28 March 2014
EMA/CHMP/163506/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Laventair

International non-proprietary name: umeclidinium bromide / vilanterol

Procedure No. EMEA/H/C/003754/0000

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:	Laventair
Applicant:	Glaxo Group Ltd 980 Great West Road Brentford Middlesex TW8 9GS United Kingdom
Active substance:	Umeclidinium bromide / vilanterol trifenatate
International Nonproprietary Name/Common Name:	Umeclidinium bromide / vilanterol
Pharmaco-therapeutic group (ATC Code):	Drugs for obstructive airway diseases, adrenergics in combination with anticholinergics (R03AL03)
Therapeutic indication(s):	Laventair 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 micrograms / 22 micrograms
Route(s) of administration:	Inhalation use
Packaging:	blister (alu)
Package size(s):	1 x 7 dose inhaler, 1 x 30 dose inhaler and 3 x 30 dose inhaler

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List of abbreviations

AC	Active controlled
ADME	Absorption, distribution, metabolism and elimination
AE	Adverse Event
AESI	Adverse event of special interest
APSD	Aerodynamic particle size distribution
$AUC_{(0-24)}$	Area under the concentration-time curve over the once-daily dosing interval
$AUC_{(0-t)}$	Area under the concentration-time curve from time zero (pre-dose) to last time of quantifiable concentration
$AUC_{(0-t')}$	Area under the concentration-time curve from zero (pre-dose) to the time of last common measurable time-point, t', within subject across treatments
BID/BD	Twice daily
BMI	Body Mass Index
bpm	Beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent clearance following oral dosing
C_{max}	Maximum observed concentration
COPD	Chronic Obstructive Pulmonary Disease
CRQ-SAS	Chronic Respiratory Disease Questionnaire – Self-Administered Standardized
CYP2D6	Cytochrome P450 2D6
CYP3A4	Cytochrome P450 3A4
DB	Double blind
DD	Double dummy
DPI	Dry Powder inhaler
ECG	Electrocardiogram
EET	Exercise Endurance Test
Emax	Maximum effective dose
EMA	European Medicines Agency
EQ-5D	EuroQol-5D
ESWT	Exercise shuttle walk test
EU	European Union
FDA	Food and Drug Administration
FEV_1	Forced expiratory volume in one second
FF	Fluticasone Furoate
FRC	Functional residual capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GOLD	Global Initiative for Obstructive Lung Disease
GSK	GlaxoSmithKline
HRQoL	Health-related quality of life
HPA	Hypothalamic-pituitary-adrenal
IC	Inspiratory capacity
ICH	International Conference on Harmonisation
ICS	Inhaled corticosteroid
IMB	Irish Medicines Board
IND	Investigational New Drug

IOP	Intraocular pressure
ITT	Intent-to-Treat
IV	Intravenous
kg	Kilogram
L	liter
LABA	Long-acting $beta_2$ agonist
LAMA	Long-acting muscarinic antagonist
LLQ	Lower limit of quantification
LOCF	Last observation carried forward
LOCS III	Lens Opacities Classification System III
LogMAR	Logarithm of the angle of resolution
LRTI	Lower respiratory tract infection
LS	Least squares
MAA	Marketing Authorization Application
MACE	Major Adverse Cardiac Event
mcg	Micrograms
MCID	Minimal clinically important difference
mITT	Modified intent-to-treat
mg	Milligrams
mMRC	Modified Medical Research Council
MHRA	Medicines and Healthcare products Regulatory Agency
Msec	millisecond
NDA	New Drug Application
NDPI	Novel Dry Powder Inhaler
NQ	Not quantifiable
OD	Once daily
OL	Open label
PD	Pharmacodynamics
PDCO	Paediatric Committee of the European Medicines Agency
PEF	Peak expiratory flow
PG	Parallel group
P-gp	P-glycoprotein
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PLA	placebo
PT	Preferred Term
QD	Once daily
QTci	QT interval individually corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fredericia's formula
R	Randomized
RV	Residual volume
SABA	Short-acting $beta_2$-agonist
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SGRQ	St. George's Respiratory Questionnaire
SOBDA	Shortness of breath with daily activities
SVE	Supraventricular ectopic
SVT	Supraventricular tachycardia
T_{max}	Time of occurrence of C_{max}

TDI	Transition dyspnoea index
UMEC	Umeclidinium bromide
URTI	Upper respiratory tract infection
US	United States
VI	Vilanterol
WHO	World Health Organisation
WM	Weighted mean
XO	Cross-over

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Glaxo Group Ltd submitted on 6 March 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Laventair, 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 24 May 2012.

The applicant applied for the following indication .

Laventair is indicated as a 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 and vilanterol were 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 test(s) or study(ies).

This application is submitted as a multiple of Laventair simultaneously being under initial assessment in accordance with Article 82.1 of Regulation (EC) No 726/2004.

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 for the condition "COPD".

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 indications.

New active Substance status

The applicant requested the active substances vilanterol (as trifenatate) and umeclidinium bromide contained in the above medicinal product to be considered each 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.

The applicant received Scientific Advice from the CHMP on 20 May 2010 and 23 September 2010 (EMA/CHMP/SAWP/568901/2010, EMA/CHMP/SAWP/568902/2010, EMA/CHMP/SAWP/568903/2010 and EMA/CHMP/SAWP/287082/2010). The Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: the United States, Canada, Switzerland, Taiwan, Australia, New Zealand, Turkey, Japan, the Philippines, South Africa, Indonesia and South Korea.

