Hawaiian or other Pacific Islander, n (%)	0	0	0	0
White, n (%)	475 (86)	354 (85)	533 (85)	1362 (85)
African American/African heritage and American Indian or Alaska native and White, n (%)	0	1 (<1)	0	1 (<1)
African American/African heritage and White, n (%)	2 (<1)	1 (<1)	0	3 (<1)
American Indian or Alaska native and White, n (%)	10 (2)	10 (2)	8 (1)	28 (2)
Asian and White, n (%)	0	0	1 (<1)	1 (<1)
Height (cm), n	555	418	629	1602
Mean	168.5	168.7	169.1	168.8
SD	9.12	9.34	8.82	9.06
Min, Max	139, 190	138, 200	142, 198	138, 200
Weight (kg), n	555	418	629	1602
Mean	76.20	75.62	75.91	75.93
SD	19.386	18.643	18.754	18.936
Min, Max	34.0, 170.0	36.2, 153.1	33.8, 160.1	33.8, 170.0
Body mass index (kg/m²), n	555	418	629	1602
Mean	26.70	26.46	26.42	26.53
SD	6.003	5.595	5.791	5.813
Min, Max	12.3, 50.7	14.5, 47.1	14.4, 56.7	12.3, 56.7

Data source: Table 3.12 and Table 3.15.
Abbreviations: ITT=intent to treat; Max=maximum; Min=minimum; N=number of subjects; SD=standard deviation; UMEC=umeclidinium bromide

The study patient population was well defined (GOLD combined assessment of COPD category B or D) and predominantly (88%) included type B. The applicant clarified that the initial estimate of 88% of subjects falling in to Group B was based on partial data (mMRC score and exacerbations). When all relevant data (including airflow limitation) was added it is seen that 58% subjects were group D and 42% were Group B. This suggests that a reasonable representation of subjects across the grade II-IV (GOLD grading based on spirometry), was represented in the study population. Therefore it is accepted that the results are likely to be relevant to the broad COPD population.

***Exercise Integration*:** Overall, most subjects were White (96%) and a greater proportion were male (56%); the mean age was 62.1 years. No subjects were of Hispanic or Latino ethnicity. The mean BMI of 26.90 kg/m2 indicated that subjects tended to be slightly overweight.

Numbers analysed

Study DB2113361

A total of 2114 subjects were screened, 1493 subjects were randomized, and 1489 subjects were included in the ITT population; 1118 subjects completed the study. A total of four subjects were randomized, but did not receive study drug and were therefore not included in the ITT population. The number of subjects (ITT) receiving UMEC/VI, UMEC, VI and placebo were 403, 407, 404 and 275 respectively.

Study DB2113373

A total of 2210 subjects were screened, 1536 were randomized, and 1532 were included in the ITT population; 1178 subjects completed the study. Four subjects were randomized in error but did not receive study drug and were therefore not included in the ITT population. The number of subjects (ITT) receiving UMEC/VI, UMEC, VI and placebo were 413, 418, 421 and 280 respectively

Study AC4115408

Approximately 198 subjects were planned to be randomized to ensure at least 168 subjects completed the Treatment Period; 206 subjects were randomized and received at least one dose of study drug (included in the ITT population) and 168 subjects completed the study. The numbers of subjects receiving UMEC 62.5mcg, UMEC 125 mcg and placebo were 69, 69 and 68 respectively.

Study DB2113374

A total of 869 subjects were randomized and received at least one dose of study drug (included in the ITT population) and 670 subjects completed the study. The number of subjects (ITT) receiving UMEC 125, UMEC/VI 62.5/25, UMEC/VI125/25 and TIO were 222, 217, 215 and 215 respectively.

Study DB2114417

A total of 596 subjects were screened, 349 were randomized, 348 were included in the ITT population, and 258 completed the study. The number of subjects (ITT) receiving UMEC/VI 125/25, UMEC/VI 62.5/25, UMEC 125, UMEC 62.5, VI and placebo were 144, 152, 50, 49, 76 and 170 respectively.

Study DB2114418

A total of 634 subjects were screened, 309 were randomized, 307 were included in the ITT population, and 217 completed the study. The number of subjects (ITT) receiving UMEC/VI 125/25, UMEC/VI 62.5/25, UMEC 125, UMEC 62.5, VI and placebo were 128, 130, 41, 40, 64 and 151 respectively.

Study DB2113359

A total of 893 subjects were screened, 563 randomized and 562 received at least 1 dose of study drug and were included in the ITT population; 342 subjects completed the study. One subject was randomized in error but did not receive study drug and was therefore not included in the ITT population. The number of subjects for UMEC/VI, UMEC and placebo were 226, 227 and 109 respectively.

The numbers analysed were based on the intent to treat population as pre-defined in the protocols which is appropriate. The number of subjects with analysable data at any time

point and the number of subjects with analysable data at the relevant time point is provided within the outcomes in the efficacy results tables below.

Outcomes and estimation

Study AC4115408

The primary efficacy endpoint was trough FEV1 on Day 85. Trough FEV1 at Day 85 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 84 (i.e., at the Week 12 Visit). Both UMEC doses demonstrated statistically and clinically relevant (>100ml) change from baseline in trough FEV1 as compared with placebo ($p<0.001$).

There were statistically significant improvements in LS mean 0 to 6 hour weighted mean FEV1 for both the UMEC 62.5 and 125 mcg treatment groups compared with placebo at Days 1, 28, and 84 ($p<0.001$).

Statistically significant improvements in LS mean change from baseline in FEV1 over time were also demonstrated for both the UMEC 62.5 and 125 mcg treatment groups compared with placebo at all serial timepoints over 24 hours on Day 1 and Day 84 ($p<0.003$).

Supportive results for TDI focal score and SGRQ score was demonstrated. Similarly the proportion of responders according to TDI focal score was also supportive.

Study DB2113361,

The UMEC 125 mcg treatment group demonstrated statistically significant greater LS mean changes from baseline in trough FEV1 at Day 169 compared with placebo (0.160 L, $p <0.001$). This improvement in trough FEV1 met the clinically relevant change of 100ml as compared to placebo.

Clinically meaningful mean improvements in TDI scores from baseline (i.e., >1; demonstrating an improvement in dyspnoea) were observed in the UMEC 125 mcg treatment groups at Day 168. However when compared to placebo, the change in TDI score was not clinically meaningful. The LS mean treatment difference between UMEC 125mcg and placebo was also not statistically significant. (0.4, $p =0.108$)

A statistically significant greater LS mean change from baseline in 0 to 6 hour weighted mean FEV1 was demonstrated for the UMEC 125 mcg treatment group compared with placebo at Day 168 (0.178 L, $p<0.001$). However in terms of the heirarachal testing pre-specified, as the comparison for the key secondary endpoint (TDI) did not achieve statistical significance, this is not conclusive statistically.

Analysis of the primary endpoint, trough FEV1 at Day 169, demonstrated that statistical significance was obtained for all treatment comparisons in the testing hierarchy. For TDI score at Day 168, statistical significance was obtained for the comparison of UMEC/VI 125/25 mcg with placebo, but not for UMEC 125 mcg compared with placebo. Therefore the statistical results for the comparison of UMEC 125 mcg with placebo on all other endpoints should be interpreted only descriptively

Study DB2113373

The UMEC 62.5 mcg treatment group demonstrated statistically significant greater LS mean changes from baseline in the primary endpoint of trough FEV1 at Day 169 compared with placebo. (0.115L, $p<0.001$). This was also clinically relevant as it is above 100ml.

Clinically meaningful mean improvements in TDI scores from baseline (i.e., >1; demonstrating an improvement in dyspnea) were observed in the UMEC 62.5 mcg treatment group at Day 168. As compared to placebo also the change in the UMEC group was clinically meaningful and statistically significant. (1.0, P< 0.001). Statistically significant greater LS mean change from baseline in 0 to 6 hour weighted mean FEV1 was demonstrated for the UMEC 62.5 mcg treatment group compared with placebo at Day 168.

Analysis of the primary endpoint, trough FEV1 at Day 169, demonstrated that statistical significance was obtained for all comparisons in the testing hierarchy. For TDI score at Day 168, statistical significance was obtained for comparisons of UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, and VI 25 mcg with placebo but not for UMEC/VI 62.5/25 mcg compared with VI 25 mcg. Therefore, for EMA purposes the statistical results for the comparison of UMEC with placebo on all other endpoints should be interpreted only descriptively.

Study DB2113374

This study was not powered for formal statistical comparisons of UMEC 125 mcg and TIO. Only indirect comparisons can be made between these 2 treatment arms in this study. No formal statistical comparisons were performed between UMEC 125 mcg and TIO. The study was not powered nor designed to compare these 2 treatment arms. Results are presented as LS mean change from baseline for UMEC 125 mcg and TIO and are included for indirect within-study comparison

The least squares (LS) mean change from baseline trough FEV1 was 0.186 L for the UMEC 125 mcg group, and 0.149 L for the TIO group.

The 0 to 6 hour weighted mean FEV1 at Day 168 increased from baseline with both UMEC 125 mcg (0.206 L) and TIO (0.180L).

The change in TDI focal score from baseline was 1.9 for UMEC 125mcg and 2.1 for tiotropium.

Study DB2114417

To account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure was applied whereby inference for a test in the predefined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. The hierarchy only included treatment comparisons for the 2 UMEC/VI doses with placebo and comparisons for the UMEC doses with placebo were considered secondary.

The co-primary efficacy endpoints were EET postdose at Week 12 and trough FEV1 at Week 12. The comparison of UMEC/VI 125/25 mcg against placebo did not achieve statistical significance at the 5% level for the co-primary endpoint of EET at Week 12; therefore, the restrictions of the step-down testing procedure were not met and the results of all further statistical analyses are described but are not strictly inferential. Therefore this is a failed study.

The change from baseline trough FEV1 was 0.054 L for the UMEC 62.5mcg mcg group, and 0.108 L for the UMEC 125 mcg group. In comparison to placebo, the difference was 0.087 L for the UMEC 62.5mcg group and 0.108 for the UMEC 125 group.

Secondary Endpoints:

The difference from placebo in LS mean change from baseline in trough IC was 0.027 L for UMEC 62.5 mcg (p=0.587) and 0.189 L for UMEC 125 mcg (p<0.001). The differences from

placebo in LS mean change from baseline in 3-hour postdose IC was 0.114 L for UMEC 62.5 mcg (p=0.024) and 0.221 L for UMEC 125 mcg (p<0.001).

The difference from placebo in LS mean change from baseline in trough FRC was -0.282 L for UMEC 62.5 mcg (p=0.005) and -0.261 L for UMEC 125 mcg (p=0.008). The difference from placebo in LS mean change from baseline in 3-hour post dose FRC was -0.276 L for UMEC 62.5 mcg (p=0.005) and -0.375 L for UMEC 125 mcg (p<0.001).

The difference from placebo in LS mean change from baseline in trough RV was -0.376 L for UMEC 62.5 mcg (p<0.001) and -0.288 L for UMEC 125 mcg (p=0.006). The difference from placebo in LS mean change from baseline in 3 hour postdose RV changes was -0.289 L for UMEC 62.5 mcg (p=0.006) and -0.365 L for UMEC 125 mcg (p<0.001).

The differences from placebo in LS mean change from baseline in 3 hour postdose FEV1 was 0.129 L (p<0.001) for UMEC 62.5 mcg and 0.163 L for UMEC 125 mcg (p<0.001).

Study DB2114418

To account for multiplicity across treatment comparisons and endpoints, a step-down closed testing procedure was applied whereby inference for a test in the predefined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. The hierarchy only included treatment comparisons for the 2 UMEC/VI doses and comparisons for the UMEC doses were considered secondary.

Statistical significance was demonstrated for all comparisons in the testing hierarchy, so inference has been drawn for all treatment comparisons in this study.

In DB2114418, the difference in LS mean change from baseline in the 3-hour EET post-dose at week 12 as compared with placebo was statistically significant for the UMEC 125 mcg treatment but not for UMEC 62.5 mcg.

Study DB2113359

This study did not have any pre-specified efficacy endpoints but the pre-specified safety endpoint of trough FEV1 was evaluated throughout the 52-week treatment period and provides additional data supporting the efficacy of UMEC 125 mcg. The UMEC 125 mcg group demonstrated greater LS mean change from baseline in trough FEV1 compared with placebo at 6 months (0.160 L; CI: 0.083, 0.236) and 12 months (0.178 L; CI: 0.098, 0.258).

In addition, greater LS mean changes from baseline in trough FEV1 were demonstrated for the UMEC 125 mcg group compared with placebo at all additional visits (i.e. at months 1, 3, and 9)

Ancillary analyses

See chapter “Analysis performed across trials” below for relevant ancillary analysis.

Summary of main studies

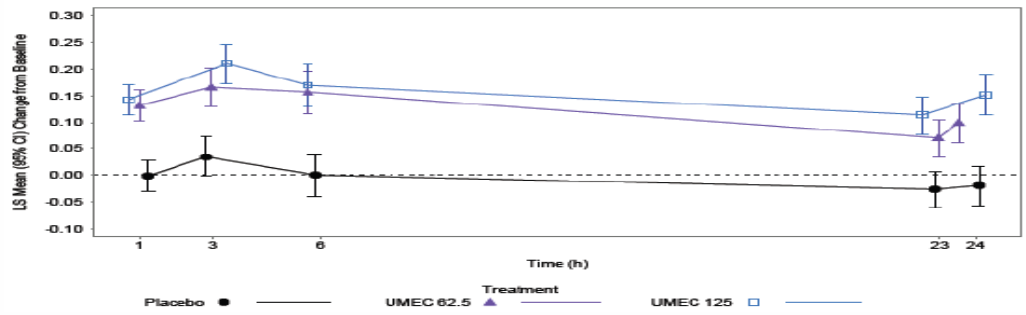
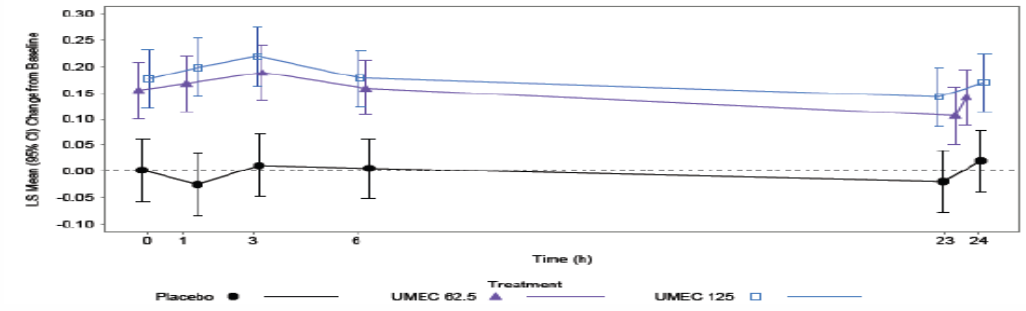
The following tables summarise the efficacy results from the seven main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Study AC4115408

Table 19. Summary of efficacy for trial AC4115408

Title: AC4115408: A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of GSK573719 Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease					
Study identifier	AC4115408				
Design	Multicenter, randomized (1:1:1), double-blind, placebo-controlled, parallel-group				
	Duration of Main phase		12 weeks		
	Duration of Run-in phase		5 to 9 days		
	Duration of Extension phase		no extension phase (safety follow-up 7 days after end of main phase)		
Hypothesis	Superiority of umeclidinium (UMEC [GSK573719]) 62.5 mcg and 125 mcg over placebo (PLA)				
Treatments groups	Placebo (PLA)		PLA, 12 weeks, 68 randomized		
	UMEC 125 mcg once daily (OD)		UMEC 125 mcg, 12 weeks, 69 randomized		
	UMEC 62.5 mcg once daily (OD)		UMEC 62.5 mcg, 12 weeks, 69 randomized		
Endpoints and definitions	Primary endpoint	Trough forced expiratory volume in 1 second (FEV_1)	Change from baseline in trough FEV_1 on Day 1, 28 and 84		
	Secondary endpoint	0-6 hour (h) weighted mean FEV_1	Change from baseline in weighted mean FEV_1 0-6 hours postdose on Day 85		
	Secondary endpoint	Serial FEV1 at 1, 3, 6, 23 and 24 h after dose	Change from baseline at Day 1 and Week 12 (Day 84)		
	Other endpoint	Transition Dyspnea Index (TDI)	TDI focal score on Days 28, 56 and 84		
Database lock	22-Mar-2012				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	The Intent-to-Treat (ITT) Population was the population of primary interest for all efficacy endpoints. The time point was Day 85 for trough FEV_1.				
Descriptive	Treatment group	PLA	UMEC 125	UMEC 62.5	

statistics and estimate variability	Number of subjects (ITT)	68	69	69
	Number of subjects at Day 85 for trough FEV_1	50	55	61
	Trough FEV_1 (L) (LS mean change from baseline)	-0.007	0.145	0.120
	Standard error (SE)	(0.0280)	(0.0268)	(0.0257)
Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups	**UMEC 125 vs. PLA**	
		Difference	0.152	
		95% CI	(0.076, 0.229)	
		P-value	**<0.001**	
	Trough FEV_1 (L)	Comparison groups	**UMEC 62.5 vs. PLA**	
		Difference	0.127	
		95% CI	(0.052, 0.202)	
		P-value	**<0.001**	
Notes	Analysis of trough FEV_1 at Day 85 demonstrated that statistical significance was obtained for all comparisons in the testing hierarchy.			
Analysis description	**Secondary Analysis**			
Analysis population and time point description	The Intent-to-Treat (ITT) Population was the population of primary interest for all efficacy endpoints. The time point was Day 85 for 0-6 hour (h) weighted mean FEV_1.			
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 125**	**UMEC 62.5**
	Number of subjects (ITT)	68	69	69
	Number of subjects at Day 85 for trough FEV_1	49	56	60
	Trough FEV_1 (L) (LS mean change from baseline)	-0.003	0.188	0.163
	Standard error (SE)	(0.0271)	(0.0256)	(0.0248)
Effect estimate per comparison	Weighed mean 0-6 h FEV_1 (L)	Comparison groups	**UMEC 125 vs. PLA**	
		Difference	0.191	
		95% CI	(0.117, 0.265)	
		P-value	**<0.001**	
	Weighed mean 0-6 h FEV_1 (L)	Comparison groups	**UMEC 62.5 vs. PLA**	

		Difference	0.166
		95% CI	(0.094, 0.239)
		P-value	**<0.001**
Notes	Analysis of weighed mean 0-6 h FEV_1 at Day 85 demonstrated that statistical significance was obtained for all comparisons in the testing hierarchy.		
Analysis description	**Secondary Analysis**		
Serial FEV1 at 1, 3, 6, 23 and 24 h after dose. Change from baseline at Day 1 and Week 12 (Day 84)	**Day 1**  **Day 84**  Data source: Modified from CSR AC4115408 Figure 6.13 and Figure 6.17.		
Notes	Statistically significant improvements in LS mean change from baseline in FEV1 over time were demonstrated for both the UMEC 62.5 and 125 mcg treatment groups compared with placebo at all serial timepoints over 24 hours on Day 1 and Day 84 ($p<0.003$)		
Analysis description	**Other analyses**		
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 85 for TDI focal score.		
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 125**	**UMEC 62.5**
	Number of subjects (ITT)	68	69	69
	Number of subjects at Day 85 for TDI focal score	49	54	61
	LS mean TDI focal score (LS mean change from baseline)	-0.3	1.0	0.7

	Standard error (SE)	(0.38)	(0.36)	(0.34)
Effect estimate per comparison	LS mean TDI focal score	Comparison groups	**UMEC 125 vs. PLA**	
		Difference	1.3	
		95% CI	(0.3, 2.3)	
		P-value	**0.01**	
	LS mean TDI focal score	Comparison groups	**UMEC 62.5 vs. PLA**	
		Difference	1.0	
		95% CI	(0, 20)	
		P-value	**0.050**	
Notes	For TDI focal score at Day 84, statistical significance was obtained for comparison of UMEC 125 mcg compared with placebo (p=0.01) but not for comparison of UMEC 62.5 mcg and placebo (p=0.05)			

Study DB2113361,

Table 20. Summary of efficacy for trial DB2113361

Title: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease		
Study identifier	DB2113361 (EUdraCT #: 2010-023348-33)	
Design	Multicenter, randomized (3:3:3:2), double-blind, placebo-controlled, parallel-group	
	Duration of Main phase Duration of Run-in phase Duration of Extension phase	24 weeks 7 to 14 days 7 ± 2day follow up following the end of the Treatment Period (Main phase); no Extension phase
Hypothesis	Superiority of umeclidinium (UMEC [GSK573719])/vilanterol (VI [GW642444]), UMEC, and VI over placebo (PLA) and contribution of each individual component to UMEC/VI combination	
Treatments groups	Placebo (PLA)	PLA, 24 weeks, 277 randomized
	UMEC 125 mcg once daily (OD)	UMEC 125 mcg, 24 weeks, 409 randomized
	VI 25 mcg OD	VI 25 mcg, 24 weeks, 404 randomized
	UMEC/VI 125/25 mcg OD	UMEC/VI 125/25 mcg, 24 weeks, 403 randomized

Endpoints and definitions	Primary endpoint	Trough forced expiratory volume in 1 second (FEV_1)	Change from baseline in troughFEV_1 on Day 169
	Secondary endpoint	0-6 hour (h) weighted mean FEV_1	Change from baseline in weighted mean FEV_1 0-6 hours postdose on Day 168
	Key Secondary endpoint	Transition Dyspnea Index (TDI) focal score	TDI focal score on Day 168
Database lock	31 May 2012		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The Intent-to-Treat (ITT) Population was the population of primary interest for all efficacy endpoints. The time point was Day 169 for trough FEV_1.				
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 125**	VI 25	UMEC/VI 125/25
	Number of subjects (ITT)	275	407	404	403
	Number of subjects at Day 169 for trough FEV_1	182	312	299	323
	Trough FEV_1 (L) (least squares [LS] mean change from baseline)	-0.031	0.129	0.093	0.207
	Standard error (SE)	(0.0153)	(0.0119)	(0.0121)	(0.0119)

Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. PLA
		Difference	0.238
		95% confidence interval (CI)	(0.200,0.276)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	**UMEC 125 vs. PLA**
		Difference	**0.160**
		95% CI	**(0.122,0.198)**
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	VI 25 vs. PLA

		Difference	0.124
		95% CI	(0.086,0.162)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. VI 25
		Difference	0.114
		95% CI	(0.081,0.148)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. UMEC 125
		Difference	0.079
		95% CI	(0.046,0.112)
		P-value	<0.001

Notes	Analysis of trough FEV_1 at Day 169 demonstrated that statistical significance was obtained for all comparisons in the testing hierarchy.				
Analysis description	**Key secondary analysis**				
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 168 for TDI focal score.				
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 125**	VI 25	UMEC/VI 125/25
	Number of subjects (ITT)	275	407	404	403
	Number of subjects at Day 168 for TDI focal score	186	313	294	324
	LS mean TDI focal score	0.8	1.2	1.3	1.8
	SE	(0.20)	(0.16)	(0.16)	(0.15)

Effect estimate per comparison	LS mean TDI focal score	Comparison groups	UMEC/VI 125/25 vs. PLA
		Difference	1.0
		95% CI	(0.5,1.5)
		P-value	<0.001
		Comparison groups	**UMEC 125 vs. PLA**
		Difference	0.4
		95% CI	(-0.1,0.9)
		P-value	**0.108**

	LS mean TDI focal score	Comparison groups	VI 25 vs. PLA
		Difference	0.5
		95% CI	(0.0,1.0)
		P-value	0.054
	LS mean TDI focal score	Comparison groups	UMEC/VI 125/25 vs. VI 25
		Difference	0.5
		95% CI	(0.1,1.0)
		P-value	0.019
	LS mean TDI focal score	Comparison groups	UMEC/VI 125/25 vs. UMEC 125
		Difference	0.6
		95% CI	(0.2,1.0)
		P-value	0.006
Notes	For TDI focal score at Day 168, statistical significance was not obtained for UMEC 125 mcg compared with placebo.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 168 for 0-6 h weighted mean FEV_1.		

Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 125**	VI 25	UMEC/VI 125/25
	Number of subjects (ITT)	275	407	404	403
	Number of subjects at Day 168 for 0-6 h weighted mean FEV_1	180	311	298	316
	0-6 h weighted mean FEV_1 (L) (LS mean change from baseline)	-0.018	0.160	0.127	0.269
	SE	(0.0150)	(0.0118)	(0.0119)	(0.0118)

Effect estimate per comparison	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. PLA
		Difference	0.287
		95% CI	(0.250,0.324)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	**UMEC 125 vs. PLA**
		Difference	0.178
		95% CI	(0.141,0.216)

		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	VI 25 vs. PLA
		Difference	0.145
		95% CI	(0.107,0.182)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. UMEC 125
		Difference	0.109
		95% CI	(0.076,0.141)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. VI 25
		Difference	0.142
		95% CI	(0.109,0.175)
		P-value	<0.001
Notes	The results of statistical analyses for 0-6 h weighted mean FEV_1 should be interpreted only descriptively based on the results of the step-down testing hierarchy described for TDI focal score.		

Study DB2113373

Table 21. Summary of efficacy for trial DB2113373

Title: A 24-Week, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of GSK573719/GW642444 Inhalation Powder and the Individual Components Delivered Once-Daily via a Novel Dry Powder Inhaler in Subjects with Chronic Obstructive Pulmonary Disease						
Study identifier	DB2113373 (EUdraCT #: 2010-023349-32)					
Design	Multicenter, randomized (3:3:3:2), double-blind, placebo-controlled, parallel-group					
	Duration of Main phase	24 weeks				
	Duration of Run-in phase	7 to 14 days				
	Duration of Extension phase	7 ± 2day follow up following the end of the Treatment Period (Main phase); no Extension phase				
Hypothesis	Superiority of UMEC/VI, UMEC, and VI over PLA and contribution of each individual component to UMEC/VI combination					
Treatments groups	PLA		PLA, 24 weeks, 280 randomized			
	UMEC 62.5 mcg OD		UMEC 62.5 mcg, 24 weeks, 421 randomized			
	VI 25 mcg OD		VI 25 mcg, 24 weeks, 421 randomized			
	UMEC/VI 62.5/25 mcg OD		UMEC/VI 62.5/25 mcg, 24 weeks, 414 randomized			
Endpoints and definitions	Primary endpoint	Trough FEV_1	Change from baseline in trough FEV_1 on Day 169			
	Secondary endpoint	0-6 h weighted mean FEV_1	Change from baseline in weighted mean FEV_1 0-6 hours postdose on Day 168			
	Key Secondary endpoint	TDI focal score	TDI focal score on Day 168			
Database lock	17 May 2012					
Results and Analysis						
Analysis description	**Primary Analysis**					
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 169 for trough FEV_1.					
Descriptive statistics and estimate variability	Treatment group		**PLA**	**UMEC 62.5**	VI 25	UMEC/VI 62.5/25
	Number of subjects (ITT)		280	418	421	413
	Number of subjects at Day 169 for trough FEV_1		201	322	317	330

	Trough FEV_1 (L) (LS mean change from baseline)	0.004	0.119	0.076	0.171
	SE	(0.0158)	(0.0126)	(0.0127)	(0.0126)

Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. PLA
		Difference	0.167
		95% CI	(0.128,0.207)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	**UMEC 62.5 vs. PLA**
		Difference	0.115
		95% CI	(0.076,0.155)
		P-value	**<0.001**
	Trough FEV_1 (L)	Comparison groups	VI 25 vs. PLA
		Difference	0.072
		95% CI	(0.032,0.112)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. VI 25
		Difference	0.095
		95% CI	(0.060,0.130)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 62.5
		Difference	0.052
		95% CI	(0.017,0.087)
		P-value	0.004
Notes	Analysis of trough FEV_1 at Day 169 demonstrated that statistical significance was obtained for all comparisons in the testing hierarchy.		
Analysis description	**Key secondary analysis**		
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 168 for TDI focal score		

Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	VI 25	UMEC/VI 62.5/25
	Number of subjects (ITT)	280	418	421	413

	Number of subjects at Day 168 for TDI focal score	204	326	317	336
	LS mean TDI focal score	1.2	2.2	2.1	2.4
	SE	(0.20)	(0.16)	(0.16)	(0.16)

Effect estimate per comparison	LS mean TDI focal score	Comparison groups	UMEC/VI 62.5/25 vs. PLA
		Difference	1.2
		95% CI	(0.7,1.7)
		P-value	<0.001
	LS mean TDI focal score	Comparison groups	**UMEC 62.5 vs. PLA**
		Difference	1.0
		95% CI	(0.5,1.5)
		P-value	**<0.001**
	LS mean TDI focal score	Comparison groups	VI 25 vs. PLA
		Difference	0.9
		95% CI	(0.4,1.4)
		P-value	<0.001
	LS mean TDI focal score	Comparison groups	UMEC/VI 62.5/25 vs. VI 25
		Difference	0.4
		95% CI	(-0.1,0.8)
		P-value	0.117
	LS mean TDI focal score	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 62.5
		Difference	0.3
		95% CI	(-0.2,0.7)
		P-value	0.244
Notes	For TDI focal score at Day 168, statistical significance was obtained for comparisons of UMEC 62.5 mcg with placebo.		
Analysis description	**Secondary analysis**		
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 168 for 0-6 h weighted mean FEV_1.		

Descriptive statistics and	Treatment group	**PLA**	**UMEC 62.5**	VI 25	UMEC/VI 62.5/25

estimate variability	Number of subjects (ITT)	280	418	421	413
	Number of subjects at Day 168 for 0-6 h weighted mean FEV_1	206	319	311	333
	0-6 h Weighted mean FEV_1 (L) (LS mean change from baseline)	0.001	0.151	0.123	0.243
	SE	(0.0158)	(0.0128)	(0.0128)	(0.0127)

Effect estimate per comparison	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. PLA
		Difference	0.242
		95% CI	(0.202,0.282)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	**UMEC 62.5 vs. PLA**
		Difference	0.150
		95% CI	(0.110,0.190)
		P-value	**<0.001**
	Weighted Mean FEV_1 (L)	Comparison groups	VI 25 vs. PLA
		Difference	0.122
		95% CI	(0.082,0.162)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. VI 25
		Difference	0.120
		95% CI	(0.084,0.155)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 62.5
		Difference	0.092
		95% CI	(0.056,0.127)
		P-value	<0.001
Notes	The results of statistical analyses for 0-6 h weighted mean FEV_1 should be interpreted only descriptively based on the results of the step-down testing hierarchy described for TDI focal score.		

Study DB2113374

Table 22. Summary of efficacy for trial DB2113374

Title: A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 with GSK573719 and with Tiotropium over 24 Weeks in Subjects with COPD					
Study identifier	DB2113374 (EUdraCT #: 2010-021802-39)				
Design	Multicenter, randomized (1:1:1:1), double-blind, double-dummy, parallel-group				
	Duration of Main phase Duration of Run-in phase Duration of Extension phase		24 weeks 7 to 10 days 7 ± 2day follow up following the end of the Treatment Period (Main phase); no Extension phase		
Hypothesis	Superiority of UMEC/VI over TIO and contribution of VI to UMEC/VI combination				
Treatments groups	UMEC 125 mcg OD		UMEC 125 mcg, 24 weeks, 222 randomized		
	UMEC/VI 62.5/25 mcg OD		UMEC/VI 62.5/25 mcg, 24 weeks, 218 randomized		
	UMEC/VI 125/25 mcg OD		UMEC/VI 125/25 mcg, 24 weeks, 217 randomized		
	TIO 18 mcg OD		TIO 18mcg, 24 weeks, 215 randomized		
Endpoints and definitions	Primary endpoint	Trough FEV_1	Change from baseline in trough FEV_1 on Day 169		
	Secondary endpoint	0-6 h Weighted mean FEV_1	Change from baseline in weighted mean FEV_1 0-6 hours postdose on Day 168		
	Other endpoint	TDI focal score	TDI focal score on Day 168		
Database lock	08 May 2012				
Results and Analysis					
Analysis description	**Primary Analysis**				
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 169 for trough FEV_1.				
Descriptive statistics and estimate variability	Treatment group	**UMEC 125**	UMEC/VI 62.5/25	UMEC/VI 125/25	**TIO**
	Number of subjects (ITT)	222	217	215	215
	Number of subjects at Day 169 for trough FEV_1	163	161	164	175
	Trough FEV_1 (L) (LS mean change from baseline)	0.186	0.208	0.223	0.149
	SE	(0.0178)	(0.0180)	(0.0179)	(0.0176)

Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. TIO		
		Difference	0.074		
		95% CI	(0.025, 0.123)		
		P-value	0.003		
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. UMEC 125		
		Difference	0.037		
		95% CI	(-0.012, 0.087)		
		P-value	0.142		
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. TIO		
		Difference	0.060		
		95% CI	(0.010, 0.109)		
		P-value	0.018		
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 125		
		Difference	0.022		
		95% CI	(-0.027, 0.072)		
		P-value	0.377		
Notes	No formal statistical comparisons were performed between UMEC 125 mcg and TIO. The study was not powered nor designed to compare these 2 treatment arms. Therefore, the data are descriptive only.				
Analysis description	**Secondary analysis**				
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 168 for 0-6 h weighted mean FEV_1				
Descriptive statistics and estimate variability	Treatment group	**UMEC 125**	UMEC/VI 62.5/25	UMEC/VI 125/25	**TIO**
	Number of subjects (ITT)	222	217	215	215
	Number of subjects at Day 168 for 0-6 h weighted mean FEV_1	161	161	164	172
	0-6 h Weighted mean FEV_1 (L) (LS mean change from baseline)	0.206	0.276	0.282	0.180
	SE	(0.0167)	(0.0168)	(0.0167)	(0.0165)
Effect estimate per comparison	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. TIO		
		Difference	0.101		

		95% CI	(0.055, 0.147)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. UMEC 125
		Difference	0.076
		95% CI	(0.029, 0.122)
		P-value	0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. TIO
		Difference	0.096
		95% CI	(0.050, 0.142)
		P-value	<0.001
	Weighted Mean FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 125
		Difference	0.070
		95% CI	(0.024, 0.117)
		P-value	0.003

Analysis description	**Other Efficacy analysis**				
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Day 168 for TDI focal score.				
Descriptive statistics and estimate variability	Treatment group	**UMEC 125**	UMEC/VI 62.5/25	UMEC/VI 125/25	**TIO**
	Number of subjects (ITT)	222	217	215	215
	Number of subjects at Day 168 for TDI focal score	163	162	167	175
	LS mean TDI focal score	1.9	2.3	2.4	2.1
	SE	(0.25)	(0.25)	(0.25)	(0.25)

Effect estimate per comparison	LS mean TDI focal score	Comparison groups	UMEC/VI 125/25 vs. TIO
		Difference	0.3
		95% CI	(-0.4, 1.0)
		P-value	0.381
	LS mean TDI focal score	Comparison groups	UMEC/VI 125/25 vs. UMEC 125
		Difference	0.5
		95% CI	(-0.2, 1.2)

		P-value	0.152
	LS mean TDI focal score	Comparison groups	UMEC/VI 62.5/25 vs. TIO
		Difference	0.2
		95% CI	(-0.5, 0.9)
		P-value	0.548
	LS mean TDI focal score	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 125
		Difference	0.4
		95% CI	(-0.3, 1.1)
		P-value	0.249

Study DB2114417

Table 23. Summary of efficacy for trial DB2114417

Title: An Exercise Endurance Study to Evaluate the Effects of Treatment of COPD Patients with a Dual Bronchodilator: GSK573719/GW642444			
Study identifier	DB2114417 (EUdraCT #: 2010-023442-75)		
Design	Multicenter, randomized (to 1 of 26 sequences), double-blind, placebo-controlled, combination and component, 2-period (12 weeks per period), incomplete block design cross-over study		
	Duration of Run-in phase Duration of Treatment Period 1 Duration of Washout Period Duration of Treatment Period 2 Duration of Extension phase:		12 to 21 days 12 weeks 14 days 12 weeks 7 day follow up following the end of the Treatment Period 2; no Extension phase
Hypothesis	Superiority of UMEC/VI over PLA and contribution of each individual component to UMEC/VI combination		
Treatments groups	PLA		PLA, 12 weeks, 170 randomized
	UMEC 62.5 mcg OD		UMEC 62.5 mcg, 12 weeks, 49 randomized
	UMEC 125 mcg OD		UMEC 125 mcg, 12 weeks, 50 randomized
	VI 25 mcg OD		VI 25 mcg, 12 weeks, 76 randomized
	UMEC/VI 62.5/25 mcg OD		UMEC/VI 62.5/25 mcg, 12 weeks, 152 randomized
	UMEC/VI 125/25 mcg OD		UMEC/VI 125/25 mcg, 12 weeks, 145 randomized
Endpoints and definitions	Co-Primary endpoints	Exercise endurance time (EET)	3-h postdose EET (measured using the endurance shuttle walk test [ESWT]) at Week 12

		Trough FEV_1	Change from baseline in trough FEV_1 at Week 12
	Secondary endpoints	Lung volumes (trough and 3-h postdose)	Inspiratory capacity (IC) at Week 12 Functional residual capacity (FRC) at Week 12 Residual volume (RV) at Week 12
		3-h postdose FEV_1	Change from baseline in 3-h postdose FEV_1 at Week 12
Database lock	13 July 2012		

Results and Analysis

Analysis description	**Co-Primary Analysis: 3-h Postdose EET (s)**						
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 for 3-hour postdose EET.						
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	170	49	50	76	152	144
	Number of subjects at Week 12 for 3-h postdose EET	145	43	44	63	131	130
	3-h postdose EET (s) (LS mean change from baseline)	36.7	**63.2**	**49.8**	26.7	58.6	69.1
	SE	(13.17)	(23.93)	(23.77)	(19.72)	(13.82)	(13.99)
Effect estimate per comparison	3-h postdose EET (s)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			32.4		
		95% CI			(-3.9,68.8)		
		P-value			0.080		
	3-h postdose EET (s)	Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			21.9		
		95% CI			(-14.2,58.0)		
		P-value			0.234		

Notes	Analysis of the 3-h postdose EET at Week 12 for the UMEC/VI 125/25 mcg vs. PLA (first comparison in the testing hierarchy) did not demonstrate statistical significance. Therefore, the results of all further statistical analyses should be interpreted only descriptively.						
Analysis description	**Co-Primary Analysis: Trough FEV_1 (L)**						
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 trough FEV_1.						
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	170	49	50	76	152	144
	Number of subjects at Week 12 for Trough FEV_1 (L)	148	43	44	64	130	132
	Trough FEV_1 (L) (LS mean change from baseline)	-0.032	0.054	**0.108**	0.067	0.178	0.136
	SE	(0.0149)	(0.0264)	(0.0263)	(0.0218)	(0.0156)	(0.0158)
Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.169		
		95% CI			(0.129, 0.209)		
		P-value			<0.001		
	Trough FEV_1 (L)	Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.211		
		95% CI			(0.172, 0.249)		
		P-value			<0.001		
Notes	The results of statistical analyses for trough FEV_1 should be interpreted only descriptively.						

Study DB2114418

Table 24. Summary of efficacy for trial DB2114418

Title: An Exercise Endurance Study to Evaluate the Effects of Treatment of COPD Patients with a Dual Bronchodilator: GSK573719/GW642444			
Study identifier	DB2114418 (EUdraCT #: 2010-023444-32)		
Design	Multicenter, randomized (to 1 of 26 sequences), double-blind, placebo-controlled, combination and component, 2-period (12 weeks per period), incomplete block design cross-over study		
	Duration of Run-in phase		12 to 21 days
	Duration of Treatment Period 1		12 weeks
	Duration of Washout Period		14 days
	Duration of Treatment Period 2		12 weeks
	Duration of Extension phase:		7 day follow up following the end of the Treatment Period 2; no Extension phase
Hypothesis	Superiority of UMEC/VI over PLA and contribution of each individual component to UMEC/VI combination		
Treatments groups	PLA		PLA, 12 weeks, 151 randomized
	UMEC 62.5 mcg OD		UMEC 62.5 mcg, 12 weeks, 41 randomized
	UMEC 125 mcg OD		UMEC 125 mcg, 12 weeks, 41 randomized
	VI 25 mcg OD		VI 25 mcg, 12 weeks, 64 randomized
	UMEC/VI 62.5/25 mcg OD		UMEC/VI 62.5/25 mcg, 12 weeks, 130 randomized
	UMEC/VI 125/25 mcg OD		UMEC/VI 125/25 mcg, 12 weeks, 128 randomized
Endpoints and definitions	Co-Primary endpoints	EET	3-h postdose EET (measured using the ESWT) at Week 12
		Trough FEV_1	Change from baseline in trough FEV_1 at Week 12
	Secondary endpoints	Lung volumes (trough and 3-h postdose)	IC at Week 12 FRC at Week 12 RV at Week 12
		3-h postdose FEV_1	Change from baseline in 3-h postdose FEV_1 at Week 12
Database lock	01 August 2012		
Results and Analysis			
Analysis description	**Co-Primary Analysis: 3-h Postdose EET (s)**		

Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 for 3-h postdose EET.						
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	151	40	41	64	130	128
	Number of subjects at Week 12 for 3-h postdose EET	117	37	32	54	115	109
	3-h postdose EET (s) (LS mean change from baseline)	**0.1**	**25.1**	**74.8**	30.7	69.5	65.9
	SE	(16.66)	(30.18)	(31.58)	(24.79)	(17.09)	(17.48)
Effect estimate per comparison	3-h postdose EET (s)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			65.8		
		95% CI			(20.3, 111.3)		
		P-value			0.005		
	3-h postdose EET (s)	Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			69.4		
		95% CI			(24.5, 114.4)		
		P-value			0.003		
Notes	In order to account for multiplicity across treatment comparisons and co-primary endpoints, a step-down closed testing procedure was applied, whereby inference for a test in the predefined hierarchy was dependent upon statistical significance having been achieved for previous tests in the hierarchy. The hierarchy consisted of the following 4 treatment comparisons, performed in the order listed: 3-h postdose EET for UMEC/VI 125/25 mcg vs. PLA; trough FEV_1 for UMEC/VI 125/25 mcg vs. PLA; 3-h postdose EET for UMEC/VI 62.5/25 mcg vs. PLA; and trough FEV_1 for UMEC/VI 62.5/25 mcg vs. PLA. Analyses of the 3-h postdose EET at Week 12 demonstrated statistical significance for both comparisons in the testing hierarchy. Only the comparison of the UMEC/VI 62.5/25 and 125/25 mcg treatments vs. PLA were powered.						
Analysis description	**Co-Primary Analysis: Trough FEV_1 (L)**						

Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 trough FEV_1.						
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	151	40	41	64	130	128
	Number of subjects at Week 12 for Trough FEV_1	119	38	33	56	117	112
	Trough FEV_1 (L) (LS mean change from baseline)	-0.043	**0.101**	**0.212**	0.069	0.200	0.218
	SE	(0.0156)	(0.0267)	(0.0287)	(0.0222)	(0.0156)	(0.0159)
Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.261		
		95% CI			(0.220, 0.303)		
		P-value			<0.001		
	Trough FEV_1 (L)	Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.243		
		95% CI			(0.202, 0.284)		
		P-value			<0.001		
Notes	Analyses of the the trough FEV_1 at Week 12 demonstrated statistical significance for both comparisons in the testing hierarchy.						
Analysis description	**Secondary Analysis: Trough and 3-h postdose IC**						
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 for trough and 3-h postdose IC.						

Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	151	40	41	64	130	128
	Number of subjects at Week 12 for Trough IC	120	38	33	56	117	111
	Trough IC (L) (LS mean change from baseline)	-0.021	0.077	0.216	0.081	0.216	0.204
	SE	(0.0271)	(0.0471)	(0.0505)	(0.0391)	(0.0274)	(0.0281)
Effect estimate per comparison	Trough IC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.225		
		95% CI			(0.154, 0.297)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.237		
		95% CI			(0.166, 0.308)		
		P-value			<0.001		
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects at Week 12 for 3-h postdose IC	120	38	33	56	117	111
	3-h postdose IC (L) (LS mean change from baseline)	-0.021	0.155	0.208	0.156	0.295	0.312
	SE	(0.0273)	(0.0465)	(0.0498)	(0.0389)	(0.0276)	(0.0283)
Effect estimate per comparison	3-h postdose IC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.334		
		95% CI			(0.264, 0.403)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		

		Difference			0.316		
		95% CI			(0.248, 0.385)		
		P-value			<0.001		
Analysis description	**Secondary Analysis: FRC**						
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 for trough and 3-h postdose FRC.						
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	151	40	41	64	130	128
	Number of subjects at Week 12 for Trough FRC	120	38	33	56	117	111
	Trough FRC (L) (LS mean change from baseline)	-0.083	-0.200	-0.263	-0.218	-0.434	-0.333
	SE	(0.0460)	(0.0804)	(0.0862)	(0.0666)	(0.0469)	(0.0480)
Effect estimate per comparison	Trough FRC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.251		
		95% CI			(-0.373, -0.128)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.351		
		95% CI			(-0.473, -0.230)		
		P-value			<0.001		

Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects at Week 12 for 3-h postdose FRC	120	38	33	56	117	111
	3-h postdose FRC (L) (LS mean change from baseline)	-0.094	-0.315	-0.405	-0.431	-0.616	-0.503
	SE	(0.0461)	(0.0786)	(0.0836)	(0.0654)	(0.0471)	(0.0480)
Effect estimate per comparison	3-h postdose FRC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.409		
		95% CI			(-0.524, -0.294)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.522		
		95% CI			(-0.636, -0.409)		
		P-value			<0.001		
Analysis description	**Secondary Analysis: RV**						
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 for trough and 3-h postdose RV.						
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	151	40	41	64	130	128
	Number of subjects at Week 12 for Trough RV	120	38	33	56	117	111
	Trough RV (L) (LS mean change from baseline)	-0.049	-0.266	-0.289	-0.291	-0.516	-0.421
	SE	(0.0491)	(0.0847)	(0.0909)	(0.0705)	(0.0500)	(0.0511)
Effect estimate	Trough RV (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		

per comparison		Difference			-0.372		
		95% CI			(-0.500, -0.244)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.466		
		95% CI			(-0.593, -0.340)		
		P-value			<0.001		
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects at Week 12 for 3-h postdose FRC	120	38	33	56	117	111
	3-h postdose RV (L) (LS mean change from baseline)	-0.071	-0.451	-0.534	-0.483	-0.714	-0.566
	SE	(0.0495)	(0.0855)	(0.0911)	(0.0711)	(0.0505)	(0.0516)
Effect estimate per comparison	3-h postdose RV (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.495		
		95% CI			(-0.622, -0.369)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.643		
		95% CI			(-0.768, -0.518)		
		P-value			<0.001		
Analysis description	**Secondary Analysis: 3-h postdose FEV_1**						
Analysis population and time point description	The ITT Population was the population of primary interest for all efficacy endpoints. The time point was Week 12 for 3-h postdose FEV_1.						

Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 62.5**	**UMEC 125**	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25
	Number of subjects (ITT)	151	40	41	64	130	128
	Number of subjects at Week 12 for 3-h postdose FEV_1	120	38	33	56	117	110
	3-h postdose FEV_1 (L) (LS mean change from baseline)	-0.019	0.168	0.215	0.143	0.297	0.343
	SE	(0.0175)	(0.0296)	(0.0317)	(0.0246)	(0.0175)	(0.0179)
Effect estimate per comparison	3-h postdose FEV_1 (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.362		
		95% CI			(0.317, 0.407)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.316		
		95% CI			(0.272, 0.361)		
		P-value			<0.001		

Study DB2113359

Table 25. Summary of efficacy for trial DB2113359

Title: A 52 Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Evaluate the Safety and Tolerability of GSK573719 125 mcg once-daily alone and in combination with GW642444 25 mcg once-daily via novel Dry Powder Inhaler (NDPI) in Subjects with Chronic Obstructive Pulmonary Disease (COPD)		
Study identifier	DB2113359 (EUdraCT #: 2010-023417-54)	
Design	Multicenter, randomized (2:2:1), double-blind, placebo-controlled, parallel-group	
	Duration of Main phase	52 weeks
	Duration of Run-in phase	7 to 10 days
	Duration of Extension phase	7 ± 2 day follow up following the end of the Treatment Period (Main phase); no Extension phase
Hypothesis	This was a long-term safety and tolerability study. No efficacy endpoints were specified. Trough FEV_1 was measured as a safety parameter.	
Treatments groups	PLA	PLA, 52 weeks, 109 randomized

	UMEC 125 mcg OD		UMEC 125 mcg, 52 weeks, 227 randomized
	UMEC/VI 125/25 mcg OD		UMEC/VI 125/25 mcg, 52 weeks, 227 randomized
Endpoints and definitions	Safety endpoint	Trough FEV_1	Change from baseline in trough FEV_1 at Months 6 and 12
Database lock	10 August 2012		

Results and Analysis

Analysis description	**FEV_1 Results**			
Analysis population and time point description	The ITT Population was the population of primary interest for all data analyses. Results are presented for trough FEV_1 at Months 6 and 12.			
Descriptive statistics and estimate variability	Treatment group	**PLA**	**UMEC 125**	UMEC/VI 125/25
	Number of subjects (ITT)	109	227	226
	Number of subjects at Month 6 for trough FEV_1	79	163	178
	Trough FEV_1 (L) (LS mean change from baseline at Month 6)	**-0.015**	**0.144**	0.181
	SE	(0.0320)	(0.0221)	(0.0214)
	Number of subjects at Month 12 for trough FEV_1	66	132	143
	Trough FEV_1 (L) (LS mean change from baseline at Month 12)	**-0.045**	**0.133**	0.186
	SE	(0.0332)	(0.0232)	(0.0224)

Comparisons	Trough FEV_1 (L) at Month 6	Comparison groups	UMEC/VI 125/25 vs. PLA
		Difference	0.197
		95% CI	(0.121,0.272)
		Comparison groups	**UMEC 125 vs. PLA**
		Difference	**0.160**
		95% CI	(0.083,0.236)
	Trough FEV_1 (L) at Month 12	Comparison groups	UMEC/VI 125/25 vs. PLA
		Difference	0.231
		95% CI	(0.153,0.310)
		Comparison groups	**UMEC 125 vs. PLA**

		Difference	**0.178**
		95% CI	(0.098,0.258)

Analysis performed across trials (pooled analyses and meta-analysis)

Integration was performed for the four Efficacy Studies as the designs were very similar. Two sets of integration were performed: 1) a 12-week integration of Study AC4115408 and the first 12 weeks from Studies DB2113361, DB2113363 and DB2113374 (Note that the primary efficacy endpoint for study AC4115408 was trough FEV1 on Day 85, but this time point was not assessed in the 24-week studies. The trough FEV1 at Day 84, which was collected in all studies, has been integrated.), 2) a 24-week integration of Studies DB2113361, DB2113363 and DB2113374.

Trough FEV - 12-Week Integration: For the integrated analysis, both doses of UMEC demonstrated statistically significant improvements in LS mean changes from baseline in trough FEV1 at Day 84 compared with placebo (130 ml and 133 ml, respectively; p<0.001; see table below).

Table 26. Primary Efficacy Analysis: Trough FEV1 (L) at Day 84 (12-Week Integration, ITT Population)

	Placebo (N=623	UMEC 62.5 mcg N=487	UMEC 125 mcg N=698
n [a]	614	485	689
n [b]	496	419	588
LS Mean (SE)	1.226 (0.0095)	1.364 (0.0109)	1.362 (0.0090)
LS Mean Change (SE)	-0.006 (0.0095)	0.133 (0.0109)	0.130 (0.0090)
Column vs Placebo			
Difference		0.139	0.136
95% CI		(0.111, 0.167)	(0.110, 0.162)
p-value		<0.001	<0.001

Data source: Table 3.45
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent to treat; LS=least squares; N=number of subjects; SE=standard error; UMEC=umeclidinium bromide.
Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 and 5 minutes predose on Day 1), smoking status, center group, Day, Day by baseline, and Day by treatment interactions.
a. Number of subjects with analyzable data for 1 or more time points.
b. Number of subjects with analyzable data at the given time point.

Trough FEV1 - 24-Week Integration: For the integrated analysis, both doses of UMEC demonstrated statistically significantc improvements in LS mean changes from baseline in trough FEV1 at Day 169 compared with placebo (146 ml and 125 ml, respectively; p<0.001; see table below).

Table 27. Primary Efficacy Analysis: Trough FEV1 (L) at Day 169 (24-Week Integration, ITT Population).

	Placebo N=555	UMEC 62.5 mcg N=418	UMEC 125 mcg N=629)
n [a]	547	416	623
n [b]	383	322	475
LS Mean (SE)	1.223 (0.0113)	1.356 (0.0131)	1.377 (0.0105)
LS Mean Change (SE)	-0.008 (0.0113)	0.125 (0.0131)	0.146 (0.0105)
Column vs Placebo			
Difference		0.133	0.154
95% CI		(0.100, 0.167)	(0.123, 0.184)
p-value		<0.001	<0.001

Data source: Table 3.69

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in one second; ITT=intent to treat; LS=least squares; N=number of subjects; SE=standard error; UMEC=umeclidinium bromide.

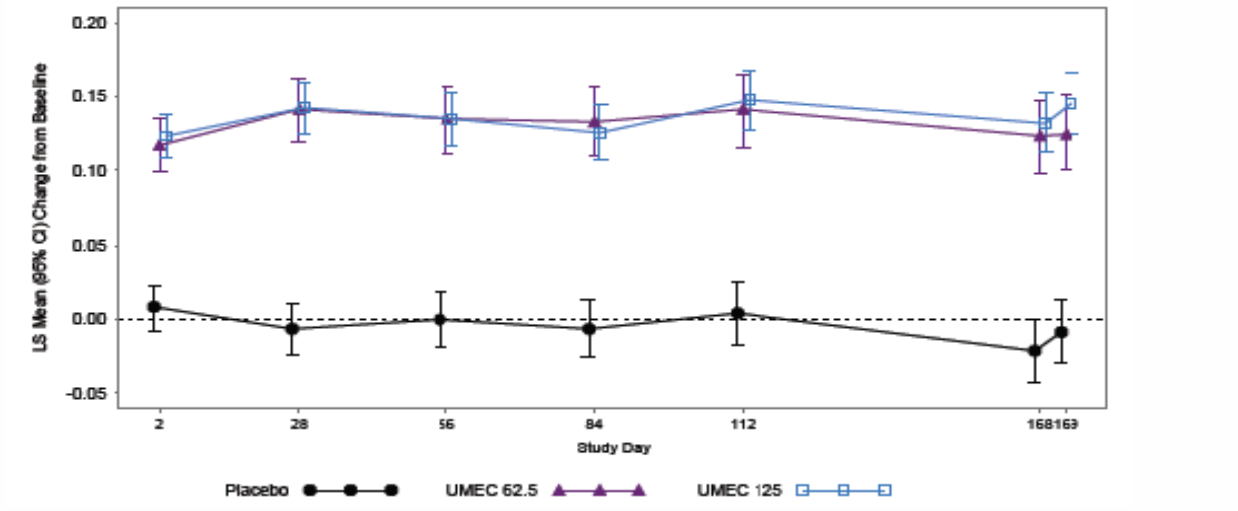
Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 and 5 minutes predose on Day 1), smoking status, center group, Day, Day by baseline, and Day by treatment interactions.

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

b. Number of subjects with analyzable data at the given time point.

Temporal pattern of increases in trough FEV1: For the 24-Week Integration there were statistically significant improvements in LS mean changes from baseline in trough FEV1 for both doses of UMEC compared with placebo at all visits (p<0.001; Figure E-03).

Figure 6. Least Squares Mean (95% CI) Change from Baseline in Trough FEV1 (L) (24-Week Integration, ITT Population)



Data source: Figure 3.15

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; UMEC=umeclidinium bromide

Note: Analysis used a repeated measures model with terms for study, treatment, smoking status at screening, baseline FEV_1 (mean of 30 and 5 minutes predose on Day 1), day, geographical region, and day by baseline and day by treatment interactions.

Weighted mean FEV1 0-6h post-dose - 12-week integration: Both UMEC doses (125 mcg and 62.5 mcg demonstrated a statistically significant difference in LS mean change from baseline compared with placebo (169 and 165 ml respectively; p<0.001 for both comparisons). The results were similar in the 24-week integration (180 ml and 163 ml; p<0.001 for both comparisons).

TDI – 24-week integration: Both doses demonstrated statistically significant improvements in LS mean TDI focal score compared with placebo (p≤0.007). However, the differences were not clearly above 1-point considered clinically relevant for the differences between UME 125 and PBO (0.6; 0.2 to 1.00) or UMEC 62.5 mcg and PBO (0.9; 95%CI: 0.5,1.4)

TDI responder analysis - 24-Week Integration: The number of responders according to TDI focal sore for UMEC 62.5 mcg was 207/394 (53%) and for UMEC 125 mcg was 255/579 (44%) compared with 176/494 (36%) for placebo. The odds of being a TDI responder vs. a non-responder were statistically significantly greater compared with placebo for both UMEC doses (UMEC 125 vs PBO: 1.6; 95%CI: 1.2, 2.2) (UMEC 62.5 vs PBO Odds Ratio 1.6; 95%CI: 1.2, 2.2; p<0.001 for both comparisons.

Mean number of puffs of rescue medication per day - 24-Week Integration: Statistical analysis of the integrated data demonstrated that treatment with UMEC 125 mcg (Diff: -0.72; p<0.001) but not the 62.5 mcg dose (Diff.: -0.29; p=0.180), resulted in a statistically significant reduction from baseline over Weeks 1 to 24 in the mean number of puffs of rescue medication per day compared with placebo.

SGRQ – 24-week integration: The comparisons with placebo in the 24-Week Integration of the Efficacy Studies were also statistically significant for both UMEC doses at Day 168 (-3.71 [95% CI -5.64, -1.77] p<0.001 for UMEC 62.5 mcg and -2.23 [95% CI -4.03, -0.43] p=0.015 for UMEC 125 mcg).

SGRQ responders: In the 12-Week Integration, the ratio of the odds of being an SGRQ responder vs. a nonresponder compared with placebo was 1.5 (95% CI 1.2, 2.0; p=0.002) for UMEC 62.5 mcg and 1.9 (95% CI1.4, 2.4 p<0.001) for UMEC 125 mcg at Day 84. In the 24-Week Integration, the ratio of the odds of being a SGRQ responder vs. a non-responder compared with placebo was 1.5 (95% CI 1.1, 2.0; p=0.010) for UMEC 62.5 mcg and 1.4 (95% CI1.1, 1.8 p=0.021) for UMEC 125 mcg at Day 168.

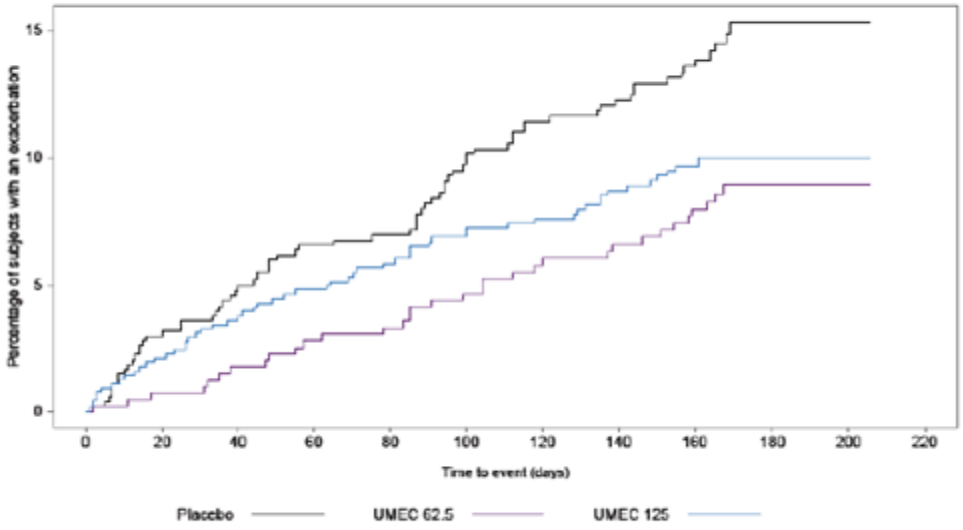
COPD exacerbations - 24-Week Integration: both doses of UMEC demonstrated a lower risk of COPD exacerbation compared with placebo (hazard ratio 0.6 [95% CI 0.4, 0.9] and 0.5 [95% CI 0.4, 0.8] for the UMEC 62.5 and 125 mcg doses, indicating a risk reduction of 40% and 50%, respectively).

Table 28. Time to First On-Treatment COPD Exacerbation (24-Week Integration, ITT Population)

	Placebo N=555	UMEC 62.5 mcg N=418	UMEC 125 mcg N=629
Number of Subjects with Event	73 (13%)	33 (8%)	58 (9%)
Number of Subjects Censored	482 (87%)	385 (92%)	571 (91%)
Probability of Having Event (%)	15.3	8.9	10.0
95% CI	(12.3, 19.0)	(6.4, 12.4)	(7.8, 12.7)
Median Time to Onset (days) [a]	NA	NA	NA
Column vs Placebo			
Hazard Ratio		0.6	0.5
95% CI		(0.4, 0.9)	(0.4 ,0.8)
p-value		0.013	0.001

Data source: Table 3.185
Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; N=number of subjects; NA=not applicable; UMEC=umeclidinium bromide
Note: Hazard ratios and CIs are from a Cox proportional hazards model stratified by study and with covariates of treatment, smoking status at screening and geographical region.
a. Kaplan-Meier estimate. If greater than 50% of data is censored then the median is not applicable.

Figure 29 Kaplan-Meier Plot of Time to First On-treatment COPD Exacerbation (24 Week Integration, ITT Population)



Data source: Figure 3.94
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent to treat; UMEC= umeclidinium bromide.

Subgroup Analyses

The results of subgroup analyses of both intrinsic and extrinsic factors that included age, gender, race, geographical region, treatment-naïve status, ICS use, GOLD status (I/II and III/IV), smoking status, reversibility to salbutamol, and reversibility to salbutamol and ipratropium indicated that there was no clinically significant impact of these factors on treatment effects.

While interactions of treatment were statistically significant for some of the subgroups for trough FEV1, Weighted Mean FEV1, and TDI at either Day 84 and/or Day 168/169, the response to treatment with both the UMEC 62.5 mcg and UMEC 125 mcg doses were greater than placebo and differences in magnitude across the subgroups based on intrinsic

and extrinsic factors and in the overall COPD population were not considered clinically relevant.

12-Week Integration: The numbers of subjects in each subgroup is summarized in table below.

Table 29. Summary of Number of Subjects by Subgroup (12-Week Integration ITT Population)

	Number (%) of Subjects			
Subgroups	Placebo N=623	UMEC 62.5 mcg N=487	UMEC 125 mcg N=698	Total N=1808
Sex, n	623	487	698	1808
Female	211 (34)	145 (30)	238 (34)	594 (33)
Male	412 (66)	342 (70)	460 (66)	1214 (67)
Age (years), n	623	487	698	1808
≤64	370 (59)	257 (53)	371 (53)	998 (55)
65 to 74	200 (32)	171 (35)	256 (37)	627 (35)
75 to 84	52 (8)	56 (11)	69 (10)	177 (10)
≥85	1 (<1)	3 (<1)	2 (<1)	6 (<1)
Race, n	623	487	698	1808
African American/ African heritage	19 (3)	15 (3)	12 (2)	46 (3)
American Indian or Alaska native	1 (<1)	3 (<1)	0	4 (<1)
Asian	57 (9)	42 (9)	83 (12)	182 (10)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	534 (86)	415 (85)	594 (85)	1543 (85)
Mixed Race	12 (2)	12 (2)	9 (1)	33 (2)
East Asian	34 (5)	27 (6)	62 (9)	123 (7)
Not East Asian	589 (95)	460 (94)	636 (91)	1685 (93)
Geographic regions [a], n	623	487	698	1808
United States	150 (24)	135 (28)	161 (23)	446 (25)
European	313 (50)	169 (35)	358 (51)	840 (46)
Other	160 (26)	183 (38)	179 (26)	522 (29)
United States	150 (24)	135 (28)	161 (23)	446 (25)
Non-United States	473 (76)	352 (72)	537 (77)	1362 (75)
Treatment naïve, n	623	487	698	1808
Treatment naïve	208 (33)	152 (31)	206 (30)	566 (31)
Not treatment naïve	415 (67)	335 (69)	492 (70)	1242 (69)
ICS use at Screening, n	623	487	698	1808
ICS user	293 (47)	234 (48)	333 (48)	860 (48)
ICS non-user	330 (53)	253 (52)	365 (52)	948 (52)
GOLD status, n	622	486	696	1804
I and II: FEV_1≥50% predicted	273 (44)	216 (44)	314 (45)	803 (45)
III and IV: FEV_1≤50% predicted	349 (56)	270 (56)	382 (55)	1001 (55)
History of smoking use, n	623	487	698	1808
Current smoker	329 (53)	244 (50)	353 (51)	926 (51)
Former smoker	294 (47)	243 (50)	345 (49)	882 (49)
Reversibility to salbutamol, n	621	483	694	1798
Not reversible	431 (69)	349 (72)	473 (68)	1253 (70)
Reversible	190 (31)	134 (28)	221 (32)	545 (30)
Reversibility to salbutamol and ipatropium, n	610	477	686	1773
Not reversible	291 (48)	226 (47)	298 (43)	815 (46)
Reversible	319 (52)	251 (53)	388 (57)	958 (54)

Data source: Table 3.08.
Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD= Global Initiative for Obstructive Lung Disease; ICS= inhaled corticosteroid; ITT=intent to treat; N=number of subjects; UMEC=umeclidinium bromide.
a. Other region includes Argentina, Australia, Canada, Chile, Japan, Korea, Mexico, Philippines, Russia, South Africa, Thailand, Ukraine.