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, Hertfordshire 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: Robert James Hemmings Co-Rapporteur: David Lyons

- The application was received by the EMA on 6 March 2013.
- The procedure started on 27 March 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 19 April 2013.
- During the PRAC meeting on 16 May 2013, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the meeting on 30 May 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 31 May.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 July 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 27 August 2013.
- During the PRAC meeting on 5 September 2013, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the CHMP meeting on 19 September 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated list of outstanding issues on 18 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the list of outstanding issues to all CHMP members on 30 October 2013.

- During the PRAC meeting on 17 November 2013, the PRAC agreed on a PRAC RMP advice and assessment overview.
- During the CHMP meeting on 21 November 2013, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP consolidated 2nd list of outstanding issues on 20 December 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 17 January 2014.
- During the CHMP meeting on 21 January 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- 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 Laventair.
- The CHMP Assessment Report was finalised by written procedure on 17 March 2014.
- On 28 March 2014, the CHMP adopted a revised opinion to amend the statement on the new active substance status.

2. Scientific discussion

2.1. Introduction

Problem statement

COPD is a preventable respiratory disorder characterised by airflow limitation, which is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response in the lungs to noxious particles or gases, primarily caused by cigarette smoking. COPD is characterized by symptoms of chronic and progressive breathlessness (or dyspnea), cough, and sputum production which can be a major cause of disability and anxiety associated with the disease.

In reality the disease is not limited to the airway and treating physicians are faced with a multi-component disease that is characterised by a range of pathological changes, which include mucous hypersecretion, airway narrowing, loss of alveoli in the lungs, and loss of lean body mass and cardiovascular effects at a systemic level. COPD patients are also heterogeneous in terms of their clinical presentation, disease severity and rate of disease progression. Their degree of airflow limitation, as measured by FEV_1, is also known to be poorly correlated to the severity of their symptoms.

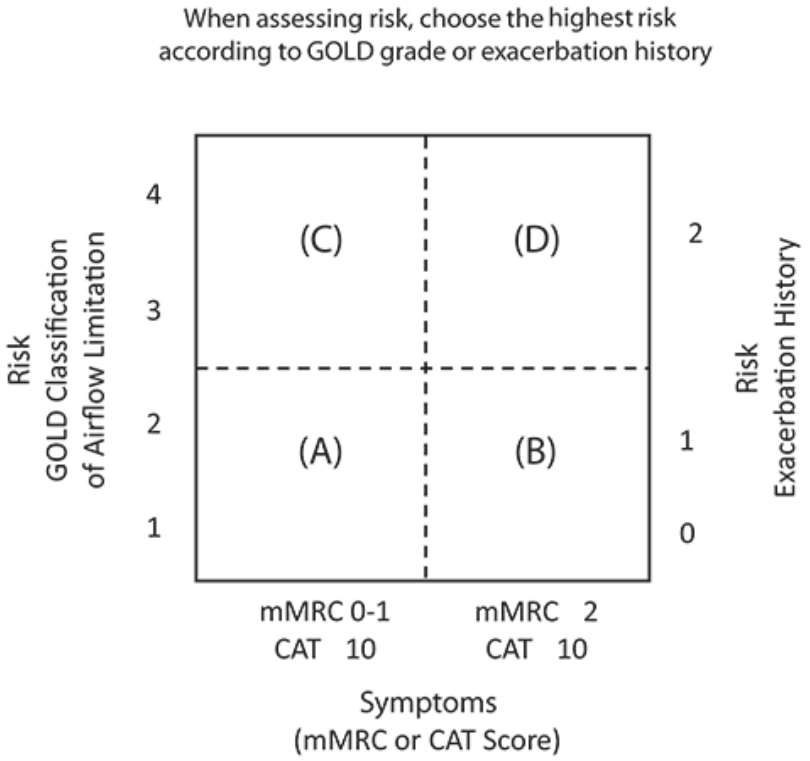
COPD is a major cause of chronic morbidity and mortality throughout the world. It is estimated that approximately eight percent of the population have COPD and approximately ten percent of those over 40 years of age. However the true prevalence of the disease is likely to be higher than this due to under-diagnosis and delayed diagnosis until the disease becomes clinically apparent and is then moderately advanced. COPD is the fourth leading cause of death in Europe and is expected to rise to third by 2020.

The goals of COPD assessment are to determine the severity of the disease, its impact on patient's health status and the risk of future events (such as exacerbations, hospital admissions or death), in

order to, eventually guide therapy. The most used classification based on severity of airflow limitation in COPD (based on post-bronchodilatory FEV1) is the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification. Patients with FEV1/FVC <0.70 are classified in to mild, moderate, severe and very severe based on spirometry as below:

GOLD 1	Mild	FEV1 ≥ 80% predicted
GOLD 2	Moderate	50% ≤ FEV1 < 80% predicted
GOLD 3	Severe	30% ≤ FEV1 < 50% predicted
GOLD 4	Very Severe	FEV1 < 30% predicted

Recently, GOLD has recommended an approach of combined COPD assessment based on the impact of COPD on an individual patient which combines symptomatic assessment with the patient's spirometric classification and/or risk of exacerbations. This approach is illustrated below.