Summary results for subgroup analyses

In the 12-Week Integration:

- Interactions of treatment with gender (male/female) and age (<65 vs. ≥65 years) and geographical region (US vs non-US) were not statistically significant for any of the primary and secondary efficacy endpoints of trough FEV1 at Day 84, 0 to 6 hour weighted mean FEV1 at Day 84, and TDI score at Day 84.

- Interactions of treatment with the following factors were investigated for the primary efficacy endpoints only and were not statistically significant at Day 84: treatment naïve status, ICS use, and smoking status (former or current). The response to UMEC in GOLD stage II subjects was greater than that in GOLD stage III/IV subjects, but both UMEC doses were consistently better than placebo in both GOLD groups and differences in the

magnitude of treatment response between GOLD groups were not considered clinically relevant.

- Interactions of treatment with race (White vs. non-White) were statistically significant for the primary efficacy endpoint of trough FEV1 at Day 84 and for 0 to 6-hour weighted mean FEV1 at Day 84. Both doses of UMEC were generally better than placebo for both endpoints in all race subgroups and differences in magnitude of treatment response between race subgroups were not considered clinically relevant.

- The interaction of treatment with race for TDI score at Day 84 was not statistically significant.

- The interactions of treatment with reversibility to salbutamol were statistically significant for trough FEV1 at Day 84 and for 0 to 6 hour weighted mean FEV1 at Day 84. The response to UMEC in reversible subjects was greater than that in nonreversible subjects for both endpoints, but both UMEC doses were consistently better than placebo in both reversibility groups and the differences in the magnitude of treatment response between reversibility groups were not considered clinically relevant.

- The interactions of treatment with reversibility to salbutamol and ipratropium were statistically significant for all primary and secondary endpoints tested. The response to UMEC in reversible subjects was greater than that in non-reversible subjects for all endpoints, but both UMEC doses were consistently better than placebo in both reversibility groups (Figure 53) and differences of magnitude of treatment response between reversibility groups were not considered clinically relevant.

In the 24-Week Integration:

- Interactions with treatment for gender (male/female) and age (<65 vs. ≥65 years) geographical region (US vs non-US) were not statistically significant for any of the primary and secondary efficacy endpoints of trough FEV1 at Day 169, 0 to 6 hour weighted mean FEV1 at Day 168, and TDI score at Day 168.

- Interactions of treatment with the following factors were investigated for the primary efficacy endpoints only and were not statistically significant at Day 169: GOLD classification (I/II and III/IV) or smoking status (former or current). There was evidence for a treatment by treatment naïve status interaction and a treatment by ICS use interaction. Both UMEC doses were consistently better than placebo for each category within each subgroup; differences in magnitude of response between categories were not considered clinically relevant

- The interactions of treatment with race (White vs. non-White) were statistically significant for the primary efficacy endpoint of trough FEV1 at Day 169 and for 0 to 6 hour weighted mean FEV1 at Day 168. Both UMEC doses were generally better than placebo in all race subgroups for both endpoints and differences in treatment response between race subgroups were not considered clinically relevant.

- Interactions of treatment with race for TDI score at Day 168 were not statistically significant.

- The interactions of treatment with reversibility to salbutamol were statistically significant for trough FEV1 at Day 169 and for 0 to 6 hour weighted mean FEV1 at Day 168. The response to UMEC in reversible subjects was greater than that in nonreversible subjects for both endpoints, but both UMEC doses were consistently better than placebo in both

reversibility groups and the differences in the magnitude of treatment response between reversibility groups were not considered clinically relevant.

- The interactions of treatment with reversibility to salbutamol and ipratropium were statistically significant for all primary and secondary endpoints tested. The response to UMEC in reversible subjects was greater than that in non-reversible subjects for all endpoints, but both UMEC doses were consistently better than placebo in both reversibility groups and the differences in the magnitude of treatment response between reversibility groups were not considered clinically relevant.

Severe and very severe COPD: The proportion of severe GOLD stage III subjects in the Efficacy Studies (45%; n= 723) and very severe GOLD stage IV subjects (10%; n = 124; 24-week integration) is representative of what is expected from clinical practice (Jones *et al*. *Respir Med*. 2011, 105:57-66), and compares favourably with the GOLD stage IV representation in recent applications (e.g.: aclidinium bromide; glycopyrronium bromide). In general, the relative improvements in lung function compared with placebo were consistent with both doses of UMEC across all of the GOLD stages. In absolute term, as the GOLD I-IV staging is based on lung function (percentage predicted FEV1), it is not unexpected that there was a decrease in the magnitude of the change from baseline in trough and 0-6 hour weighted mean FEV1 from GOLD stage II to GOLD stage IV. However, for the symptomatic endpoint of TDI focal score and for the respiratory-related quality of life measured with SGRQ, the improvements seen in the GOLD stage IV subjects tended to be comparable to those seen in the severe GOLD stage III subjects, suggesting that subjects with very severe GOLD stage IV also experienced a benefit with UMEC treatment in addition to improvements in lung function. There was variation with the TDI focal score and SGRQ endpoints at a few timepoints which may have been driven partly by the endpoints themselves which are more subjective and partly by the relatively small numbers of subjects at some timepoints. The number of subjects experiencing an exacerbation, split by GOLD stage, was relatively small and increased from GOLD stage II to IV. However, irrespective of GOLD stage, the percentage of subjects with an exacerbation was lower in the active treatment groups compared with placebo. There were no trends or patterns in the treatment response based on GOLD stage to suggest there was a difference in efficacy between UMEC 62.5 mcg and 125 mcg.

History of cardiovascular disease at baseline:

In the 24-Week Integration, the proportion of subjects with CV risk factors present at screening was 58% in the UMEC 62.5 mcg group, 55% in the UMEC 125 mcg group, and 58% in the placebo group. Conditions that were included under the Cardiovascular Risk Factors category were ‘Angina pectoris’, ‘Myocardial Infarction’, ‘Stroke’, ‘Diabetes’, ‘Hypertension’ and ‘Hyperlipidemia’. Overall there were no consistent differences in the effect of UMEC on any of the efficacy endpoints between the groups of subjects with and without CV risk factors at screening.

Clinical studies in special populations

All studies have been conducted in a generally broad GOLD category Type II to IV COPD patient population. There are no other studies in special populations. Any particular population which is not adequately covered in this development is addressed by suitable restrictions in the labelling.

Supportive studies

There are no other studies other than the ones mentioned above which are supportive of the efficacy of UMEC alone in COPD.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The four primary efficacy studies (12-week AC4115408 and 24-week DB2113361, DB2113363 and DB2113374) were all double-blind, randomized, controlled parallel group studies. Three were placebo controlled and one was active controlled study. The studies were all multicentre and all started around the beginning of 2011 and were completed by mid-2012. The studies appear to be well conducted and only one study centre was detected a deviation from GCP resulting in unblinding. However, only 20 subjects were recruited in to one primary efficacy study from this centre and the removal of the 20 subjects did not impact on the results. Therefore it is accepted that this does not affect the conclusions drawn from the primary efficacy studies. All the four primary efficacy studies evaluated the lung function endpoint of change in trough FEV1 from baseline as the primary efficacy endpoint. The symptomatic endpoint of TDI focal score was a secondary endpoint in all the primary efficacy studies. The treatment duration in these studies was 12-24 weeks. The primary efficacy studies all had at least three treatment groups and there were a number of statistical comparisons planned. Therefore, to avoid multiplicity, a hierarchal system of statistical testing was pre-specified for each study.

Two exercise studies have been submitted as additional evidence of efficacy. These were double-blind, randomized, placebo-controlled, incomplete-block, 2-period cross-over studies, where each treatment period was for 12 weeks. These studies were also conducted around the same time as the primary efficacy studies and appear to be well conducted. These studies had co-primary endpoints of change in exercise endurance time and trough FEV1. The exercise studies also had a number of parallel treatment arms in each study and different comparisons were planned. Therefore to avoid multiplicity, a hierarchal system of statistical testing was pre-specified for each study.

In addition a long-term safety study which also collected data on trough FEV1 was performed to provide evidence on maintenance of treatment effects over the long-term. This was a double-blind, placebo controlled, randomized study for 52 weeks.

Efficacy data and additional analyses

Lung function

The efficacy data from the primary efficacy studies indicate that both doses of UMEC produce a statistically significant and clinically relevant improvement in trough FEV1 as compared to placebo (24-week integration: 146 ml improvement with UMEC 125 and 125 ml with UMEC 62.5, respectively; $p<0.001$).

Symptoms

TDI: not always the differences versus PBO reached the minimally important difference (> 1 unit). In individual studies statistically and clinically relevant improvements in TDI focal score were found in study AC4115408 and in the TIO study, but not in study DB2113361. In the 24-week integration, both doses demonstrated statistically significant improvements in LS mean TDI focal score compared with placebo ($p\leq0.007$). However, the differences

were not clearly above 1-point considered clinically relevant for the differences between UMEC 125 and PBO (0.6; 0.2 to 1.00) or UMEC 62.5 mcg and PBO (0.9; 95%CI: 0.5,1.4). The number of responders according to TDI focal sore for UMEC 62.5 mcg was 207/394 (53%) and for UMEC 125 mcg was 255/579 (44%) compared with 176/494 (36%) for placebo. The odds of being a TDI responder vs. a non-responder were statistically significantly greater compared with placebo for both UMEC doses (UMEC 125 vs PBO: 1.6; 95%CI: 1.2, 2.2) (UMEC 62.5 vs PBO Odds Ratio 1.6; 95%CI: 1.2, 2.2; p<0.001 for both comparisons. These results are in line with the results obtained for other LAMA recently authorised in the EU (aclidinium bromide).

SGRQ: The comparisons with placebo in the 24-Week integration of the Efficacy Studies were statistically significant for both UMEC doses for change in SGRQ at Day 168 (-3.71 [95% CI -5.64, -1.77] p<0.001 for UMEC 62.5 mcg and -2.23 [95% CI -4.03, -0.43] p=0.015 for UMEC 125 mcg), but were below the 4 points considered clinically relevant. In the 24-Week Integration, the ratio of the odds of being a SGRQ responder vs. a non-responder compared with placebo was 1.5 (95% CI 1.1, 2.0; p=0.010) for UMEC 62.5 mcg and 1.4 for UMEC 125 mcg (95% CI1.1, 1.8 p=0.021). Results were very similar in the 12-week integration. These results are in line with the results obtained for other LAMA recently authorised in the EU (aclidinium bromide).

Rescue medication use: Treatment with UMEC 125 mcg (Diff: -0.72; p<0.001) but not the 62.5 mcg dose (Diff.: -0.29; p=0.180), resulted in a statistically significant reduction from baseline over Weeks 1 to 24 in the mean number of puffs of rescue medication per day compared with placebo.

COPD exacerbations: Both doses of UMEC demonstrated a lower risk of COPD exacerbation compared with placebo (hazard ratio 0.6 [95% CI 0.4, 0.9] and 0.5 [95% CI 0.4, 0.8] for the UMEC 62.5 and 125 mcg doses, indicating a risk reduction of 40% and 50%, respectively).

Studies with active comparators:

Only the 24-week study DB2113374 included an active-controlled group (TIO), but neither formal statistical comparisons were planned nor conducted post-hoc between UMEC mcg and TIO. In addition, only the UMEC 125 mcg dose was tested. For FEV1, the least squares (LS) mean change from baseline trough FEV1 was 186 ml for the UMEC 125 mcg group and 149 ml for the TIO group. The weighted mean FEV1 0-6 h at Day 168 increased from baseline with both UMEC 125 mcg (206 ml) and TIO (180 ml). The LS mean change from baseline TDI focal score was 1.9 for the UMEC 125 mcg group and 2.1 for the TIO group. COPD exacerbation rate was 12% (26 of 222 patients) with UMEC 125 mcg and 7% (14/215) with TIO. The study was not either powered or designed to compare these 2 treatment arms. Therefore, no definitive conclusions can be made.

According to the EMA COPD guideline (Guideline on the clinical investigation of medicinal products in the treatment of chronic obstructive pulmonary disease (COPD) - EMA/CHMP/483572/2012 -corr1), “for symptomatic treatment, the most useful comparators are either a placebo and an active comparator or an active comparator alone depending on the type of drug being studied and its place in the therapeutic armamentarium.”

No direct formal comparison of the efficacy of UMEC 62.5 mcg against tiotropium has been conducted. However, the DB2113374 study showed that the efficacy of UMEC 125 mcg was similar to TIO 18 mcg. Given the similarity in the efficacy profile of UMEC 62.5 mcg and UMEC 125 mcg, the results of this study may be an indirect estimation of the expected

effect size of UMEC 62.5 mcg in relation to tiotropium. Comparisons with published literature also suggest that the improvements seen with UMEC 62.5 mcg in efficacy (e.g.: FEV1, SGRQ, TDI score) are similar to what has been observed in studies with other LAMAs (e.g.: aclidinium bromide, glycopyrronium bromide) in COPD patients [Karabis et al. *Int J COPD*. 2013;8:405-23].

Long-term efficacy

Long-term effects of UMEC 125 mcg (for approximately 52-weeks) were assessed in study DB2113359. The UMEC 125 mcg group demonstrated greater LS mean change from baseline in trough FEV1 compared with placebo at 6 months (160 ml; CI: 83 to 236) and 12 months (178 ml; CI: 98 to 258). In addition, greater LS mean changes from baseline in trough FEV1 were demonstrated for the UMEC 125 mcg group compared with placebo at all additional visits (i.e. at months 1, 3, and 9). In this long term study, analysis of time to first COPD exacerbation indicated that treatment with UMEC 125 mcg resulted in a lower risk of COPD exacerbation (with marginal significance) compared with placebo (hazard ratio 0.6, [95% CI: 0.3, 1.0], risk reduction 40%).

The study was not designed to assess the long-term effects of the UMEC 62.5 mcg dose but available data from the 24-Week Integration of the Efficacy Studies suggest that the efficacy of UMEC is maintained for both UMEC 62.5 mcg and 125 mcg over the entire 6-month treatment period across measures of lung function, dyspnea, health-related quality of life, and COPD exacerbation. Given the similarity in efficacy observed between the 2 UMEC doses during the 6 month studies and the persistence of effect observed with UMEC 125 mcg in the long-term safety study, it is expected that UMEC 62.5 mcg would demonstrate sustained efficacy at 1 year, similar to that observed with UMEC 125 mcg.

Efficacy by disease severity

The patient population selected for the primary efficacy studies included patients with moderate to very severe COPD, according to GOLD classification based on airflow limitation whereas in the Long-term Safety study (DB2113359) patients with severe COPD were excluded due to safety concerns of having subjects with very severe airflow obstruction on placebo treatment for 52 weeks.

Therefore the applicant provided additional data by disease severity showing that the proportion of severe GOLD stage III subjects in the Efficacy Studies (45%; n= 723) and very severe GOLD stage IV subjects (10%; n = 124; 24-week integration) is representative of what is expected from clinical practice (Jones et al. Respir Med. 2011, 105:57-66), and compares favourably with the GOLD stage IV representation in recent applications (e.g.: aclidinium bromide; glycopyrronium bromide).

In general, the relative improvements in lung function compared with placebo were consistent with both doses of UMEC across all of the GOLD stages. In absolute term, as the GOLD I-IV staging is based on lung function (percentage predicted FEV1), it is not unexpected that there was a decrease in the magnitude of the change from baseline in trough and 0-6 hour weighted mean FEV1 from GOLD stage II to GOLD stage IV. However, for the symptomatic endpoint of TDI focal score and for the respiratory-related quality of life measured with SGRQ, the improvements seen in the GOLD stage IV subjects tended to be comparable to those seen in the severe GOLD stage III subjects, suggesting that subjects with very severe GOLD stage IV also experienced a benefit with UMEC treatment in addition to improvements in lung function. There was variation with the TDI focal score and SGRQ endpoints at a few timepoints which may have been driven partly by the endpoints

themselves which are more subjective and partly by the relatively small numbers of subjects at some timepoints.

The number of subjects experiencing an exacerbation, split by GOLD stage, was relatively small and increased from GOLD stage II to IV. However, irrespective of GOLD stage, the percentage of subjects with an exacerbation was lower in the active treatment groups compared with placebo. There were no trends or patterns in the treatment response based on GOLD stage to suggest there was a difference in efficacy between UMEC 62.5 mcg and 125 mcg.

Exercise studies

The results in the exercise endurance time of the first study (study DB2114417) did not show a statistical or clinically relevant improvement in the UMEC/VI arm as compared to placebo (first step of the hierarchal testing) and hence this was a failed study and no inferences can be drawn from it. In the other exercise study (DB2114418), the 3-h postdose LS mean increase from baseline in EET (s) was 74.8 seconds for UMEC 125 mcg, 25.1 seconds with UMEC 62.5 mcg and 0.1 seconds with placebo, which suggests a relevant increase in exercise endurance time with UMEC 125 mcg but not with UMEC 62.5 mcg. The results of the two exercise endurance studies, Studies DB2114417 and DB2114418, are very different in terms of both the pattern of significance and the size of the treatment differences. For example the estimated treatment difference for EET for the comparison of UMEC/VI 125/25mcg and placebo is approximately 32 seconds in the first study but 66 seconds in the second.

In study DB2114418 as well as in study DB2113361, it is noted that the change in trough FEV1 from baseline in the placebo group is large (- 43 ml and -31 ml respectively), which is not usually expected over the 12 weeks and 24 weeks period respectively. Generally the treatment effect size on trough FEV1 was large for all treatment groups in the DB2114418 study and this study showed a large difference in effect size between UMEC 125 and 62.5 which was not seen in other studies. The Applicant has explained the inconsistency in the results of the primary efficacy endpoint in the two exercise studies based on the higher than anticipated response in the placebo group only in one study. However despite a thorough analysis of the data and factors that might affect the data, it has not been possible to identify a cause for this placebo response.

However the applicant has not made any claims on exercise tolerance in the SmPC. These studies are therefore only supportive studies and not considered pivotal for deciding the risk-benefit of this application. The remaining studies do provide a sufficiently robust basis to conclude on the efficacy of UMEC.

Dosing

UMEC 62.5 mcg is the only dose proposed for registration by the applicant. From the Phase IIIa studies, both UMEC 62.5 mcg and 125 mcg were shown to be efficacious. Although greater differences from placebo with UMEC 125 mcg compared to UMEC 62.5 mcg were noted in some studies in the efficacy endpoints related to lung function and rescue use at several time points, these differences were not observed consistently at each time point measured and tended to be modest. Confidence intervals for these endpoint differences were often overlapping suggesting that there were no substantial clinical benefits with the UMEC 125 mcg dose over the UMEC 62.5 mcg dose. In the analyses of subgroups by, for example, gender, age, geographical region, GOLD stage, and ICS use, no subgroup appeared to benefit to a greater extent with 125 mcg dose compared with the 62.5 mcg

dose. There was an indication that subjects reversible to salbutamol and reversible to salbutamol followed by ipratropium achieved slightly higher trough FEV1 values with UMEC 125 mcg than with 62.5 mcg, but the differences were generally small and not considered clinically relevant and were not shown consistently at every time point (i.e. not at Day 84 in the integrations).

The data overall suggest that both doses were efficacious with no substantial clinically meaningful differentiation in efficacy between them.

2.5.4. Conclusions on the clinical efficacy

The results of the Phase III studies are considered to provide adequate consistent evidence of efficacy of both doses of UMEC versus placebo in terms of improvement of lung function (trough FEV1).

Outcome measures on symptomatic improvement did not always reach a clinically relevant difference versus PBO (e.g.: TDI score, SGRQ score) but are in general in line with the results obtained for other LAMA recently authorised in the EU (aclidinium bromide). Also acceptable consistency has been shown across patients' subgroups.

Although greater differences from placebo with UMEC 125 mcg compared to UMEC 62.5 mcg were noted in some studies in the efficacy endpoints related to lung function and rescue use at several timepoints, these differences were not observed consistently at each timepoint measured and tended to be modest. Confidence intervals for these endpoint differences were often overlapping suggesting that there were no substantial clinical benefits with the UMEC 125 mcg dose over the UMEC 62.5 mcg dose. In the analyses of subgroups by, for example, gender, age, geographical region, GOLD stage, and ICS use, no subgroup appeared to benefit to a greater extent from 125 mcg dose compared with the 62.5 mcg dose.

On the other hand a dose-trend in some adverse events (e.g.: CV adverse events and respiratory infections) could be seen (see also discussion on safety) and no authorisation of the higher dose was sought by the applicant.

The overall documentation of efficacy for UMEC 62.5 mcg (55mcg delivered dose) is considered to be satisfactory.

2.6. Clinical safety

Patient exposure

A total of 2706 subjects with COPD were treated with at least one dose of UMEC or placebo in the 8 studies comprising the "All Clinical Studies" grouping. A total of 1663 subjects received UMEC (576 subjects received 62.5 mcg and 1087 subjects received 125 mcg), representing approximately 656 subject-years of exposure compared with 1124 subjects receiving placebo.

Table 30. Summary of Subjects Exposure (All Clinical Studies ITT Population)

Study Grouping/ Study Number	Number of Subjects			
	Placebo	UMEC 62.5	UMEC 125	Treated [a,b]
Efficacy Studies				
AC4115408 DB2113361 DB2113373 DB2113374	623	487	698	1808
Long-term Safety Study				
DB2113359	109	NA	227	336
Exercise Studies				
DB2114417 [c,d] DB2114418 [c,d]	321	89	91	420
Other Studies Integrated with All Clinical Studies				
AC4113589	71	NA	71	142
All Clinical Studies	1124	576	1087	2706

Data Source: Table 1.01, Table 1.02, Table 1.03, Table 1.04, CSR DB2113359 Table 7.01; CSR AC4113589 Table 7.01

Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; NA=not applicable; UMEC=umeclidinium bromide

a. Number of subjects treated with at least 1 dose of study medication.
b. Total number of subjects treated in one or more of the relevant treatment arms.
c. Some subjects may have been enrolled in a previous study.
d. Subjects in cross-over studies received more than 1 treatment and are counted for each treatment received and once in the Total column.