Patient Category	Characteristics	Spirometric Classification	Exacerbations Per Year	mMRC	CAT
A	Low Risk, Less Symptoms	GOLD 1-2	1	0-1	<10
B	Low Risk, More Symptoms	GOLD 1-2	1	2	10
C	High Risk, Less Symptoms	GOLD 3-4	2	0-1	<10
D	High Risk, More Symptoms	GOLD 3-4	2	2	10

The most important aspect of management of the condition is educational and social: the avoidance and cessation of tobacco smoking. However, once COPD is established the recommendations for the pharmacological treatment of COPD are based on the severity of the condition. The current GOLD recommendations on the pharmacological therapy for stable COPD are depicted below:

Patient Group	Recommended first choice	Alternative choice	Other possible treatments
A	SA anticholinergics prn or SA beta2-agonist prn	LA anticholinergic or LA beta2- agonist or SA beta2-agonist and SA anticholinergic	Theophylline
B	LA anticholinergic or LA beta2-agonist	LA anticholinergic and LA beta2-agonist	SA beta2-agonist and/or SA anticholinergic Theophylline
C	ICS + LA beta2-agonist or LA anticholinergic	LA anticholinergic and LA beta2-agonist or LA anticholinergic and PDE-4 inhibitor or LA beta2-agonist and PDE4 inhibitor	SA beta2-agonist and/or SA anticholinergic Theophylline
D	ICS + LA beta2-agonist and/or LA anticholinergic	ICS + LA beta2-agonist and LA anticholinergic or ICS + LA beta2-agonist and PDE4 inhibitor or LA anticholinergic and LA beta2-agonist or LA anticholinergic and PDE-4 inhibitor	Carbocysteine SA beta2-agonist and/or SA anticholinergic Theophylline

The GOLD recommendation is that the combined use of long-acting beta agonists and anticholinergics may be considered if symptoms are not improved with single agents (Evidence - B which is randomized controlled trials – limited body of data).

About the product

Laventair is a novel fixed dose combination of two new active substances: umeclidinium bromide, a novel long acting muscarinic antagonist (LAMA) and vilanterol trifenatate, a novel long-acting β_2 agonist (LABA). Approved bronchodilators, such as LABAs and LAMAs, have been available for the treatment of COPD patients since 2004 and they can be used alone or together.

Laventair 62.5 µg/25 µg & 125 µg/25 µg inhalation powder is a pre-dispensed multi dose dry powder for oral inhalation. The active ingredients are umeclidinium bromide (UMEC) and Vilanterol (VI) (as trifenatate). UMEC is a long acting muscarinic receptor antagonist (also referred to as an anticholinergic), while VI is a selective long-acting, beta$_2$-adrenergic agonist (LABA).

The novel dry powder inhaler (NDPI), called Ellipta, incorporates two blister strips, one containing a blend of micronised FF and lactose monohydrate and the other containing a blend of micronised VI, lactose monohydrate and magnesium stearate. Upon actuation, the inhaler delivers the contents of one blister containing UMEC blend and one blister containing VI blend.

Laventair is a novel LAMA/LABA fixed dose combination for oral inhalation administered from a Novel Dry Powder Inhaler (NDPI). It contains umeclidinium bromide (UMEC; GSK573719), a LAMA, and vilanterol (VI; vilanterol trifenatate; GW642444M), an inhaled LABA. Neither UMEC nor VI is currently available as an individual component for oral inhalation. However, VI is one of the active substances in Relvar Ellipta, a fixed dose combination of an ICS and a LABA, recently authorised via the Centralised Procedure.

It should be noted that the data submitted in the application dossier referred to Laventair 62.5 µg/25 µg and 125 µg/25 µg as the finished medicinal product, which corresponds to the metered dose of both active substances. 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 both active substances and therefore the name of the medicinal product finally approved by the Committee was expressed as follows: Laventair 55 µg/22 µg, in all official approved documents (CHMP opinion/future EC decision and CHMP assessment report). Since 62.5 µg/25 µg and 125 µg/25 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.

The Applicant initially applied for the following indication:

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

The posology requested was one inhalation of Laventair 55/22 micrograms once daily. The proposed maximum dose was one inhalation of Laventair 113/22 micrograms once daily. Use of Laventair 113/22 micrograms once daily in patients who are responsive to salbutamol has been shown to provide additional clinical benefit with regard to lung function and rescue medication use.

2.2. Quality aspects

2.2.1. Introduction

The finished product contains umeclidinium bromide and vilanterol trifenatate as the active substances, the active moieties being umeclidinium and vilanterol, respectively. It is a pre-dispensed inhalation powder which is presented in a plastic inhaler. The inhaler contains two multi-dose blister strips, having either 7 or 30 doses. One strip has blisters containing 62.5 micrograms of umeclidinium (as bromide) and the other strip has blisters containing 25 micrograms of vilanterol (as trifenatate).

When actuated, the inhaler delivers the contents of a single blister simultaneously from each of the two blister strips. Each actuation provides a delivered dose of 55 micrograms of umeclidinium (as bromide) and 22 micrograms of vilanterol (as trifenatate). The inhaler is packaged in a sealed tray with a desiccant.

Other ingredients in both inhalation powders are lactose monohydrate and magnesium stearate.