Median exposure duration across the UMEC groups was 165 days (UMEC 62.5 mcg) and 166 days (UMEC 125 mcg) compared with 88 days for placebo; with mean days: 128 and 153 days for UMEC 62.5 mcg and UMEC 125 mcg respectively compared with 122 days in the placebo group. The number of patients treated for >24 weeks was 154 (27%) for UMEC 62.5 mcg dose and 370 (34%) for UMEC 125 mcg. Exposure to study drug for >48 weeks was reported for 133 (12%) subjects in the UMEC 125 mcg treatment group. There were no data for UMEC 62.5 mcg. This exposure came from the Long-term Safety Study.

Adverse events

All Clinical Studies

In the All Clinical Studies grouping, the incidence of any on-treatment AEs reported for the UMEC 62.5 mcg and UMEC 125 mcg treatment groups was 45% and 52% respectively, compared with 41% for placebo. AEs leading to permanent discontinuation or withdrawal were reported at a slightly higher incidence for UMEC 62.5 mcg and UMEC 125 mcg (6%) compared with placebo (5%). The incidences of any on- or post-treatment fatal AEs were low and the same across the two UMEC treatment groups (<1%) and placebo (<1%). The incidence of any on-treatment SAE was slightly higher in the UMEC groups (UMEC 62.5mcg 5% and UMEC 125mcg 6%) compared with placebo (4%), and the incidence of any drug-related AEs was slightly higher in the UMEC 125 mcg (9%) treatment group compared with UMEC 62.5 mcg (6%) and placebo (6%). An overall summary of AE in the All Clinical Studies grouping is provided in the below table:

Table 31. Summary of Adverse Events (All Clinical Studies Grouping ITT Population)

Events	Placebo (N=1124)	UMEC 62.5 (N=576)	UMEC 125 (N=1087)
Incidence	**Number (%) of Subjects**		
Any on-treatment AEs	466 (41)	261 (45)	562 (52)
Any on-treatment drug-related AEs	62 (6)	36 (6)	97 (9)
Any on-treatment AEs leading to permanent discontinuation of study drug or withdrawal from study	55 (5)	34 (6)	68 (6)
Any on-treatment SAEs	44 (4)	29 (5)	61 (6)
Any on-treatment or post-treatment fatal AEs	3 (<1)	3 (<1)	7 (<1)
Exposure-Adjusted Frequency	**Number of Subjects with Events per 1000 Subject-Years**		
	SY=374	**SY=202**	**SY=454**
Any on-treatment AEs	1246.5	1289.7	1236.9
Any on-treatment drug-related AEs	165.8	177.9	213.5
Any on-treatment AEs leading to permanent discontinuation of study drug or withdrawal from study	147.1	168.0	149.7
Any on-treatment SAEs	117.7	143.3	134.3
Any on-treatment or post-treatment fatal AEs	8.0	14.8	15.4

Data Source: Table 2.01, Table 2.146, Table 2.04, Table 2.33, Table 2.36, Table 2.17, Table 2.147, Table 2.20, Table 2.49, Table 2.52
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; SY=subject-years; UMEC=umeclidinium bromide;
Note: Numbers represent the number of subjects with an event per 1000 subject-years of exposure.
Note: Exposure-adjusted frequency was calculated as (1000 * number of subjects with AE) divided by (total duration of exposure in days / 365.25).

Efficacy studies (AC4115408, DB2113361, DB2113373 and DB2113374)

In the Efficacy studies, the incidence of any on-treatment AEs reported for the UMEC 62.5 mcg and UMEC 125 mcg treatment groups was 50% and 54% respectively, compared with 46% for placebo. AEs leading to permanent discontinuation or withdrawal were reported at a slightly higher incidence for UMEC 62.5 mcg (7%) and UMEC 125 mcg (6%) compared with placebo (4%). The incidences of any on- or post-treatment fatal AEs were low and the same across the two UMEC treatment groups (<1% both groups) and placebo (<1%). The incidence of any on-treatment SAE was slightly higher in both the UMEC groups (6%) compared with placebo (4%), and the incidence of drug-related AEs was slightly higher in the UMEC 125 mcg (9%) and UMEC 62.5 mcg (7%) treatment groups compared with placebo (5%).

Table 32. Summary of Adverse Events (Efficacy Studies Integration – ITT Population)

Events	Number (%) of Subjects		
	Placebo (N=623)	UMEC 62.5 (N=487)	UMEC 125 (N=698)
Any on-treatment AEs	288 (46)	243 (50)	376 (54)
Any drug related AEs [a]	32 (5)	36 (7)	63 (9)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study [a]	26 (4)	32 (7)	44 (6)
Any on-treatment SAEs	27 (4)	28 (6)	39 (6)
Any post-treatment SAEs	2 (<1)	5 (1)	3 (<1)
Any drug related SAEs [a]	0	1 (<1)	2 (<1)
Any on-treatment or post-treatment fatal AEs	2 (<1)	3 (<1)	2 (<1)

Data Source: Table 2.02, Table 2.34, Table 2.87, Table 2.105, Table 2.50, Table 2.18, Table 7.05
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; UMEC=umeclidinium bromide
a. Includes only on-treatment AEs.

Long-term safety study (DB2113359)

In the long-term safety study, at least one on-treatment AE was reported by 58% of subjects in the UMEC 125 mcg treatment group compared with 52% for placebo (Table below). The incidences of drug-related AEs (UMEC 125 mcg: 12%; Placebo: 13%) and on-treatment SAEs (UMEC 125 mcg: 7%; Placebo: 6%) were similar across the two treatment groups. AEs leading to permanent discontinuation or withdrawal were reported for 9% of subjects in the UMEC 125 mcg treatment group compared with 12% for placebo. Four fatal AEs were reported in the UMEC 125 mcg treatment group, two of which (<1%) were classified as on-treatment; two were classified as post-treatment. One fatal AE (<1%) was reported in the placebo group, which was classified as post-treatment.

Table 33. Summary of Adverse Events in UMEC 125 mcg and Placebo Groups (Long-Term Safety Study – ITT Population)

Exercise studies (DB2114417 and DB2114418)

In the Exercise Studies, the incidence of on-treatment AEs was higher on UMEC 125 mcg treatment (40%) compared with UMEC 62.5 mcg and placebo treatment (20% and 33%, respectively, Table below). The incidences of drug-related AEs were the same (4%) for UMEC 125 mcg and placebo, with no drug-related events reported for UMEC 62.5 mcg. The incidences of AEs leading to withdrawal were slightly lower for subjects on UMEC treatment (2% for UMEC 62.5 mcg and 3% for UMEC 125 mcg) compared with 5% for placebo. The incidences of on-treatment SAEs were lowest on UMEC 62.5 mcg treatment (1%) and similar for UMEC 125 mcg (4%) and placebo (3%). No post-treatment SAEs were reported for subjects on UMEC treatments compared with 2 subjects (<1%) on placebo. No drug-related SAEs were reported for subjects on UMEC treatments or placebo. One fatal AE (1%), which was classified as on-treatment, was reported in the UMEC 125 mcg group.

Table 34. Summary of Adverse Events (Exercise Studies Integration – ITT Population)

Adverse Events	Number (%) of Subjects		
	Placebo (N=321)	UMEC 62.5 (N=89)	UMEC 125 (N=91)
Any on-treatment AEs	105 (33)	18 (20)	36 (40)
Any on-treatment drug related AEs	14 (4)	0	4 (4)
Any on-treatment AEs leading to permanent discontinuation of study drug or withdrawal from study	17 (5)	2 (2)	3 (3)
Any on-treatment SAEs	10 (3)	1 (1)	4 (4)
Any post-treatment SAEs	2 (<1)	0	0
Any on-treatment drug related SAEs	0	0	0
Any on-treatment or post-treatment fatal AEs	0	0	1 (1)

Data Source: Table 2.03, Table 2.19, Table 2.35, Table 2.51, Table 2.106, Table 7.06, Table 2.88,
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; UMEC=umeclidinium bromide

Common Adverse Events

All Clinical Studies

A summary of the exposure adjusted frequency of subjects with on-treatment AEs reported by ≥3% of subjects in any treatment group for the All Clinical Studies grouping is presented in table below. The most frequently reported AEs were headache and nasopharyngitis, with incidences across the UMEC treatment groups and placebo ranging between 7% to 10% for headache, and 7% for nasopharyngitis (Table below).

Table 35. Summary of the Most Frequent On-Treatment Adverse Events Reported by 3% or More of Subjects on any Treatment Group (All Clinical Studies ITT Population)

Preferred Term	Placebo (N=1124)	UMEC 62.5 (N=576)	UMEC 125 (N=1087)
Incidence	**Number (%) of Subjects**		
Any AE	**466 (41)**	**261 (45)**	**562 (52)**
Headache	92 (8)	38 (7)	105 (10)
Nasopharyngitis	83 (7)	42 (7)	77 (7)
Cough	32 (3)	16 (3)	42 (4)
Back pain	36 (3)	10 (2)	40 (4)
Upper respiratory tract infection	25 (2)	23 (4)	33 (3)
Exposure-adjusted frequency	**Number of Subjects with Events per 1000 Subject-Years**		
	SY=374	**SY=202**	**SY=454**
Any AE	**1246.5**	**1289.7**	**1236.9**
Headache	246.1	187.8	231.1
Nasopharyngitis	222.0	207.5	169.5
Cough	85.6	79.1	92.4
Back pain	96.3	49.4	88.0
Upper respiratory tract infection	66.9	113.6	72.6

Data Source: Table 2.01, Table 2.55, Table 2.04, Table 2.58
Abbreviations: AE=adverse event; ITT=intent-to-treat; SY=subject-years; UMEC=umeclidinium bromide
Note: Numbers represent the number of subjects with an event per 1000 subject-years of exposure.
Note: Exposure-adjusted frequency was calculated as (1000 * number of subjects with AE) divided by (total duration of exposure in days / 365.25).

Efficacy studies (AC4115408, DB2113361, DB2113373 and DB2113374)

In the Efficacy Studies, the most frequently reported AEs were headache and nasopharyngitis, with incidences across both UMEC treatment groups and placebo ranging from 8% to 10% and 7% to 9%, respectively (Table below).

Table 36. Summary of the Most Frequent On-Treatment Adverse Events – AEs Reported by 3% or More of Subjects with Any Treatment Group (Efficacy Studies Integration – ITT Population)

	Number (%) of Subjects		
Preferred Term	Placebo (N=623)	UMEC 62.5 (N=487)	UMEC 125 (N=698)
Any AE	**288 (46)**	**243 (50)**	**376 (54)**
Headache	65 (10)	37 (8)	72 (10)
Nasopharyngitis	55 (9)	37 (8)	50 (7)
Cough	24 (4)	16 (3)	34 (5)
Upper respiratory tract infection	21 (3)	23 (5)	25 (4)
Back pain	24 (4)	10 (2)	27 (4)
Hypertension	10 (2)	10 (2)	19 (3)

Data Source: Table 2.02, Table 2.56
Abbreviations: AE=adverse event; ITT=intent-to-treat; UMEC=umeclidinium bromide

In the Efficacy studies, cough, upper respiratory tract infection (URTI), hypertension, arthralgia, contusion and viral URTI were on-treatment AEs reported by more than 1% of subjects in any UMEC treatment group and having an incidence in any UMEC treatment group greater than 1% over the placebo (Table below).

Table 37. Summary of On-Treatment Adverse Events Reported by More than 1% of Subjects on Any UMEC Group and having > 1% Incidence over the Placebo Incidence (Efficacy Studies Integration – ITT Population)

Preferred Term	Number (%) of Subjects		
	Placebo (N=623)	UMEC 62.5 (N=487)	UMEC 125 (N=698)
Cough	24 (4)	16 (3)	34 (5)
Upper respiratory tract infection	21 (3)	23 (5)	25 (4)
Hypertension	10 (2)	10 (2)	19 (3)
Arthralgia	9 (1)	12 (2)	11 (2)
Contusion	1 (<1)	7 (1)	4 (<1)
Viral upper respiratory tract infection	1 (<1)	7 (1)	1 (<1)

Source: Table 2.173

Long-term safety study (DB2113359)

A summary of on-treatment AEs reported by >3% of subjects in any treatment group in the Long-term Safety Study is presented in table below.

Table 38. Summary of Most Frequent On-Treatment Adverse Events – AEs Reported by 3% or More of Subjects in UMEC 125 mcg or Placebo Groups (Long-Term Safety – ITT Population)

Preferred Term	Number (%) of Subjects	
	Placebo N=109	UMEC 125 N=227
Any event	57 (52)	132 (58)
Headache	9 (8)	25 (11)
Nasopharyngitis	5 (5)	20 (9)
Ventricular extrasystoles	5 (5)	12 (5)
Extrasystoles	4 (4)	10 (4)
Back pain	3 (3)	9 (4)
Hypertension	5 (5)	4 (2)
Sinusitis	3 (3)	6 (3)
Influenza	5 (5)	5 (2)
Cough	1 (<1)	6 (3)
Upper respiratory tract infection	3 (3)	8 (4)
Chronic obstructive pulmonary disease	3 (3)	6 (3)
Ventricular tachycardia	4 (4)	3 (1)
Supraventricular tachycardia	1 (<1)	6 (3)
Supraventricular extrasystoles	1 (<1)	6 (3)
Sinus tachycardia	1 (<1)	6 (3)
Dyspnoea	3 (3)	0
Pneumonia	0	6 (3)

Data Source: DB2113359 CSR Table 7.03 and DB2113359 CSR Table 7.05
Abbreviations: ITT=intent-to-treat; UMEC=umeclidinium bromide

A summary of on-treatment AEs reported by >1% of subjects in the UMEC 125 mcg treatment group and having an incidence >1% over the placebo incidence is presented in the table below.

Table 39. Summary of On-Treatment Adverse Events Reported by More than 1% of Subjects on UMEC 125 mcg and having > 1% Incidence over the Placebo Incidence (Long-term Safety Study – ITT Population)

Preferred Term	Number (%) of Subjects	
	Placebo (N=109)	UMEC 125 (N=227)
Headache	9 (8)	25 (11)
Nasopharyngitis	5 (5)	20 (9)
Back pain	3 (3)	9 (4)
Cough	1 (<1)	6 (3)
Sinus tachycardia	1 (<1)	6 (3)
Supraventricular extrasystoles	1 (<1)	6 (3)
Supraventricular tachycardia	1 (<1)	6 (3)
Pneumonia	0	6 (3)
Neck pain	0	5 (2)
Rash	0	5 (2)
Rhythm idioventricular	0	5 (2)
Urinary tract infection	0	5 (2)
Diarrhoea	0	4 (2)
Pain in extremity	0	4 (2)
Sinus headache	0	4 (2)
Lower respiratory tract infection	0	3 (1)
Myalgia	0	3 (1)
Rhinitis	0	3 (1)

Source: Table 2.174

In the Long-term Safety Study, the following adverse events occurred with an incidence in the UMEC 125 mcg treatment group 3% higher than the incidence in the placebo group: headache, nasopharyngitis, cough, supraventricular tachycardia, supraventricular extrasystoles and sinus tachycardia. Rash and rhythm idioventricular occurred with an incidence in UMEC group 2% higher than the incidence in the placebo group with no events reported in the placebo group. These adverse reactions have been included in Section 4.8 of SmPC.

Exercise studies (DB2114417 and DB2114418)

In the Exercise Studies, the incidence of on-treatment AEs (by PT) reported by 3% of subjects was similar for UMEC 125 mcg and placebo and lower for UMEC 62.5 mcg, with the exception of nasopharyngitis). No noteworthy differences in the incidence of AEs (by PT) reported by >3% of subjects for any treatments were observed between subjects on either UMEC treatments or placebo. The most frequently reported AEs were nasopharyngitis and headache, with incidences across the UMEC treatments and placebo ranging from 5% to 6% and 1% to 5%.

Serious adverse event / deaths / other significant events

On-treatment Serious Adverse Events

For the All Clinical Studies group, the incidence of at least one on-treatment SAE was reported for 5% and 6% of subjects for the UMEC 62.5 mcg and UMEC 125 mcg treatment groups respectively; compared with 4% for the placebo group. The only SAE reported by at least 1% of subjects in any treatment group was COPD, reported in 1% of subjects in the UMEC 125 mcg and placebo groups and 2% of subjects in the UMEC 62.5 mcg treatment group. The exposure-adjusted frequency of subjects with on-treatment SAEs was 143 subjects with an event per 1000 subject-years of exposure and 134 subjects with an event per 1000 subject-years in the in the UMEC 62.5 mcg and UMEC 125 mcg groups, respectively, compared with 118 subjects with an event per 1000 subject-years of exposure in the placebo group.

On-treatment Drug-related Serious Adverse Events

A total of 5 on-treatment drug-related SAEs were reported among 4 subjects receiving UMEC in the All Clinical Studies grouping. The incidence of on-treatment drug-related SAEs was <1% for the UMEC treatment groups compared with 0% for the placebo treatment group. Of the 5 SAEs reported, 4 events were reported in the Cardiac Disorders SOC: 1 event each of atrial fibrillation, rhythm idioventricular and ventricular extrasystoles was reported in the UMEC 125 mcg group and 1 event of tachycardia in the UMEC 62.5 mcg group. A drug-related SAE of chest pain in the General Disorders and Administrative site conditions SOC was also reported for UMEC 125 mcg.

Adjudicated Serious Adverse Reports

All serious adverse report narratives, including deaths and hospitalisations, were adjudicated by an external independent, adjudication committee in a blinded manner for the Phase IIIa studies in subjects with COPD treated with UMEC or placebo for at least 12 weeks. The adjudication was carried out on the case/report as a whole; thus, the case was adjudicated on the primary event (*i.e.*, the event of the greatest medical significance, such as death, or hospitalisation, or other reason for seriousness). Fatal events were categorised on pre-defined composite endpoints of respiratory, cardiovascular, cancer, other cause of death, or unknown. Non-fatal events were categorised to pre-defined composite endpoints of respiratory, cardiovascular, other, or unknown.

A summary of adjudicated serious adverse reports is presented for the following Phase IIIa studies or combination of studies:

- Efficacy Studies: AC4115408, DB2113361, DB2113373 and DB2113374
- Long-term Safety Study: DB2113359
- Exercise Studies: DB2114417 and DB2114418

Efficacy studies (AC4115408, DB2113361, DB2113373 and DB2113374)

In the Efficacy Studies, the respiratory category had the highest incidence of non-fatal serious adverse reports: 3% in the UMEC 62.5 mcg group and 2% in UMEC 125 mcg and placebo (Table below). In each treatment group, the most common respiratory subcategory was COPD exacerbation without evidence of pneumonia, which was reported at an incidence of 2% and <1% of subjects in the UMEC 62.5 mcg and UMEC 125 mcg treatment groups respectively, compared with 1% of subjects in placebo.

Table 40. Adjudicated Non-Fatal Serious Adverse Reports (Efficacy Studies Integration – ITT Population)

Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects		
	Placebo (N=623)	UMEC 62.5 (N=487)	UMEC 125 (N=698)
Any serious adverse report	26 (4)	28 (6)	39 (6)
Cardiovascular – any type	2 (<1)	4 (<1)	12 (2)
Myocardial infarction/ischemic heart disease	0	3 (<1)	5 (<1)
Congestive heart failure	0	0	1 (<1)
Stroke – any type	1 (<1)	0	1 (<1)
Haemorrhagic	0	0	0
Thromboembolic	1 (<1)	0	0
Indeterminate	0	0	1 (<1)
Other cardiovascular cause	1 (<1)	1 (<1)	5 (<1)
Respiratory – any type	13 (2)[a]	14 (3)	11 (2)
COPD exacerbation with evidence of pneumonia	3 (<1)	1 (<1)	4 (<1)
COPD exacerbation without evidence of pneumonia	9 (1)	12 (2)	4 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	0	1 (<1)
Asthma associated	0	0	0
Pulmonary embolism	0	0	1 (<1)
Other respiratory cause	2 (<1)	1 (<1)	1 (<1)
Other-any type	10 (2)	12 (2)	16 (2)
Unknown – any type	2 (<1)	0	0
Inadequate information	0	0	0
Indeterminate	2 (<1)	0	0

Data Source: Table 2.140 Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide.
a. Subject 6727 in Study DB2113361 reported 2 SAEs in the respiratory subgroup that were adjudicated independently.

Long-term Safety Study (DB2113359)

In the Long-term Safety Study, the "other" causes (i.e., not of a cardiovascular or respiratory nature) category had the highest incidence of non-fatal serious adverse reports: 3% in the UMEC 125 mcg group and 2% in the placebo group. Nonfatal serious adverse reports assigned to respiratory causes and cardiovascular causes had higher incidences in the placebo group (3% and 2%, respectively) than in the UMEC 125 mcg group (2% and 1%, respectively). Serious adverse reports that were categorized to "other cardiovascular cause" had a similar incidence (<1%) across all both treatment groups.

Table 41. Adjudicated Non-Fatal Serious Adverse Reports within UMEC 125 mcg and Placebo Treatment Groups (Long-Term Safety Study – ITT Population)

	Number (%) of Subjects	
Serious Adverse Report Category – Subcategory (Where Applicable)	**Placebo N=109**	**UMEC 125 N=227**
Any serious adverse report	7 (6)	15 (7)
Cardiovascular – any type	2 (2)	3 (1)
Myocardial infarction/ischemic heart disease	1 (<1)	2 (<1)
Congestive heart failure	1 (<1)	0
Other cardiovascular cause	1 (<1)	1 (<1)
Respiratory – any type	3 (3)	5 (2)
COPD exacerbation with evidence of pneumonia	0	1 (<1)
COPD exacerbation without evidence of pneumonia	3 (3)	2 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	1 (<1)
Other respiratory cause	0	1 (<1)
Other – any type	2 (2)	7 (3)
Unknown – any type	1 (<1)	0
Indeterminate	1 (<1)	0

Data Source: Table 2.142
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide

Exercise studies (DB2114417 and DB2114418)

In the Exercise Studies, the "other" causes (i.e., not of a cardiovascular or respiratory nature) category had the highest incidence of non-fatal serious adverse reports: 3% on UMEC 125 mcg, 2% on placebo and no reports categorized with UMEC 62.5 mcg. Non-fatal serious adverse reports were assigned to respiratory causes in 1% of subjects in the UMEC 62.5 mcg and placebo groups and none for UMEC 125mcg. There were no serious adverse reports categorized as cardiovascular in nature for either of the UMEC treatment groups, compared with <1% for placebo. Two non-fatal serious adverse reports in the placebo group (<1%) were categorised to the "other cardiovascular cause" with no reports for either UMEC treatment groups. No reports were categorized as respiratory in nature for UMEC 125 mcg, compared with 1% for UMEC 62.5mcg and placebo.

Table 42. Adjudicated Non-Fatal Serious Adverse reports (Exercise Studies Integration – ITT Population)

	Number (%) of Subjects		
Serious Adverse Report Category – Subcategory (Where Applicable)	**Placebo (N=321)**	**UMEC 62.5 (N=89)**	**UMEC 125 (N=91)**
Any serious adverse report	11 (3) [a]	1 (1)	3 (3)
Cardiovascular – any type	3 (<1)	0	0
Stroke – any type	1 (<1)	0	0
Haemorrhagic	1 (<1)	0	0
Other cardiovascular cause	2 (<1)	0	0
Respiratory – any type	4 (1)	1 (1)	0
COPD exacerbation with evidence of pneumonia	0	0	0
COPD exacerbation without evidence of pneumonia	4 (1)	0	0
Pulmonary embolism	0	1 (1)	0
Other – any type	5 (2)	0	3 (3)

Data Source: Table 2.141
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide
a. Subject 81 in Study DB2114417 reported 2 SAEs (one in the cardiovascular subgroup and one in the respiratory subgroup) that were adjudicated independently.

Adverse Events of Special Interest (AESI)

The main safety concerns with UMEC relate to the known LAMA effects. Pharmacologic class effects of LAMAs include cardiovascular effects (atrial arrhythmias), ocular disorders (e.g., blurred vision), urinary retention, gastrointestinal disorders, and gallbladder disorders, along with anticholinergic effects including dry mouth and cough. In addition, pneumonia and Lower Respiratory Tract Infections (LRTIs) are commonly reported in patients with

COPD. These Adverse Events of Special Interest (AESI) were proactively assessed (i.e., defined a priori) in the clinical development program.

Appropriate Standardized MedDRA Queries (SMQs) or MedDRA Higher Level Terms (HLTs) were selected for AESI categorisations. When MedDRA SMQs or HLTs were not available, an appropriate selection of MedDRA PTs was used.

Cardiovascular AESIand MACE

In the clinical development program, cardiovascular safety was monitored via AE reporting with categorization and analysis of AESI including acquired long QT, cardiac arrhythmias, cardiac failure, cardiac ischemia, hypertension, sudden death, and stroke subgroups. ECGs and vital signs were measured in all patients and Holter monitoring was performed in a predefined subset. In addition, an analysis of Major Adverse Cardiac Events (MACE) was performed.

In the Long-Term Safety Study (DB2113359), a higher incidence of dropouts due to protocol-defined stopping criteria was reported in the UMEC 125 mcg (16%) compared with placebo (7%), particularly for ECG abnormalities (UMEC 125 mcg: 5%; placebo: 0%) and Holter abnormalities (UMEC 125 mcg: 11%; placebo: 7%). However only one of the event was due to increase in QTc > 60msec and none of the patients in the UMEC arm met the QTc > 450 msec, which was another criteria for withdrawal. The ECG/holter abnormalities had no specific pattern and also did not have any clinically significant symptom associated with the abnormality, and so this imbalance is not a significant concern. In addition, the thorough QTc study and the remaining ECG data from the clinical efficacy studies also do not raise any specific concern on the QTc prolongation potential of UMEC. Therefore taking the overall data in to consideration it is accepted that the risk of QTc prolongation by UMEC is low.

Although a higher number of subject withdrawals due to ECG and Holter abnormalities were noted in the UMEC 125 mcg group compared with placebo in the Long-term Safety Study, the majority of these withdrawals were associated with asymptomatic cardiac arrhythmias and unlikely to have led to more severe cardiovascular events. Appropriate risk minimisation includes atrial fibrillation and tachycardia in the SmPC, and a patient appropriate equivalent message is also included in the patient information leaflet, similar to other marketed anticholinergics. It is agreed that UMEC treatment does not pose a particular risk of arrhythmias and therefore it is agreed to include a equivalent SPC information (e.g.: warnings about CV effects) to that of other recently approved anticholinergics, as proposed by the applicant, which does not include the need for ECG/Holter monitoring (e.g.: aclidinium bromide, glycopyrronium bromide).

Cardiovascular AESI

- In All Clinical Studies grouping, the incidence of <u>on-treatment</u> cardiovascular AESI was 7% for placebo (209 subjects with an event per 1000-subject years), 8% for UMEC 62.5 mcg (222 subjects with an event per 1000-subject years) and 10 % for UMEC 125 mcg (236 subjects with an event per 1000-subject years).

- The incidence of <u>post-treatment</u> cardiovascular AESIs was <1% for both UMEC treatment groups adn placebo.

<u>Cardiovascular AESI by Subgroup</u>

Following table presents the incidence and exposure-adjusted frequencies of subjects with on treatment cardiovascular AESI by subgroup for the All Clinical Studies Grouping.

Table 43. On-Treatment Cardiovascular AESI Incidence and Exposure-Adjudicated Frequency by Special Interest Subgroup (All Clinical Studies ITT Population)

Cardiovascular AESI Subgroups	Placebo N=1124	UMEC 62.5 N=576	UMEC 125 N=1087
Incidence		**Number (%) of Subjects**	
Acquired long QT	0	1 (<1)	0
Cardiac arrhythmias	37 (3)	22 (4)	61 (6)
Cardiac failure	8 (<1)	8 (1)	11 (1)
Cardiac ischaemia	13 (1)	7 (1)	10 (<1)
Hypertension	23 (2)	13 (2)	30 (3)
Sudden death	0	0	0
Stroke	4 (<1)	1 (<1)	2 (<1)
Exposure-adjusted frequency	**Number of Subjects with Events per 1000 Subject-Years**		
	SY=374	**SY=202**	**SY=454**
Acquired long QT	0	4.9	0
Cardiac arrhythmias	99.0	108.7	134.3
Cardiac failure	21.4	39.5	24.2
Cardiac ischaemia	34.8	34.6	22.0
Hypertension	61.5	64.2	66.0
Sudden death	0	0	0
Stroke	10.7	4.9	4.4

Data Source: Table 2.112 and Table 2.116
Abbreviations: AE=adverse event; AESI=adverse event of special interest; ITT=intent-to-treat; SY=subject-years; UMEC=umeclidinium bromide
Note: Numbers represent the number of subjects with an event per 1000 subject-years of exposure
Note: Exposure-adjusted frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

The table below below presents the incidence and exposure-adjusted frequencies of subjects with on treatment cardiovascular AESIs by subgroups for the Long Term Safety Study.

Table 44. On-Treatment Cardiovascular AESI Incidence and Exposure – Adjusted Frequency by Special Interest Subgroup within UMEC 125 mcg and Placebo Groups (Long-Term Safety Study – ITT Population)

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

Data Source: Table 2.115 and Table 2.119
Abbreviations: AE=adverse event; AESI=adverse events of special interest; ITT=intent-to-treat; SY=subject-years; UMEC=umeclidinium bromide
Note: Numbers represent the number of subjects with an event per 1000 subject-years of exposure
Note: Exposure-adjusted frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

Cardiovascular AESI by PT

Among on-treatment cardiovascular AESI in the All Clinical Studies grouping, all PTs were reported for ≤1% of subjects in each treatment group with the exception of hypertension, which was reported for 2% of subjects (all treatment groups) and ventricular extrasystoles, reported for 2% of subjects receiving UMEC 125 mcg and <1% of subjects receiving UMEC 62.5 mcg or placebo.

Serious Cardiovascular AESI by Subgroup and PT

Table 45. On-Treatment Cardiovascular Serious AESI Incidence by Special Interest Subgroup and Preferred Term (All Clinical Studies ITT Population)

Cardiovascular AESI Group	Subgroup / Preferred Term	Number (%) of Subjects		
		Placebo N=1124	UMEC 62.5 N=576	UMEC 125 N=1087
Cardiovascular	Any term	7 (<1)	7 (1)	15 (1)
Acquired long QT	Any term	0	1 (<1)	0
	Electrocardiogram QT prolonged	0	1 (<1)	0
Cardiac arrhythmias	Any term	0	4 (<1)	5 (<1)
	Atrial fibrillation	0	1 (<1)	2 (<1)
	Bradycardia	0	1 (<1)	0
	Electrocardiogram QT prolonged	0	1 (<1)	0
	Rhythm idioventricular	0	0	1 (<1)
	Syncope	0	1 (<1)	0
	Tachycardia	0	1 (<1)	0
	Ventricular extrasystoles	0	0	3 (<1)
Cardiac failure	Any term	1 (<1)	0	2 (<1)
	Cardiac failure	0	0	1 (<1)
	Cardiac failure congestive	1 (<1)	0	1 (<1)
Cardiac ischemia	Any term	4 (<1)	4 (<1)	6 (<1)
	Acute myocardial infarction	0	0	2 (<1)
	Angina pectoris	2 (<1)	0	0
	Angina unstable	0	1 (<1)	2 (<1)
	Coronary artery disease	1 (<1)	2 (<1)	1 (<1)
	Coronary artery stenosis	0	0	1 (<1)
	Myocardial infarction	1 (<1)	0	1 (<1)
	Troponin increased	0	1 (<1)	0
Hypertension	Any term	1 (<1)	0	2 (<1)
	Accelerated hypertension	0	0	1 (<1)
	Hypertension	1 (<1)	0	1 (<1)
Sudden death	Any term	0	0	0
Stroke	Any term	3 (<1)	0	2 (<1)
	Carotid artery stenosis	1 (<1)	0	0
	Cerebrovascular accident	2 (<1)	0	2 (<1)

Data Source: Table 2.120
Abbreviations: AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; ITT=intent-to-treat; UMEC=umeclidinium bromide;

In the All Clinical Studies Grouping, the overall incidence of serious cardiovascular AESI was <1% in the placebo group and 1% in both UMEC treatment groups. A higher incidence of cardiac arrhythmias was seen in the UMEC groups (<1%) compared with placebo (0%).

Three SAEs were reported in the hypertension subgroup; 1 event of accelerated hypertension in the UMEC 125 mcg group and 1 event of hypertension each in the UMEC 125 mcg and placebo groups.

Three subjects had fatal AEs in the cardiovascular special interest group; sudden death in 1 subject on UMEC 62.5 mcg, cardiac failure acute in 1 subject on UMEC 125 mcg and coronary artery insufficiency in 1 subject on placebo.

Major Adverse Cardiac Events (MACE)

The broad criteria were defined *a priori* as follows (and the group of events meeting these criteria are referenced in the results as "broad-definition MACE"):

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

To investigate events relating specifically to myocardial infarction rather than other cardiac ischaemic events, the narrow MACE definition included only the PTs of "myocardial infarction" and "acute myocardial infarction". The following table shows the MACE results for combined Efficacy Studies, Exercise Studies and Long-term Safety Study..

Table 46. Major Adverse Cardiac Events (Efficacy Studies and Exercise Studies Integrations, Long-Term Safety-Study – ITT Population)

	Number (%) of Subjects		
	Placebo N=1053 SY=369	UMEC 62.5 N=576 SY=202	UMEC 125 N=1016 SY=449
Incidence	**Number (%) of Subjects**		
Broad-definition MACE	20 (2)	9 (2)	14 (1)
Narrow-definition MACE	7 (<1)	2 (<1)	7 (<1)
Adjudicated cardiovascular death	2 (<1)	0	1 (<1)
Non-fatal myocardial infarction	1 (<1)	1 (<1)	4 (<1)
Non-fatal cardiac ischemia AESI	14 (1)	8 (1)	11 (1)
Non-fatal stroke AESI	4 (<1)	1 (<1)	2 (<1)
Incidence Rate	**Number of Subjects with Events per 1000 Subject-Years**		
Broad-definition MACE	54.3	44.5	31.2
Narrow-definition MACE	19.0	9.9	15.6
Adjudicated cardiovascular death	5.4	0	2.2
Non-fatal myocardial infarction	2.7	4.9	8.9
Non-fatal cardiac ischemia AESI	38.0	39.5	24.5
Non-fatal stroke AESI	10.9	4.9	4.5
Total Number of MACE Events			
Total broad-definition MACE events	22	11	15
Total narrow-definition MACE events	8	2	7

Data Source: Table 2.143, Table 2.152
Abbreviations: AESI=adverse event of special interest; ITT=intent-to-treat; MACE=major adverse cardiac event; SY=subject-years; UMEC=umeclidinium bromide
Note: Numbers represented the number of subjects with an event per 1000 subject-years of exposure. This is referenced as "Exposure-adjusted frequency" in other similar outputs.
Note: Incidence rate frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

The following observations were made with respect to each category of events within the MACE definitions:

- The percentage of subjects with non-fatal MI was similar across treatment groups including placebo (<1%). The exposure-adjusted frequency of subjects with non-fatal MI was lower for placebo (3 subjects with events per 1000 subject-years of exposure) than for the UMEC 62.5 mcg and UMEC 125 mcg groups (5 and 9 subjects with events per 1000 subject-years of exposure, respectively).
- The percentage of subjects with non-fatal cardiac ischemia (from broad-definition MACE) was the same across treatment groups (all 1%, including placebo). Exposure adjusted frequencies for UMEC treatment groups were similar to or less than that for placebo (40, 25, and 38 subjects with events per 1000 subject-years of exposure for UMEC 62.5 mcg, UMEC 125 mcg and placebo respectively).
- Non-fatal stroke: The exposure-adjusted frequencies for the UMEC treatments were less than that for placebo (5 subjects for UMEC 62.5 mcg and UMEC 125 mcg) with events per 1000 subject years of exposure, compared with 11 subjects for placebo).

Urinary retention AESI

Pharmacologic class effects of LAMAs include urinary retention.

In the Efficacy Studies and the All Clinical Studies grouping, 2 subjects (<1%) in the UMEC 125 mcg group reported 3 AEs (one AE of urinary hesitation and 2 AEs of urinary retention) in the urinary retention AESI category. No events were reported in the UMEC 62.5 mcg or placebo groups. No events in this AESI group were reported for subjects in the Long-term Safety Study or the Exercise Studies. No on-treatment or post-treatment deaths or other on-treatment SAEs in the urinary retention AESI group were reported for subjects in the Efficacy Studies, Long-term Safety Study, Exercise Studies or All Clinical Studies

groupings.Post-hoc summaries of on-treatment AESI were provided for the combined UMEC treatment doses (62.5 mcg and 125 mcg for “Combined UMEC Doses”) in the Efficacy Studies. The incidence of urinary retention AESI was 0% in the placebo group and <1% in the combined UMEC treatment groups, with 1 AE of urinary hesitation and 2 AEs of urinary retention reported in the combined UMEC treatment doses.

Ocular Effects AESI

Pharmacologic class effects of LAMAs also include ocular disorders including worsening narrow-angle glaucoma.

The incidence of on-treatment ocular effects AESI in the Efficacy Studies, Exercise Studies and All Clinical Study Groupings, was <1% in the UMEC 62.5 mcg and placebo groups and 1% in the UMEC 125 mcg group. In the Longterm Safety Study, the incidence of on-treatment ocular effects AESI was <1% in both the UMEC 125 mcg and placebo groups. Similar exposure-adjusted frequencies were observed in the Efficacy Studies and Exercise Studies for UMEC 125 mcg and placebo, with lower frequencies observed for UMEC 62.5 mcg.

In the All Clinical Studies grouping, the incidence of post-treatment events in the ocular effects AESI group was <1% in teh UMEC 125mcg treatment group with no events in the UMEC 62.5mcg and placebo groups. One subject (<1%) receiving UMEC 125 mcg in the Efficacy Studies (and All Clinical Studies Grouping) reported a post-treatment ocular effect AESI with a PT of cataract.

Gallbladder Disorders AESI

In the All Clinical Studies grouping, the incidence of on-treatment events in the gallbladder disorders special interest group was <1% in any treatment group including placebo. No clinically noteworthy dose- or treatment-related patterns were identified in either incidence or exposure-adjusted frequencies of on-treatment AEs in this AESI group.

One subject (<1%) receiving UMEC 62.5 mcg in the Efficacy Studies (and All Clinical Studies Groupings) reported a post-treatment gallbladder disorders AESI with a PT of cholecystitis.

Intestinal Obstruction AESI

Pharmacologic class effects of LAMAs include effects on the gastrointestinal system such as reduced peristalsis and complications that may result from inhibition of gastrointestinal tract activity. No on-treatment AEs were reported in the intestinal obstruction AESI in either UMEC dose group for any study grouping, nor were any post-treatment intestinal obstruction AESI reported for subjects randomized to UMEC or placebo

Anticholinergic Effects AESI

In the Efficacy Studies, the incidence of on-treatment anticholinergic effects AESI was 4% for each UMEC treatment group and placebo. In the Long-term Safety Study, both the placebo and UMEC 125 mcg treatment groups had AESI incidence rates of 2%. In the Exercise Studies, the incidence of on-treatment anticholinergic effects AESI was low (3% in UMEC 125 mcg compared with 2% in placebo and 0% in UMEC 62.5 mcg); the pattern of exposure-adjusted frequency was similar. In the All Clinical Studies Grouping, the incidence was 3% in both the UMEC 62.5 mcg and placebo groups and 4% in the UMEC 125 mcg group. The exposure adjusted frequencies were lower in the UMEC 125 mcg group compared with placebo and UMEC 62.5 mcg. In the All Clinical Studies grouping, the

incidence of post-treatment events in the anticholinergic effects special interest group were <1% for UMEC 62.5 mcg and placebo, and no AESI in this special interest group were recorded for any subjects receiving UMEC 125 mcg.

Pneumonia and LRTI AESI

Pneumonia and LRTI are commonly reported in patients with COPD. There are risk factors for development of pneumonia independent of treatment in patients with COPD including older age (especially >65 years), lower % predicted FEV1 (especially <30% predicted), COPD exacerbations in the year prior, worse MRC dyspnoea score (especially categories 4 and 5) and lower BMI [Crim et al *Eur Respir J.* 2009;34:641-7]. Although impairment of respiratory function does not in itself make patients susceptible to infection, it does influence the outcome of a LRTI [Wilson et al. Eur Respir J. 2001;17:995-1007]. The pneumonia and LRTI group was therefore further categorized to subgroups that describe pneumonia-associated events and lower respiratory tract infection-associated terms (excluding pneumonia).

Pneumonia

A summary of the incidences and exposure-adjusted frequencies of subjects in the Pneumonia AESI subgroup is presented by study grouping in the table below.

Table 47. On-Treatment Pneumonia AESI by Incidence Exposure-Adjusted Frequency by Study Grouping (ITT Population)

Study Grouping/ Pneumonia AESI	Placebo	UMEC 62.5	UMEC 125
Incidence	**Number (%) of Subjects**		
Primary Efficacy	N=623	N=487	N=698
	4 (<1)	3 (<1)	10 (1)
Long-term Safety Study	N=109	----	N=227
	0	----	7 (3)
Exercise	N=321	N=89	N=91
	0	1 (1)	0
All Clinical Studies	N=1124	N=576	N=1087
	4 (<1)	4 (<1)	17 (2)
Exposure-adjusted frequency	**Number of Subjects with Events per 1000 Subject-Years**		
Primary Efficacy	SY=220	SY=183	SY=263
	18.2	16.4	38.1
Long-term Safety Study	SY=80	---	SY=167
	0	---	41.9
Exercise	SY=68	SY=20	SY=19
	0	50.4	0
All Clinical Studies	SY=374	SY=202	SY=454
	10.7	19.8	37.4

Data Source: Table 2.113, Table 2.115, Table 2.114, Table 2.112, Table 2.117, Table 2.119 Table 2.118, Table 2.116
Abbreviations: AESI=adverse event of special interest; ITT=intent-to-treat; SY=subject-years; UMEC=umeclidinium bromide
Note: Numbers represent the number of subjects with an event per 1000 subject-years of exposureNote: Exposure-adjusted frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

In the Efficacy Studies, a higher incidence was reported for the UMEC 125 mcg treatment group (1%; 38 subjects with an event per 1000 subject-years of exposure) compared with <1% in the UMEC 62.5 mcg group (16 subjects with an event per 1000 subject-years of exposure) and placebo group (18 subjects with an event per 1000 subject-years of exposure). In the Long-term Safety Study, the incidence of Pneumonia-associated AESI was 3% in the UMEC 125 mcg group (42 subjects with an event per 1000 subject-years of exposure), compared with 0% in the placebo group. In the Exercise studies, the incidence of Pneumonia-associated AESI was 1% in the UMEC 62.5 mcg group and 0% in both the UMEC 125 mcg and placebo groups. In the All Clinical Studies Grouping, the highest incidence and exposure-adjusted frequency of Pneumonia AESI subgroup was with UMEC

125 mcg (2%; 37 subjects with an event per 1000 subject-years of exposure), compared with <1% for UMEC 62.5 mcg (20 subjects with an event per 1000 subject-years of exposure) and placebo (11 subjects with an event per 1000 subject-years of exposure).