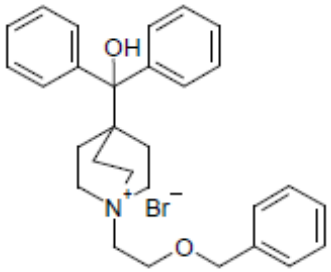
The Applicant has followed the CHMP Scientific Advice received for parallel Relvar Ellipta centralised procedure (fluticasone furoate/vilanterol inhalation powder).

2.2.2. Active Substance

Laventair contains two active substances: umeclidinium bromide a novel long acting muscarinic antagonist, and vilanterol trifenatate, a novel long-acting β2 agonist.

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 slightly soluble in water, propan-1-ol, butan-1-ol, toluene, ethanol and acetonitrile, sparingly soluble in methanol and freely soluble in dimethyl sulfoxide.

The molecular structure has been fully characterised by elemental analysis, proton and carbon NMR, MS, IR, X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC). Umeclidinium bromide has a non-chiral molecular structure. Polymorphism has been observed but the synthesis process consistenly yields one polymorphic form.

Manufacture

Non-micronised active substance is supplied by one manufacturer. It is synthesised by a 3-stage process which is followed by a micronisation step perfomed at another site. 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 active substance. Proven acceptable ranges (PARs) 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 PARs.

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 contentby 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 active substance. Impurities present at higher level than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

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.

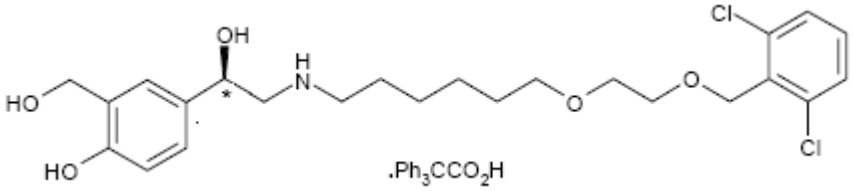
All stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container and proposed storage conditions.

Vilanterol trifenatate

Vilanterol trifenatate is the second active substance in Laventair. It is a white, non-hygroscopic powder that is practically insoluble in water; practically insoluble in heptane; very slightly soluble in toluene

and t-methyl butyl ether; slightly soluble in acetonitrile, ethanol and 2-propanol; soluble in methanol; freely soluble in dichloromethane and dimethyl sulfoxide.

The chemical name of vilanterol trifenatate is: triphenylacetic acid - 4-{(1R)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol and it has the following structural formula:



Vilanterol trifenatate is the triphenylacetate salt of vilanterol (INN), a secondary amine. It contains one asymmetric carbon; the active substance is the R-isomer. The molecular structure of vilanterol has been elucidated by proton and carbon NMR, MS, IR, elemental analysis and X-ray crystallography.

Vilanterol (INN) exhibits stereoisomerism due to the presence of one chiral center. Enantiomeric purity is controlled routinely by chiral HPLC. Polymorphism has not been observed for vilanterol trifenatate.

Manufacture

Non-micronised vilanterol trifenatate is supplied by one active substance manufacturer. It is synthesised by a 4-step process followed by micronisation. Micronisation is performed at another site.

Vilanterol trifenatate 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 active substance. Proven acceptable ranges (PAR) were set for the CPPS. A detailed description of the manufacturing process has been provided and the scaling-up of the PARs has been justified. Well defined starting materials and reagents have been used and adequate in-process controls are applied during the synthesis.

Specification

The active substance specification includes tests for description (visual), identity (IR), vilanterol trifenatate content by HPLC, related impurities (HPLC), enantiomer content (chiral HPLC), residual solvent (GC), water content (Karl Fischer titration), residue on ignition and particle size distribution (laser diffraction). The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines.

Batch analysis data have been provided for eleven production scale batches of non-micronised vilanterol trifenatate manufactured using the commercial process. From these batches, up to 51 batches of micronised vilanterol trifenatate have been produced and analysed. All batches tested were found to comply with the pre-defined specifications. The results demonstrate that the active ingredient can be manufactured reproducibly.

Stability

Stability data obtained under ICH long-term conditions (25ºC/60% RH), and accelerated conditions (40ºC/75% RH) have been provided for 6 batches of micronized vilanterol and two batches of non-micronised vilanterol. Up to 36 months long term data and up to 6 months accelerated stability data were presented. The stability batches have been manufactured by the proposed commercial process at

the commercial scale and were packed in the containers representative of those intended for marketing.

The following parameters were tested: description, vilanterol trifenatate content, impurities, enantiomer content, water content, particle size distribution of the micronised and non-micronised active substance by laser diffraction, specific surface area of the non-micronised active substance and of the micronised vilanterol trifenatate (nitrogen gas adsorption), solid state form (XRPD) and the melting point/amorphous content (differential scanning calorimetry). The analytical tests used are stability indicating.

Photostability and stress testing was performed on 2 batches each of micronised and non-micronised vilanterol trifenatate. The stress testing conditions include: 50°C/ambient humidity; freeze/thaw conditions, storage under reduced packaging and exposure to light.

Furthermore, forced degradation studies were conducted in the solid state (14 days at 80 ºC under ambient and 75% relative humidities) and under exposure to UV/visible light; and in solution at 60 ºC and under acidic, basic and oxidative conditions.