LRTI

In the Efficacy Studies, 2% of subjects in the UMEC 125 mcg group (46 subjects with an event per 1000 subject-years of exposure) reported an LRTI-associated AESI, compared with <1% in the UMEC 62.5 mcg group (22 subjects with an event per 1000 subject-years of exposure) and placebo group (18 subjects with an event per 1000 subject-years of exposure). In the Long-term Safety Study, the incidence of LRTI-associated AESI was 3% in the UMEC 125 mcg group (36 subjects with an event per 1000 subject-years of exposure) compared with 2% in the placebo group (25 subjects with an event per 1000 subject-years of exposure). In the Exercise studies, the incidence of LRTI-associated AESI was 0% in the UMEC treatments, compared with <1% in placebo. In the All Clinical Studies Grouping, the highest incidence and exposure-adjusted frequency of LRTI-associated AESI occurred in subjects treated with UMEC 125 mcg (2%; 40 subjects with an event per 1000 subject-years of exposure, compared with <1% for UMEC 62.5 mcg group (20 subjects with an event per 1000 subject-years of exposure) and placebo (24 subjects with an event per 1000 subject-years of exposure).

A summary of the incidences and exposure-adjusted frequencies of subjects in the LRTI AESI subgroup is presented by study grouping in table below:

Table 48. On-Treatment LRTI AESI by Incidence and Exposure-Adjusted Frequency by Study Grouping (ITT Population)

Study Grouping/ LRTI AESI	Placebo	UMEC 62.5	UMEC 125
Incidence	**Number (%) of Subjects**		
Primary Efficacy	N=623	N=487	N=698
	4 (<1)	4 (<1)	12 (2)
Long-term Safety Study	N=109	----	N=227
	2 (2)	----	6 (3)
Exercise	N=321	N=89	N=91
	3 (<1)	0	0
All Clinical Studies	N=1124	N=576	N=1087
	9 (<1)	4 (<1)	18 (2)
Exposure-adjusted frequency	**Number of Subjects with Events per 1000 Subject-Years**		
Primary Efficacy	SY=220	SY=183	SY=263
	18.2	21.9	45.7
Long-term Safety Study	SY=80	----	SY=167
	24.9	----	35.9
Exercise	SY=68	SY=20	SY=19
	43.9	0	0
All Clinical Studies	SY=374	SY=202	SY=454
	24.1	19.8	39.6

Data Source: Table 2.113, Table 2.115, Table 2.114, Table 2.112, Table 2.117, Table 2.119 Table 2.118, Table 2.116
Abbreviations: AE=adverse event; AESI=adverse event of special interest; ITT=intent-to-treat; SY=subject-years; UMEC=umeclidinium bromide; LRTI=lower respiratory tract infection
Note: Numbers represent the number of subjects with an event per 1000 subject-years of exposure
Note: Exposure-adjusted frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

There is a consistent dose-trend in the increase in risk of pneumonia/LRTI with UMEC. However, the events are commonly associated to COPD and the incidence of on-treatment serious events observed in both UMEC doses is low is similar to that reported with other LAMAs.

Laboratory findings

Clinical chemistry and hematology parameters were measured in all clinical studies.

Based on the review of shifts with respect to the normal reference range for hematology and clinical chemistry analytes, no trends were observed suggesting an effect of UMEC on the occurrence of laboratory values outside the normal range.

Safety in special populations

Elderly: In clinical studies, 235 total patients were ≥75 years, of which 183 received treatment with UMEC. There were no remarkable differences in the pattern of incidence of on-treatment AE, serious individual case reports, or AEs leading to drop-out across the age subgroupings and treatment groups. There were no remarkable differences in the pattern of incidence of on-treatment AEs related to Psychiatric disorders, Nervous system disorders, Accidents and injuries, Vascular disorders, Cerebrovascular disorders, or Infections and infestations across the age subgroupings and treatment groups. A higher incidence of AEs in the Cardiac disorders SOC was noted in the older subjects (75 - <80 years, and 80 - <85 years) in the UMEC treatment groups compared with the placebo group and compared with the other age groups, but the analyses are hampered by the low number of subjects and low frequency of events. Current safety database is very limited for patients ≥75 years. The applicant will ensure that PASS includes a sufficient representation of patients aged ≥75 years to allow for an appropriate assessment of relevant adverse events, particularly of cardio- and cerebral-vascular adverse events.

Table 49. Number of Elderly Patients Involved in the Specified Studies for UMEC

Table 2 Number of Elderly Patients Involved in the Specified Studies for UMEC

eCTD Module	Age 65-74 n/N (all ages)	Age 75-84 n/N (all ages)	Age 85+ n/N (all ages)
Efficacy and Safety Studies[a]	627/1808	177/1808	6/1808
Human PK Studies	26/254	1/254	0/254
Human PD Studies	0/103	0/103	0/103
Biopharmaceutical Studies	0/31	0/31	0/31

Data Sources: Table 1210.9 (Efficacy and Safety Studies); data on file for remaining studies.
n=number; N=total number
a = Studies AC4115408, DB2113361, DB2113373, DB2113374.

COPD severity: Regarding the representation of severe/very severe COPD patients, a total of 362 subjects and 149 subjects, classified as GOLD stage III, were exposed to either UMEC 62.5 mcg or UMEC 125 mcg for greater than 20 weeks and 24 weeks, respectively. For subjects classified as GOLD stage IV, 79 subjects and 33 subjects were exposed to either UMEC 62.5 mcg or UMEC 125 mcg for greater than 20 weeks and 24 weeks, respectively. The distribution of COPD subjects by GOLD staging in the UMEC studies was consistent with the prevalence reported in standard practice [Jones et al, Respir Med. 2011; 105:57-66; Mapel DW, Int J Chron Obstruct Pulmon Dis. 2011; 6:573-81]. GOLD stage IV patients represented about 9-14% of all patients included in umeclidinium studies, which compares favourably with the GOLD stage IV representation in recent applications (e.g.:

aclidinium bromide; glycopyrronium bromide). Subjects with GOLD stage I disease were excluded from the UMEC Phase III studies, as maintenance treatment with long-acting bronchodilators is not recommended for this patient population [GOLD, Updated 2013; http://www.goldcopd.org]. This is endorsed. An assessment of the safety profile (any on-treatment AE, SAE, or fatal SAE) of UMEC in the Efficacy Studies and the Long-term Safety Study showed no remarkable differences in the overall pattern of AEs across treatment groups based on GOLD grade. There was no dose- or treatment-related patterns in the incidence of AEs in the CV AESI categories (acquired long QT, cardiac arrhythmias, cardiac failure, cardiac ischaemia, hypertension, sudden death, and stroke) in any GOLD stage. The most commonly reported CV AESI category for all GOLD stages was cardiac arrhythmias followed by hypertension in the UMEC and placebo groups.

Concomitant CV disease: In the Efficacy Studies, 58% of subjects reported at least one cardiovascular risk factor (e.g., hypertension [49%], hyperlipidaemia [27%], or diabetes [13%]); 20% reported a current cardiac disorder and approximately half (51%) of the subjects were current smokers. In addition, subjects with a past medical history of myocardial infarction (5%) and stroke (3%) were included in the Efficacy Studies. Similarly, the majority of subjects enrolled in the UMEC 125 mcg (68%) and placebo (64%) groups in the Long-term Safety Study reported a concurrent cardiovascular risk factor at Screening. A total of 35% and 34% of subjects in the UMEC 125 mcg and placebo groups, respectively, presented with a current cardiac disorder at Screening. Subjects with a prior history of myocardial infarction (6% in UMEC 125 mcg and 5% in the placebo group) and stroke (4% in both the UMEC 125 mcg and placebo groups) were included in the Long-term Safety Study.

Therefore, it is endorsed that there was a sufficient representation of patients with concomitant CV disease. That patients with significant uncontrolled cardiovascular disease were excluded from pivotal trials is reflected appropriately in the product information.

An analysis of CV AESI by the presence/absence of cardiovascular risk factor at Screening showed some increases with UMEC versus placebo in the incidence of cardiac arrhythmias, hypertension, and cardiac ischaemia in subjects with CV risk factors at baseline, which was not apparent in subjects without CV risk factors at baseline (see tables below).

Table 50. Summary of Incidence and Exposure-adjusted Frequency of On-treatment CV AESs of Special Interest Group/Subgroup by Cardiovascular Risk Factor at Screening (Efficacy Studies, ITT Population)

Table 22 Summary of Incidence and Exposure-adjusted Frequency of On-treatment CV AEs of Special Interest Group/Subgroup by Cardiovascular Risk Factor at Screening (Efficacy Studies, ITT Population)

Special Interest Group/ Subgroup	Number (%) of Subjects [exposure adjusted frequency, subject years]					
	Presence of CV Risk Factor at Screening			Absence of CV Risk Factor at Screening		
	Placebo (N=623) [SY=220]	UMEC 62.5 mcg (N=487) [SY=183]	UMEC 125 mcg (N=698) [SY=263]	Placebo (N=623) [SY=220]	UMEC 62.5 mcg (N=487) [SY=183]	UMEC 125 mcg (N=698) [SY=263]
Presence or Absence of CV Risk Factor at Screening	373 (60) [132]	287 (59) [105]	384 (55) [142]	250 (40) [88]	200 (41) [77]	314 (45) [121]
Any CV Event	27 (7) [205.3]	29 (10) [275.3]	34 (9) [239.8]	14 (6) [158.5]	14 (7) [181.3]	22 (7) [182.0]
Acquired Long QT	0 [0]	1 (<1) [9.5]	0 [0]	0 [0]	0 [0]	0 [0]
Cardiac arrhythmias	11 (3) [83.6]	14 (5) [132.9]	15 (4) [105.8]	8 (3) [90.6]	8 (4) [103.6]	7 (2) [57.9]
Cardiac failure	5 (1) [38.0]	7 (2) [66.5]	5 (1) [35.3]	1 (<1) [11.3]	0 [0]	2 (<1) [16.5]
Cardiac ischaemia	2 (<1) [15.2]	6 (2) [57.0]	3 (<1) [21.2]	3 (1) [34.0]	1 (<1) [13.0]	3 (<1) [24.8]
Hypertension	9 (2) [68.4]	6 (2) [57.0]	13 (3) [91.7]	2 (<1) [22.6]	6 (3) [77.7]	9 (3) [74.5]
Sudden death	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Stroke	2 (<1) [15.2]	1 (<1) [9.5]	0 [0]	0 [0]	0 [0]	1 (<1) [8.3]

Data Source: Table 1210.5, Table 1230.9, Table 1230.10, Table 1230.11, Table 1230.12.
Abbreviations: AE=adverse event; CV=cardiovascular; ITT=intent-to-treat; SY=subject years; UMEC=umeclidinium bromide
Note: Percentages are based on the number of subjects within each subgroup.
Note: Exposure adjusted frequency: numbers represent the number of subjects with an event per 1000 subject-years of exposure.
Note: Exposure-adjusted frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

Table 51. Summary of Incidence and Exposure-adjusted Frequency of On-treatment AEs of Special Interest Group/Subgroup by Cardiovascular Risk Factor at Screening (Long-term Safety Study, ITT Population)

Table 23 Summary of Incidence and Exposure-adjusted Frequency of On-treatment AEs of Special Interest Group/Subgroup by Cardiovascular Risk Factor at Screening (Long-term Safety Study, ITT Population)

Special Interest Group/ Subgroup	Number (%) of Subjects [exposure adjusted frequency, subject years]			
	Presence of CV Risk Factor at Screening		Absence of CV Risk Factor at Screening	
	Placebo (N=109) [SY=80]	UMEC 125 mcg (N=227) [SY=167]	Placebo (N=109) [SY=80]	UMEC 125 mcg (N=227) [SY=167]
Presence /Absence of CV Risk Factor at Screening	70 (64) [50]	155 (68) [113]	39 (36) [31]	72 (32) [54]
Any CV Event	14 (20) [281.5]	37 (24) [326.4]	11 (28) [358.7]	12 (17) [222.9]
Acquired Long QT	0 [0]	0 [0]	0 [0]	0 [0]
Cardiac arrhythmias	10 (14) [201.1]	31 (20) [273.5]	7 (18) [228.3]	8 (11) [148.6]
Cardiac failure	1 (1) [20.1]	2 (1) [17.6]	0 [0]	2 (3) [37.1]
Cardiac ischaemia	3 (4) [60.3]	1 (<1) [8.8]	1 (3) [32.6]	3 (4) [55.7]
Hypertension	2 (3) [40.2]	3 (2) [26.5]	5 (13) [163.0]	3 (4) [55.7]
Sudden death	0 [0]	0 [0]	0 [0]	0 [0]
Stroke	0 [0]	1 (<1) [8.8]	0 [0]	0 [0]

Data Source: Table 330.26, Table 330.27, Table 410.14, Table 430.42, Table 430.43
Abbreviations: AE=adverse event; CV=cardiovascular; ITT=intent-to-treat; SY=subject years; UMEC=umeclidinium bromide
Note: Percentages are based on the number of subjects within each subgroup.
Note: Exposure adjusted frequency: numbers represent the number of subjects with an event per 1000 subject-years of exposure.
Note: Exposure-adjusted frequency was calculated as (1000 * Number of subjects with AE) divided by (Total duration of exposure in days / 365.25).

The increase was more apparent for the low UMEC dose intended for authorisation than for the high UMEC dose. This can be at least partly explained with the more severe patient population (based on COPD disease severity and CV disease at baseline) compared with UMEC 125 mcg and placebo.

Safety related to drug-drug interactions and other interactions

Patients with COPD usually receive combination therapies. Drug-drug interaction studies with common drugs used for treating COPD drug have not been performed. Although no

formal in vivo drug interaction studies have been performed, inhaled umeclidinium bromide has been used concomitantly with other COPD medicinal products including short and long acting sympathomimetic bronchodilators and inhaled corticosteroids without clinical evidence of drug interactions. Co-administration of umeclidinium bromide with other long-acting muscarinic antagonists or medicinal products containing this agent has not been studied and is not recommended due to the potential for synergistic effects. This information is appropriately labelled in accordance with other LAMA.

Discontinuation due to adverse events

For the All Clinical Studies group, the incidence of at least one on-treatment AE leading to permanent discontinuation of study drug or withdrawal from a study was similar across treatment groups: 6% for both UMEC treatment groups and 5% for placebo (as shown in Table 15, under the epigraph "Subject disposition". Overall, the exposure-adjusted frequencies of subjects withdrawn were lower in the UMEC treatment groups compared with placebo, which was mainly at expenses of a higher rate of withdrawals due to lack of efficacy with placebo. There were no significant differences for withdrawals due to AEs across all treatment groups in the overall study population.

Table 52. Summary of Withdrawal Study Record (Exposure Adjusted) (All Clinical Studies – ITT Population)

Table 2 Summary of Withdrawal Study Record (Exposure Adjusted) (All Clinical Studies - ITT Population)

	Placebo (SY=374)	UMEC 62.5 mcg (SY=202)	UMEC 125 mcg (SY=454)
Withdrawn	767.7	543.5	616.3
Primary/Subreason for Withdrawal [a]			
Adverse event	147.1	187.8	151.9
Lack of efficacy	339.7	133.4	167.3
Exacerbation	248.8	123.5	127.7

Data Source: Table 1210.2
Abbreviations: ITT=intent-to-treat; SY=subject years; UMEC=umeclidinium bromide; yrs=years
Note: In crossover studies, subjects were only included if they were randomised to and received a treatment of interest. They were counted under each treatment of interest. Subjects withdrawn during Period 2 were counted as a completer under their Period 1 treatment (only presented if a treatment of interest) and as a withdrawal under their Period 2 treatment of interest.
Note: Exacerbation is a sub-reason for withdrawal due to lack of efficacy
Note: Numbers represent the number of subjects in each withdrawal category per 1000 subject-yrs of exposure. Exposure-adjusted frequency was calculated as (1000 * Number of subjects in category) divided by (Total duration of exposure in days / 365.25).
a. Subjects only recorded one primary reason for withdrawal and were not required to indicate subreasons. However, subjects could have selected more than one subreason if appropriate

As expected, overall withdrawal rates increased as severity of the disease increased (from GOLD stage II to IV), but consistently favoured UMEC groups versus placebo regardless disease severity.

Post marketing experience

At the time of submission umeclidinium bromide was not marketed in any country in the world.

2.6.1. Discussion on clinical safety

The safety database comprises 1663 subjects that received UMEC (576 subjects received 62.5 mcg and 1087 subjects received 125 mcg), representing approximately 656 subject-years of exposure, compared with 1124 subjects receiving placebo. Median exposure duration across the UMEC groups was 165 days (UMEC 62.5 mcg) and 166 days (UMEC 125 mcg) compared with 88 days for placebo; with mean days: 128 and 153 days for UMEC 62.5 mcg and UMEC 125 mcg respectively compared with 122 days in the placebo group. Patient exposure is in line with the minimum exposure recommendations of ICH-E1

(e.g.: at least 300 patients treated for a minimum of 6 months, and at least 100 patients treated for a minimum of 1 year).

Regarding the representation of severe/very severe COPD patients in the Efficacy Studies, a total of 362 subjects and 149 subjects, classified as GOLD stage III, were exposed to either UMEC 62.5 mcg or UMEC 125 mcg for greater than 20 weeks and 24 weeks, respectively. For subjects classified as GOLD stage IV, 79 subjects and 33 subjects were exposed to either UMEC 62.5 mcg or UMEC 125 mcg for greater than 20 weeks and 24 weeks, respectively. The distribution of COPD subjects by GOLD staging in the UMEC studies was consistent with the prevalence reported in standard practice [Jones et al, Respir Med. 2011; 105:57-66; Mapel DW, Int J Chron Obstruct Pulmon Dis. 2011; 6:573-81]. GOLD stage IV patients represented about 9-14% of all patients included in umeclidinium studies, which compares favourably with the GOLD stage IV representation in recent applications (e.g.: aclidinium bromide; glycopyrronium bromide).

In the Efficacy Studies, 58% of subjects reported at least one cardiovascular risk factor (e.g., hypertension [49%], hyperlipidaemia [27%], or diabetes [13%]); 20% reported a current cardiac disorder and approximately half (51%) of the subjects were current smokers. In addition, subjects with a past medical history of myocardial infarction (5%) and stroke (3%) were included in the Efficacy Studies. Similarly, the majority of subjects enrolled in the UMEC 125 mcg (68%) and placebo (64%) groups in the Long-term Safety Study reported a concurrent cardiovascular risk factor at Screening. A total of 35% and 34% of subjects in the UMEC 125 mcg and placebo groups, respectively, presented with a current cardiac disorder at Screening. Subjects with a prior history of myocardial infarction (6% in UMEC 125 mcg and 5% in the placebo group) and stroke (4% in both the UMEC 125 mcg and placebo groups) were included in the Long-term Safety Study.

A higher proportion of subjects on UMEC 62.5 mcg, with a CV risk factor at Screening, reported a CV event compared with subjects on UMEC 125 mcg and placebo.

Occasional differences were observed in the incidence or exposure-adjusted frequency in subjects with a CV risk factor at Screening in the cardiac arrhythmias, hypertension, and cardiac ischaemia categories. However, few individual events were reported across treatment groups and the data showed no consistent trend in the events reported with either the UMEC 62.5 mcg or UMEC 125 mcg treatments in subjects with a CV risk factor at Screening.

Furthermore the observed numerical differences in the CV events reported between the treatment groups in the cardiac arrhythmias, cardiac ischaemia and hypertension AESI categories could be at least in part explained by differences in baseline characteristics. Overall, the UMEC 62.5 mcg treatment group had a more severe patient population (based on COPD disease severity and CV disease at baseline) compared with UMEC 125 mcg and placebo.

In the All Clinical Studies grouping, the incidence of on-treatment cardiovascular AESI showed a dose-trend for UMEC, being 8% for UMEC 62.5 mcg (222 subjects with an event per 1000-subject years), 10 % for UMEC 125 mcg (236 subjects with an event per 1000-subject years) and 7% for placebo (209 subjects with an event per 1000-subject years). Cardiac arrhythmias were the most frequently reported subgroup of cardiovascular AESI, followed by hypertension and cardiac ischemia in all clinical studies (ITT population). Arrhythmias included supraventricular tachycardia (SVT), atrial fibrillation, and supraventricular extrasystoles, as assessed by AE reports and ECG and Holter findings,

which occurred at a higher incidence in the UMEC treatment groups compared with placebo. Appropriate risk minimisation includes atrial fibrillation and tachycardia in the SmPC, and a patient appropriate equivalent message is also included in the patient information leaflet, similar to other marketed anticholinergics.

The ECG/holter abnormalities had no specific pattern and also did not have any clinically significant symptom associated with the abnormality, and so this imbalance is not a significant concern. In addition, the thorough QTc study and the remaining ECG data from the clinical efficacy studies also do not raise any specific concern on the QTc prolongation potential of UMEC. Therefore taking the overall data in to consideration it is accepted that the risk of QTc prolongation by UMEC is low.

However and in the context of being a possible class effect of LAMAs cardio and cerebrovascular events were included as an important potential risk in the RMP. As it is considered that UMEC treatment, compared to other recently approved LAMA, does not pose a particular risk of arrhythmias the product information outlines the risk of cardiovascular effects in accordance with other LAMA.

In order to assess if the presence/absence of CV risk factors at screening is a factor linked to the development of CV adverse events the applicant will evaluate overall absolute and relative risks relating to cardio- and cerebrovascular disorders in two post authorisation safety studies (201038 and WWE117397) in patients with and without CV risk factor at screening, and will provide with interaction p-values. As the current safety database is very limited for patients ≥75 years the applicant will also ensure sufficient representation of this age group.

The overall safety profile of UMEC was generally consistent with the known class effects of LAMAs and comorbidities often present in patients with COPD. However, although UMEC belongs to a well-established and known class of molecules (LAMA), it is a new active substance and safety data from this class may not be necessarily applicable.

In addition the only active 24-week tiotropium controlled study was not designed to compare the safety of UMEC and tiotropium and no direct comparisons with other LAMA are available. The imposed Post-Authorisation Safety Observational study and the DUS (described in the RMP) will provide further data to compare safety of these products.

A higher incidence of pneumonia-associated AESIs and LRTI was noted in the UMEC treatment groups compared with placebo. In the Long-term Safety Study, the incidence of Pneumonia-associated AESI was 3% in the UMEC 125 mcg group (42 subjects with an event per 1000 subject-years of exposure), compared with 0% in the placebo group. The corresponding incidences for LRTI were 3% in the UMEC 125 mcg group (36 subjects with an event per 1000 subject-years of exposure) compared with 2% in the placebo group (25 subjects with an event per 1000 subject-years of exposure). These events are commonly associated to COPD and the incidence of on-treatment serious events observed in both UMEC doses is low and similar to that reported with other LAMAs.

The magnitude of the difference is not enough to suggest a causal relationship but considering the indication of a dose trend the important potential risk of pneumonia and LRTI will be followed up within the imposed non-interventional PASS as outlined in the RMP.

In the Long-term Safety Study, the following adverse events occurred with an incidence in the UMEC 125 mcg treatment group 3% higher than the incidence in the placebo group:

headache, nasopharyngitis, cough, supraventricular tachycardia, supraventricular extrasystoles and sinus tachycardia, with an incidence in the UMEC 125 mcg treatment group 3% higher than the incidence in the placebo group. Rash and rhythm idioventricular occurred with an incidence in UMEC group 2% higher than the incidence in the placebo group with no events reported in the placebo group. These adverse reactions have been included in Section 4.8 of the SmPC..

Also the current safety database is very limited for patients ⩾75 years. The applicant will ensure that both PASS will include a sufficient representation of patients aged ⩾75 years to allow for an appropriate assessment of relevant adverse events, particularly in the cardio- and cerebrovascular category.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics

2.6.2. Conclusions on the clinical safety

The overall safety profile of UMEC was generally consistent with the known class effects of LAMAs and comorbidities often present in patients with COPD. However, although UMEC belongs to a well-established and known class of molecules (LAMA), it is a new active substance and safety data from this class may not be necessarily applicable.

The Post-Authorisation Safety Observational study (201038) and the DUS (WWE117397) will complement the safety profile with a comparison on cardiovascular safety with other LAMAs and follow up on the important potential risk of LRTI as described in the RMP.

In line with the safety follow up of other LAMA (aclidinium and glycopyrronium) and LAMA/LABA (umeclidinium/vilanterol) further investigation of the potential risk of cardio- and cerebrovascular events is considered to be key to benefit risk and therefore the prospective non-interventional PASS (study 20103) is made a condition of the MA

The CHMP considers the following measures necessary to address issues related to safety:

Description	Due date
Submission of the final clinical study report on a Post-Authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients with Incruse compared with tiotropium (study 201038), according to a protocol agreed by the PRAC.	By Q3 2024

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

The PRAC considers that the risk management plan system version 3.0 could be acceptable with revisions required as described in the attached PRAC endorsed PRAC Rapporteur assessment report.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of safety concerns	
Important Identified risks	None identified
Important Potential risks	Cardio- and Cerebrovascular Disorders
	Paradoxical bronchospasm (which may be life threatening)
	Narrow angle glaucoma
	Bladder outflow obstruction and urinary retention
Missing information	Safety in pregnancy and lactation
	Safety in long-term use
	Safety in severe hepatic impairment
	Additional *in vitro* investigations to determine the potential for DDI's with respect to: a) binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations b) provide data for UMEC as a substrate for BCRP and BSEP c) provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers d) provide data for UMEC as a substrate of OATP1B1 and 1B3

- **Pharmacovigilance plans**

III.5.1. Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
A Post-Authorisation Safety Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD patients using Inhaled UMEC/VI or Inhaled UMEC versus Tiotropium Handihaler (Study 201038). [Category 1]	To quantify the incidence of selected cardiovascular and cerebrovascular events of interest after the start of exposure to UMEC/VI combination or UMEC in the licensed indication, in the post marketing setting, specifically in the COPD patients managed in primary care in multiple European countries and compare with the incidence of cardiovascular and cerebrovascular events of interest after the start of exposure to tiotropium (Handihaler) over 24 months follow-up.	Cardio- and Cerebrovascular Disorders Safety in long-term use	Planned	Final report: Q3 2024

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
WWE117397 (formerly WEUSKOP6679): 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 [Category 3]	*Primary:* Drug utilisation review of new users of UMEC/VI and new users of UMEC compared to the COPD patients initiating long-acting bronchodilators. *Secondary:* Quantify the disease burden of COPD and estimate the incidence of selected cardiovascular and cerebrovascular events of interest among new users of UMEC/VI, new users of UMEC and a comparator (selected from new long-acting bronchodilator users) among those with no ongoing management for the events of interest at observation start.	Cardio- and Cerebrovascular Disorders	Planned	Final report: Q2 2020
Regulatory review of the submission has highlighted additional *in vitro* drug interaction investigations which should be completed. [Category 3]	Additional investigations to provide information to address: a) binding of UMEC to microsomes and recalculation of I/K_i in the gut based on free drug concentrations b) providing data for UMEC as a substrate for BCRP and BSEP c) provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers d) provide data for UMEC as a substrate of OATP1B1 and 1B3	A series of post authorisation *in vitro* studies will determine the potential for drug-drug interactions.	Planned	Final report: Q1 2015

- **Risk minimisation measures**

VI.1.4 Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardio- and Cerebrovascular Disorders	Prescription-only medication. Proposed text in EU SmPC: "*4.4 Special warnings and precautions for use* *Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists including umeclidinium bromide. In addition, patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium bromide should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.*" 4.8 Undesirable Effects Atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, rhythm idioventricular and tachycardia included as 'uncommon' in table of adverse reactions. A patient appropriate equivalent message will also be	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	included in the user tested patient information leaflet.	
Paradoxical bronchospasm (which may be life-threatening)	Prescription-only medication. Proposed text in EU SmPC: "*4.4 Special warnings and precautions for use* *Paradoxical bronchospasm* *Administration of umeclidinium bromide may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy instituted if necessary.*"	Not applicable
Narrow angle glaucoma	Prescription-only medication. Proposed text in EU SmPC: "*4.4 Special warnings and precautions for use* *Antimuscarinic activity* *Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.*"	Not applicable
Bladder outflow obstruction and urinary retention	Prescription-only medication. Proposed text in SmPC: "*4.4 Special warnings and precautions for use* *Antimuscarinic activity* *Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.*"	Not applicable
Pregnancy and lactation	Prescription-only medication. Proposed text in EU SmPC: "*4.6 Fertility, pregnancy and lactation* *Pregnancy* *There are no data from the use of umeclidinium bromide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.* *Umeclidinium bromide should be used during pregnancy*	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	only if the expected benefit to the mother justifies the potential risk to the fetus. *Breast-feeding* *It is unknown whether umeclidinium bromide is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded.* *A decision must be made whether to discontinue breast-feeding or to discontinue INCRUSE therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman."*	
Safety in severe hepatic impairment	Prescription-only medication. Proposed text in SmPC: "*4.2 Posology and method of administration* *Hepatic impairment* *No dosage adjustment is required in patients with mild or moderate hepatic impairment. INCRUSE has not been studied in patients with severe hepatic impairment and should be used with caution.* *5.2 Pharmacokinetic properties* *Hepatic impairment* *Subjects with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to umeclidinium bromide (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium bromide has not been evaluated in subjects with severe hepatic impairment."*	Not applicable

Following the PRAC advice the Applicant submitted an updated RMP (version 5.0) with the following information:

- **Safety concerns**

Summary of safety concerns	
Important Identified risks	None identified
Important Potential risks	Cardio- and Cerebrovascular Disorders
	Paradoxical bronchospasm (which may be life threatening)
	Narrow angle glaucoma
	Bladder outflow obstruction and urinary retention
	Lower Respiratory Tract Infection (incl. pneumonia)
Missing information	Safety in pregnancy and lactation
	Safety in long-term use

	Safety in severe hepatic impairment
	Additional *in vitro* investigations to determine the potential for DDI's with respect to: a) binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations b) provide data for UMEC as a substrate for BCRP and BSEP c) provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers d) provide data for UMEC as a substrate of OATP1B1 and 1B3

- **Pharmacovigilance plans**

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned /started)	Date for submission of interim or final reports (planned or actual)
A Post-Authorisation Safety Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebro-vascular Events in COPD patients using Inhaled UMEC/VI or Inhaled UMEC versus Tiotropium Handihaler (Study 201038). [Category 1]	To quantify the incidence of selected cardiovascular and cerebrovascular events of interest after the start of exposure to UMEC/VI combination or UMEC in the licensed indication, in the post marketing setting, specifically in the COPD patients managed in primary care in multiple European countries and compare with the incidence of cardiovascular	Cardio- and Cerebro-vascular Disorders LRTI (incl. pneumonia) Safety in long-term use	Planned	Final report: Q3 2024

	and cerebro-vascular events of interest after the start of exposure to tiotropium (Handihaler) over 24 months follow-up.			
WWE117397 (formerly WEUSKOP6679): 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 [Category 3]	*Primary:* Drug utilisation review of new users of UMEC/VI and new users of UMEC compared to the COPD patients initiating long-acting broncho-dilators. *Secondary:* Quantify the disease burden of COPD and estimate the incidence of selected cardio-vascular and cerebro-vascular events of interest among new users of UMEC/VI, new users of UMEC and a comparator (selected from new long-acting bronchodilator users) among those with no ongoing management for the events of interest at observation start.	Cardio- and Cerebrovascular Disorders LRTI (incl. pneumonia)	Planned	Final report: Q2 2020
Regulatory review of the submission has highlighted additional *in vitro* drug interaction investigations which should be completed. [Category 3]	Additional investigations to provide information to address: a) binding of UMEC to microsomes and recalculation of I/K_i in the gut based on free drug con-centrations b) providing data for UMEC as a	A series of post authorisation *in vitro* studies will determine the potential for drug-drug interactions.	Planned	Final report: Q1 2015

	substrate for BCRP and BSEP c) provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers d) provide data for UMEC as a substrate of OATP1B1 and 1B3			

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Cardio- and Cerebrovascular Disorders	Prescription-only medication. Proposed text in the SmPC: "*4.4 Special warnings and precautions for use* *Cardiovascular effects, such as cardiac arrhythmias e.g. atrial fibrillation and tachycardia, may be seen after the administration of muscarinic receptor antagonists including umeclidinium bromide. In addition, patients with clinically significant uncontrolled cardiovascular disease were excluded from clinical studies. Therefore, umeclidinium bromide should be used with caution in patients with severe cardiovascular disorders, particularly cardiac arrhythmias.*" 4.8 Undesirable Effects Atrial fibrillation, supraventricular tachycardia, supraventricular extrasystoles, rhythm idioventricular and tachycardia included as 'uncommon' in table of adverse reactions. A patient appropriate equivalent message will also be included in the user tested patient information leaflet.	Not applicable
Paradoxical bronchospasm (which may be life-threatening)	Prescription-only medication. Proposed text in the SmPC: "*4.4 Special warnings and precautions for use* *Paradoxical bronchospasm* *Administration of umeclidinium bromide may produce paradoxical bronchospasm that may be life-threatening. Treatment should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy*	Not applicable

	instituted if necessary."	
Narrow angle glaucoma	Prescription-only medication. Proposed text in the SmPC: "*4.4 Special warnings and precautions for use* *Antimuscarinic activity* *Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.*"	Not applicable
Bladder outflow obstruction and urinary retention	Prescription-only medication. Proposed text in the SmPC: "*4.4 Special warnings and precautions for use* *Antimuscarinic activity* *Consistent with its antimuscarinic activity, umeclidinium bromide should be used with caution in patients with urinary retention or with narrow-angle glaucoma.*"	Not applicable
Lower respiratory tract infection (incl. pneumonia)	Prescription-only medication.	Not applicable
Pregnancy and lactation	Prescription-only medication. Proposed text in the SmPC: "*4.6 Fertility, pregnancy and lactation* *Pregnancy* *There are no data from the use of umeclidinium bromide in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.* *Umeclidinium bromide should be used during pregnancy only if the expected benefit to the mother justifies the potential risk to the fetus.* *Breast-feeding* *It is unknown whether umeclidinium bromide is excreted in human milk. A risk to breastfed newborns/infants cannot be excluded.* *A decision must be made whether to discontinue breast-feeding or to discontinue INCRUSE therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.*"	Not applicable
Safety in severe hepatic impairment	Prescription-only medication. Proposed text in SmPC: "*4.2 Posology and method of administration* *Hepatic impairment* *No dosage adjustment is required in patients with mild or moderate hepatic impairment.*	Not applicable

	INCRUSE has not been studied in patients with severe hepatic impairment and should be used with caution. *<u>5.2 Pharmacokinetic properties</u>* *<u>Hepatic impairment</u>* *Subjects with moderate hepatic impairment (Child-Pugh Class B) showed no evidence of an increase in systemic exposure to umeclidinium bromide (C_{max} and AUC), and no evidence of altered protein binding between subjects with moderate hepatic impairment and healthy volunteers. Umeclidinium bromide has not been evaluated in subjects with severe hepatic impairment.*"	

In accordance with the PRAC advice, the Applicant addressed in version 5.0 all open issues as outlined in the PRAC Rapporteur assessment report. LRTI incl. Pneumonia was added as important potential risk to the safety concerns and will be addressed within the imposed PASS as outlined in the pharmacovigilance plans. The RMP version 5.0 was considered acceptable.

The CHMP endorsed this advice without changes.

2.9. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Anoro Ellipta. The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The results of the Phase III studies are considered to provide adequate consistent evidence of efficacy UMEC versus placebo in terms of improvement of lung function (trough FEV1). In terms of clinically relevant symptomatic improvement (TDI focal score, SGRQ), not always the differences versus PBO reached the minimally important difference (e.g.: TDI score, SGRQ score). However, in terms of TDI score responders and SGRQ responders versus placebo, the odds ratio of being responder was statistically significant and in line with the results obtained in comparison with placebo for other LAMA recently authorised in the EU (aclidinium bromide). UMEC 62.5 mcg (55 mcg delivered dose) demonstrated a lower risk of COPD exacerbation compared with placebo (hazard ratio 0.6 [95% CI 0.4, 0.9] indicating a risk reduction of 40%.

Uncertainty in the knowledge about the beneficial effects

Long-term effects of UMEC 125 mcg (for approximately 52-weeks) were assessed in study DB2113359. The study was not designed to study the long-term effects of UMEC 62.5 mcg (55 mcg delivered dose) for which the company is seeking approval. However, available

data at 6 months suggest that the efficacy of UMEC is maintained for both UMEC 62.5 mcg and 125 mcg over the entire 6-month treatment period across measures of lung function, dyspnea, health-related quality of life, and COPD exacerbation. Given the similarity in efficacy observed between the 2 UMEC doses during the 6 month studies and the persistence of effect observed with UMEC 125 mcg in the long-term safety study, it is expected that UMEC 62.5 mcg (55 mcg delivered dose) would demonstrate sustained efficacy at 1 year, similar to that observed with UMEC 125 mcg and no further efficacy follow up is required by the CHMP.

No direct comparisons between UMEC 62.5 mg (55 mcg delivered dose) and TIO or other established bronchodilators have been conducted. However, the DB2113374 study showed that the efficacy of UMEC 125 mcg was similar to TIO 18 mcg. Given the similarity in the efficacy profile of UMEC 62.5 mcg and UMEC 125 mcg, the results of this study are accepted as an indirect estimation of the expected effect size of UMEC 62.5 mcg in relation to tiotropium. Comparisons with published literature also suggest that the improvements seen with UMEC 62.5 mcg in efficacy (e.g.: FEV1, SGRQ, TDI score) are similar to what has been observed in studies with other LAMAs (e.g.: aclidinium bromide, glycopyrronium bromide) in COPD patients [Karabis et al. Int J COPD. 2013;8:405-23]. Therefore extrapolation to the 62.5 mcg dose is considered acceptable for the efficacy evaluation.

Risks

Unfavourable effects

In the Long-Term Safety study, the following adverse events events occurred with an incidence in the UMEC 125 mcg treatment group 3% higher than the incidence in the placebo group: headache, nasopharyngitis, cough, supraventricular tachycardia, supraventricular extrasystoles and sinus tachycardiaRash and rhythm idioventricular occurred with an incidence in UMEC group 2% higher than the incidence in the placebo group with no events reported in the placebo group. All the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics. With respect to risks, common adverse events were in line with the expected safety profile of a LAMA in COPD.

In all study groupings, the incidence of on-treatment cardiovascular AESI showed a dose-trend for UMEC. Cardiac arrhythmias were the most frequently reported subgroup of cardiovascular AESI, followed by hypertension and cardiac ischemia in all clinical studies (ITT population). The ECG/holter abnormalities had no specific pattern and also did not have any clinically significant symptom associated with the abnormality, and so this imbalance is not a significant concern.

Therefore UMEC treatment is not considered to pose a particular risk of arrhythmias and the product information outlines the risk of cardiovascular effects in accordance with other LAMAs. In the context of being a possible class effect of LAMAs cardio and cerebrovascular events were included as an important potential risk in the RMP and will be followed up with two post authorisation safety studies 201038 and WWE117397.

Uncertainty in the knowledge about the unfavourable effects

A higher incidence of pneumonia-associated AESIs and LRTI was noted in the UMEC 125mcg treatment groups compared with placebo. In the Long-term Safety Study, the incidence of Pneumonia-associated AESI was 3% in the UMEC 125 mcg group (42 subjects with an event

per 1000 subject-years of exposure), compared with 0% in the placebo group. The corresponding incidences for LRTI were 3% in the UMEC 125 mcg group (36 subjects with an event per 1000 subject-years of exposure) compared with 2% in the placebo group (25 subjects with an event per 1000 subject-years of exposure). These events are commonly associated to COPD and the incidence of on-treatment serious events observed in both UMEC doses is low and similar to that reported with other LAMAs. The magnitude of the difference is not enough to suggest a causal relationship but considering the indication of a dose related trend in incidence, pneumonia and LRTI will be followed up within the non-interventional PASS and as important potential risk as outlined in the RMP.

An analysis of CV AESI by the presence/absence of cardiovascular risk factor at Screening showed some increases with UMEC versus placebo in the incidence of cardiac arrhythmias, hypertension, and cardiac ischaemia in subjects with CV risk factors at baseline, which was not apparent in subjects without CV risk factors at baseline. In efficacy studies, the increase was much more apparent for the low UMEC dose intended for authorisation than for the high UMEC dose. The warning about cardiovascular effects in the SmPC has further been complemented with the information that patients with clinically significant uncontrolled cardiovascular disease were excluded from the clinical studies.

Although UMEC belongs to a well-established and known class of molecules (LAMA), it is a new active substance. In this light further investigation of the potential risk of cardio- and cerebrovascular events and LTRI including pneumonia in comparison to tiotropium is considered to be key to benefit risk and will be studied in an imposed prospective post-authorisation safety study (Study 201038) to allow for an appropriate assessment of relevant adverse events, particularly in the cardio- and cerebral-vascular category.

As the current safety database is very limited for patients $\geqslant$75 years the applicant will ensure that the PASS will include a sufficient representation of patients aged $\geqslant$75 years. Data from this study will be complemented by a second PASS (Drug utilisation study) as outlined in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

COPD is a chronic, progressive condition with high morbidity. The efficacy data from primary efficacy studies indicate that UMEC 62.5 mcg (55 mcg delivered dose) produce a statistically significant and clinically relevant improvement in lung function as compared to placebo. With regards to COPD symptoms, the differences versus PBO reached not always the minimally important difference in the transition dyspnoea score (> 1 unit). However, the responders' analyses for TDI score were consistently in favour of UMEC vs. placebo.

UMEC 62.5 mcg (55 mcg delivered dose) demonstrated a lower risk of COPD exacerbation compared with placebo (hazard ratio 0.6 [95% CI 0.4, 0.9] indicating a risk reduction of 40%. These results overall are considered clinically relevant.

Comparisons with published literature also suggest that the improvements seen with UMEC 62.5 mcg (55 mcg delivered dose) in efficacy (e.g.: FEV1, SGRQ, TDI score) are similar to what has been observed in studies with other LAMAs (e.g.: aclidinium bromide, glycopyrronium bromide) in COPD patients [Karabis et al. Int J COPD. 2013;8:405-23].

With respect to unfavourable effects, the nature and incidence of common adverse events are in line with the expected safety profile of a LAMA in the COPD population. UMEC is not considered to pose a particular risk of arrhythmias and cardiovascular side effects, overall in line with other LAMAs, are appropriately manageable with the approved labelling and RMP.

Benefit-risk balance

UMEC has shown clinically relevant effects on lung function and symptoms in comparison with placebo similar to what has been observed in studies with other LAMAs. Common adverse events are in line with the expected safety profile of a LAMA in COPD. It is considered that UMEC treatment does not pose a particular risk of arrhythmias and the potential risks of cardiovascular adverse events and LRTI including pneumonia can be balanced with the appropriate risk minimisation measures in accordance with other approved LAMAs as discussed in detail above. Further data to allow comparative safety assessment to other LAMA will be generated through two post authorisation safety studies.

Balancing favourable and unfavourable effects and in accordance with the companies proposed posology for authorisation the risk benefit balance for the 62.5 mcg dose (equivalent to 55 mcg delivered dose) once daily is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of umeclidinium bromide as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the

medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Submission of the final clinical study report on a Post-Authorisation Safety (PAS) Observational Cohort Study to Quantify the Incidence and Comparative Safety of Selected Cardiovascular and Cerebrovascular Events in COPD Patients with Incruse compared with tiotropium (study 201038), according to a protocol agreed by the PRAC.	By Q3 2024

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that umeclidinium bromide is qualified as a new active substance.