The stability results indicate that the active 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 umeclidinium bromide in combination with vilanterol trifenatate. It was decided to formulate the active substances in two separate powders for inhalation within a single inhaler. This approach allowed for independent formulation development and optimisation of the inhalation powders and required the development of a novel dry powder inhaler capable of delivering pre-metered doses from two blister strips simultaneously. The inhaler 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 following critical quality attributes (CQAs) were identified for the finished product: identity, drug-related impurities, emitted/delivered dose, particle size distribution of the emitted/delivered dose (PSD), foreign particulate matter, microbiological quality and leachables. Three of the finished product CQAs (identity, PSD and drug-related impurities) were found to be strongly related to the quality attributes of the micronized umeclidinium bromide and vilanterol trifenatate. Multiple linear regression (MLR) was used to model the fine particle mass per inhalation from the particle size distribution of both active substances.

The applicant performed a risk assessment (Failure Modes and Effects Analysis) to identify the manufacturing process parameters that needed to be further studied in development and defined their criticality. Univariate and multivariate (DOE) studies have been performed to identify and confirm CPP and PARs have been defined for the critical process parameters.

The excipients used in Laventair 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 in the umeclidinium bromide and vilanterol blisters are magnesium stearate (stabiliser) and lactose monohydrate (diluent/carrier).

A novel inhalation device containing two separate blister strips has been developed to allow optimal inhalation of the active substances. 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 red mouthpiece. 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

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

A 'quality by design' (QbD) approach was adopted for product development. For each finished product CQA, the CQAs of starting materials and intermediates, and the critical process parameters (CPPs) of the unit operations have been identified; proven acceptable ranges have been set for the critical process parameters.

The process has been validated for ten commercial batches of inhalers containing umeclidinium /vilanterol 62.5/25 µg. The data collected as part of process qualification 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 and vilanterol (UV, HPLC-UV, HPLC-fluorescence), mean umeclidinium content and mean vilanterol content per blister (both 100 ± 5% of nominal blister content by HPLC), umeclidinium uniformity of delivered dose (HPLC), vilanterol uniformity of delivered dose (HPLC), fine particle mass of umeclidinium and vilanterol (by next generation impaction) and microbiological quality of umeclidinium and of vilanterol. The analytical methods have been adequately validated.

Batch analysis data have been presented for eight production-scale batches of umeclidinium /vilanterol 62.5/25 µg inhalation powders. Results have been presented for five 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 /vilanterol inhalation powder are presented for three batches. These batches were produced at production-scale and assembled at the proposed commercial site and equipment. 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 one. 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 timepoint 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 or drug-related impurity content of umeclidinium and vilanterol. 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: umeclidinium bromide and vilanterol 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 substances 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

A comprehensive non-clinical development was conducted to support the chronic use of umeclidinium bromide and of vilanterol in humans. The non-clinical pharmacology, pharmacokinetic, and toxicology studies reported in this dossier were conducted respecting the established guidelines. Non-clinical studies conducted with the combination of umeclidinium bromide and vilanterol were limited to safety pharmacology, pharmacokinetics, repeat-dose toxicity and reproduction toxicity studies in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005). This was considered acceptable by the CHMP.

Pivotal studies regarding umeclidinium bromide, vilanterol and the combination of umeclidinium bromide and vilanterol were performed in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Umeclidinium bromide (GSK573719)

In vitro studies

Binding studies:

Binding studies were performed to investigate the binding kinetics of GSK573719 in membranes prepared from transfected Chinese hamster ovary (CHO) cells expressing individual muscarinic receptor subtypes (mAChR-1 to mAChR-5) (Report CH2006/00020).

GSK573719 was shown to be a potent, pan-active, human muscarinic antagonist. The compound competed with ^{3}H-N-methyl-scopolamine binding for human recombinant receptor membranes from CHO cells stably expressing the mAChR-1, mAChR-2, mAChR-3, mAChR-4 and mAChR-5 receptors (n=3) with affinity values in the sub-nM range for the 5 human mAChRs

Kinetic binding studies were conducted with GSK573719 to determine if it was a competitive antagonist at the mAChR-3 receptor. Saturation binding of ^{3}H-N-methyl scopolamine in the absence (vehicle) and presence of increasing concentrations of GSK573719 showed a shift to the right with no change in maximal binding. The data were analyzed with a Scatchard plot. The K_d increased with increasing concentrations of compound while the maximum number of binding sites (Bmax) was unchanged (average of 5.75 pmol/mL). This data suggests that GSK573719 is a surmountable competitive antagonist.

A study was conducted with ^{3}H-GSK573719 and ^{3}H-tiotropium (a commercially available muscarinic antagonist) in CHO cell membranes recombinantly expressing either the mAChR subtype mAChR-2 or mAChR-3 using a radioligand filtration binding assay (Report 2012N138876). Saturation, association and dissociation binding studies were performed for ^{3}H-GSK573719 (~0.01 to 2.4 nM, ~0.02 to 0.43 nM or ~0.1 nM respectively) and ^{3}H-tiotropium (~0.01 to 2.9 nM, ~0.02 to 0.38 nM or ~0.02 to 0.38 nM respectively) to determine receptor binding kinetics at mAChR-2 and mAChR-3 receptors. ^{3}H-GSK573719 exhibited a high affinity for both subtypes. ^{3}H-GSK573719 demonstrated a comparable affinity for the mAChR-3 receptor but a greater selectivity (~5-fold) for mAChR-3 over mAChR-2 when

compared with ^{3}H-tiotropium (~3-fold). The receptor binding kinetic studies showed that both ^{3}H-GSK573719 and ^{3}H-tiotropium associated faster with the mAChR-2 receptor compared with the mAChR-3 receptor. The k_{on} values determined at each individual receptor subtype were comparable between radioligands. The dissociation studies showed that ^{3}H-GSK573719 had a faster $t_{½}$ value for the mAChR-2 receptor than that observed for the mAChR-3 receptor. When comparing $t_{½}$ values for ^{3}H-GSK573719 at each receptor subtype with ^{3}H-tiotropium, ^{3}H-GSK573719 displayed a faster $t_{½}$ value for both the mAChR-2 and mAChR-3 receptor.

Receptor potency

A microtiter plate based calcium mobilization FLIPR (Fluorometric Imaging Plate Reader) assay was used for the functional characterization of antagonist inhibition of mAChR-1, mAChR-2 (w/Gqi5) and mAChR-3 stably expressed in CHO cells (Report CH2006/00020). The FLIPR assay monitors the compound inhibition of ACh-induced intracellular calcium fluxes mediated through cloned receptors. The EC_{50} values (mean ± standard error) for ACh were 0.80 ± 0.09, 5.30 ± 0.30 and 0.30 ± 0.07 nM, respectively. In similar assays GSK573719 was assayed for agonist activity in the cells and there was no significant calcium mobilization response, indicating a lack of muscarinic agonist activity.

Kinetic studies were conducted for GSK573719 at mAChR-1, mAChR-2 and mAChR-3 using human recombinant mAChR-1, mAChR-2 and mAChR-3 expressed in CHO cells. mAChR-1 and mAChR-3 receptors were expressed directly in CHO cells, while mAChR-2 receptors were coupled to calcium mobilization via co-expression with the chimeric G protein, Gqi5, in CHO cells. GSK573719 demonstrated pan-active potent functional inhibition of mAChR-1, mAChR-2 and mAChR-3.

GSK573719 was characterized as a competitive inhibitor at mAChR-1, mAChR-2 and mAChR-3 with slopes of 0.829, 0.928 and 0.963 against mAChR-1, mAChR-2 and mAChR-3, respectively, slopes which are consistent with competitive kinetics.

The reversibility of GSK573719 (0, 3.3, 33 and 330 nM) and tiotropium (a commercially available muscarinic antagonist) (0, 3.3, 10 or 33 nM) was evaluated by washout from mAChR-3 using the FLIPR assay. The data indicate that both antagonists washed off to some extent but both appeared to cause decreased receptor affinity for ACh after the pre-treatment followed by washout. Pre-treatment and washout by tiotropium resulted in a ~10- to 15-fold decrease in receptor affinity, while GSK573719 showed a 5- to 20-fold decrease in receptor affinity.

In vitro efficacy

Carbachol (a cholinomimetic)-mediated contractions and their blockade by GSK573719 were investigated in isolated human bronchus. Atropine and ipratropium, both competitive mAChR antagonists, and tiotropium, a non-competitive mAChR inhibitor, were included in the study for reference (Report CH2006/00014). GSK573719 (1, 10 or 100 nM) caused a concentration-dependent rightward shift of carbachol concentration-response curves in human bronchus yielding a pA2 of 9.5 (Schild slope = 1.4). Some suppression, 10 to 25% of the maximal carbachol response, was observed at all 3 concentrations of GSK573719. Atropine (10 nM) induced a parallel shift of the carbachol response, yielding a pKB of 9.6. In the same studies, atropine reached the same maximal response obtained with the vehicle.

In some studies, the effects of GSK573719, ipratropium or tiotropium on carbachol concentration-response curves were evaluated in paired tissues. GSK573719 (1, 10 or 100 nM) caused a concentration-dependent rightward shift of carbachol response curves with suppression of the maximal carbachol response (pA2 = 9.5, slope = 1.5). Ipratropium (1, 10 or 100 nM) was a potent inhibitor of carbachol-induced contraction with a pA2 of 9.2 (Schild slope = 1.4). Ipratropium and atropine did not suppress the maximal carbachol response. Tiotropium had no effect at 0.1 nM, yet suppressed the maximal carbachol response by 68% and 66% at 1 and 10 nM, respectively.

GSK573719 at 1, 10 or 100 nM was a potent inhibitor of carbachol-induced contraction of isolated human bronchus. GSK573719 also demonstrated inhibition of maximal carbachol responses between 10 and 25%.

In vitro onset and duration of action

A study was performed in which superfusion was used to determine the onset and duration of inhibition of carbachol-induced contraction by GSK573719 using isolated strips of human bronchus and guinea pig trachea. The onset and duration of inhibition by reference compounds ipratropium and tiotropium were also determined in paired tissues (Report CH2006/00015).

In initial studies in human bronchus, where tissues were washed once, maximum inhibition of carbachol-induced contraction was established. The onset half-times for GSK573719 at 1, 10 or 100 nM were 63 minutes, 27 minutes and 14 minutes, and the corresponding offset half-times were 119 minutes, 145 minutes and 299 minutes, respectively. In further studies where antagonists were infused for 6 hours, the recovery half-time for GSK573719 at 1, 10 and 100 nM ranged from 122 minutes to greater than 10 hours. Similar studies conducted in guinea pig trachea indicated a similar concentration-dependent reversibility profile.

GSK573719 was shown in this study to have a rapid, concentration-dependent onset of response in both human bronchus and guinea pig trachea. In human bronchus, reversal of GSK573719-induced inhibition of carbachol contraction was slow and concentration-dependent, particularly when the tissues had been pre-incubated with the antagonist for 6 hours. Reference compounds ipratropium and tiotropium had rapid, concentration-dependent onset of response. Ipratropium had a short reversal time whereas tiotropium showed slow recovery. Similar studies conducted in guinea pig airway indicated a similar reversibility profile for each antagonist. Following a 10 hour washout of the antagonists, both GSK573719 and tiotropium exhibited residual inhibition of maximal carbachol-induced contraction. Ipratropium had no remaining effect.

Characterisation of GSK573719 metabolites

The inhibitory potency and direct agonist potential of GSK1761002A and GSK339067A, metabolites of GSK573719, against the cloned human mAChR-1, mAChR-2+Gqi5 or mAChR-3 receptors were investigated using the FLIPR assay (Report CH2009/00016). Studies determined the antagonist potency of GSK1761002A (M33) and GSK339067A (M14), as well as any compound-induced activation of these muscarinic receptors, by monitoring the compound inhibition of ACh-induced intracellular calcium fluxes mediated through cloned human mAChR-1, mAChR-2+Gqi5 and mAChR-3 (antagonist potency determination), or by monitoring any direct compound-induced receptor-mediated calcium flux (compound agonist characterization). No data was obtained for metabolite GSK1761002A (M33) against mAChR-2+Gqi5. GSK1761002A (M33) showed functional potencies (pIC_{50}s) >8.0 against mAChR-1 and against mAChR-3. Further characterization of potency against mAChR-3, using single compound concentration kinetics, showed a pA2 of 9.87 ± 0.08 (mean ± SEM).

GSK339067A (M14) showed potencies (pIC_{50}s) of 5.92 ± 0.14, 5.78 (n=2) and 6.25 ± 0.04 against mAChR-1, mAChR-2+Gqi5 and mAChR-3, respectively. GSK1761002A (M33) showed no direct activation of either mAChR-1 or mAChR-3. GSK339067A (M14) showed no direct activation of mAChR-1, mAChR-2+Gqi5 or mAChR-3.

The data show GSK1761002A (M33) to be a functional inhibitor of cloned mAChR-1 and mAChR-3 (~10-fold less potent than GSK573719 [pA2 value of 9.87]) while GSK339067 had negligible pharmacological activity (antagonist potency [pIC_{50}] was $\leq$6.25 against mAChR-1, mAChR-2 and mAChR-3). GSK1761002A (M33) and GSK339067A (M14) were shown to have no direct stimulatory affect at any of the mAChR tested.

In Vivo Studies

Mice

A study in a murine model of MCh-induced bronchoconstriction evaluated the potency and duration of action of GSK573719 (Report CH2006/00018). Conscious Balb/c mice (4/group) were pre-treated at before MCh challenge with vehicle (0.9% saline, 50 mcgL/mouse, intranasally) or GSK573719 (0.005, 0.01, 0.05, 0.1, 0.5, 1.0 and 5 mcg/mouse, intranasally). After dosing the mice were placed into individual plethysmograph chambers where airway responsiveness (PENH) to a MCh challenge was measured. The ED_{50} was 0.02 mcg/mouse at 5 hours post-treatment.

In a time response study, mice were treated with GSK573719 (0.05 mcg/mouse, intranasally) and inhibition of bronchoconstriction evaluated at 0.25, 5, 24 hours and each 24 hours thereafter until 168 hours (Day 7) after the initial dose. A single dose of 0.05 mcg of GSK573719 inhibited MCh-induced bronchoconstriction for up to 7 days. A significant level of inhibition ($p<0.001$) was maintained (range = 47 to 80%) from 5 to 72 hours post-treatment. In a separate parallel experiment, a single dose of 0.05 mcg of tiotropium also inhibited bronchoconstriction for up to 7 days. The level of inhibition was maintained between 46 to 92% inhibition ($p<0.001$) from 5 to 72 hours post-treatment.

GSK573719 did not inhibit MCh-induced bronchoconstriction when given orally at a dose of 50 mcg/mouse (2.0 mg/kg in water).

Repeated daily dosing of GSK573719 (0.025 mcg, intranasally) for a period of 5 consecutive days to mice did not enhance efficacy after the first day of dosing. The drug was then allowed to washout for 5 days and on Day 11 a single dose of 0.025 mcg of GSK573719 was again administered. A similar level of inhibition was observed on Day 11 (35%, $p<0.01$ bronchoprotection) compared to that obtained on the first day (34%, $p<0.001$ bronchoprotection). These data provide no evidence for muscarinic receptor tolerance after repeat dosing under the experimental conditions used.

Guinea pigs:

A study was conducted to determine the effect of locally administered GSK573719 on ACh aerosol-induced bronchoconstriction in conscious Dunkin Hartley guinea pigs (Report CH2005/00954). A dose-response relationship for the determination of duration of action of GSK573719 (0.25, 2.5 and 25 mcg) was established and a side by side study to compare with tiotropium at the same dose (2.5 mcg) was performed. GSK573719 dose-dependently inhibited ACh-induced bronchoconstriction and exhibited a dose-related duration of action. The highest dose of GSK573179, 25 mcg/animal, caused inhibition greater than 50% up to 5 days post-treatment. The duration of inhibition for GSK573719 and tiotropium was evaluated in side by side studies after administration of 2.5 mcg/animal doses to groups of guinea pigs and was compared to animals receiving vehicle only. Greater than 90% inhibition was observed at 4 hours post dosing for both compounds. At 24 hours, GSK573719 and tiotropium exhibited 68.9% ± 11.3 (mean ± standard error of the mean) ($p<0.0005$) and 87.6% ± 6.5 ($p<0.0005$) inhibition, respectively, and at 48 hours 37.7% ± 10.2 ($p<0.002$) and 65.9% ± 9.4 ($p<0.0005$), respectively. At 72 hours, the levels of inhibition were 19.1% ± 8.6 (not significant) for GSK573719 and 32.4% ± 10.9 ($p<0.05$) for tiotropium. Levels of inhibition for both compounds were below 20% on Days 4 and 5 post-treatment.

A study was conducted to determine the effect of intratracheal GSK573719 (0.025, 0.25 or 2.5 mcg) on ACh-induced bronchoconstriction and bradycardia in guinea pigs (Report CH2005/00953). GSK573719 demonstrated potent activity in inhibiting intravenous ACh-induced bronchoconstriction as evidenced by a dose-dependent shift of the ACh dose response. This was represented as airway resistance measurements (cm H20/ML/sec, mean ± SEM) at the highest dose of ACh (100 mcg/kg) of: vehicle control = 5.93 ± 1.05; GSK573719 (0.025 mcg) = 4.19 ± 0.395; GSK573719 (0.25 mcg) = 1.51± 0.266, $p<0.01$ vs control; GSK573719 (2.5 mcg) = 0.420 ± 0.0484, $p<0.001$ vs control.

Tiotropium (25 mcg/animal, intratracheally) demonstrated activity similar to GSK573719 (2.5 mcg/animal) in inhibiting ACh-induced bronchoconstriction.

Vilanterol (GW64244)

In vitro studies

Radioligand binding studies:

Radioligand binding studies were performed to investigate the binding kinetics of 3H-GW642444 (as the triphenylacetate salt, GW642444M) in membranes prepared from either transfected Chinese hamster ovary (CHO) cells expressing the human beta2-receptor or from human lung parenchyma. GW642444 binds to the human beta2-receptor with high affinity coupled with fast K (pKD range 9.44 to 10.8) similar to that of salmeterol and higher than R,R-formoterol and indacaterol. Competition binding curves for a range of beta2-receptor agonist and antagonists were completed against 3H-GW642444. The pKi values determined were in good agreement with literature values generated against antagonist radioligands. ^{3}H-GW642444M demonstrates a fast k_{off} from the low affinity receptor state and a moderately slow k_{off} from the high affinity receptor state at ambient temperature.

In vitro efficacy:

GW642444 (as the acetate salt, GW642444A) was assessed in a variety of in vitro functional assays and its potency compared with that of salmeterol and R,R-formoterol (beta2-receptor agonists) or isoprenaline (non-selective beta-agonist).

GW642444 caused a concentration-dependant pigment dispersal in melatonin pre-treated frog melanophores expressing the beta2-receptor. GW642444 was found to be a potent agonist at the human beta2-receptor with a slightly greater potency than salmeterol and similar potency to R,R-formoterol and isoprenaline (log half-maximal effective concentration (pEC50) 9.3, 8.8, 9.4 and 9.1, respectively).

In functional adenyl cyclase assays utilising CHO cells stably expressing human beta2-receptors, GW642444 had a similar potency to salmeterol. In the CHO cells stably expressing the human beta2 adrenoceptors (at levels which allow for partial agonists to be discriminated), GW642444 has an intrinsic activity greater than salmeterol but lower than R,R-formoterol. The effects of GW642444 were also antagonised by propranolol and sotalol in a competitive manner, with the dissociation constant pKbs obtained being similar to those against salmeterol (estimated pKb values for propranolol [9.6 and 9.7] and sotalol [7.3 and 7.3] against salmeterol and GW642444, respectively). These data indicate that GW642444 and salmeterol act as orthosteric agonists at the human beta2-receptor.

In vitro selectivity:

GW642444 (as the acetate salt, GW642444A and the triphenylacetate salt, GW642444M) was assessed *in vitro* in a Luciferase reporter gene selectivity assay or a TR-FRET LANCE cAMP assay in CHO cells stably expressing human beta1-, beta2- and human beta3-receptors. Its potency compared with that of salmeterol, R,R-formoterol and indacaterol (beta2-receptor agonists) or isoprenaline (non-selective beta-agonist). GW642444 demonstrated similar selectivity to salmeterol for beta2 over human beta1 and human beta3-receptors. GW642444 was significantly more selective than R,R-formoterol and indacaterol against human beta1 and human beta3-receptors.

In vitro onset and duration of action:

In assessing the potency and duration of action of GW642444, GW642444 caused a concentration dependent increase in the TR-FRET LANCE cAMP assay carried out in CHO cells expressing recombinant beta2-receptors. GW642444, salmeterol and indacaterol showed long persistence of action (duration) at the beta2-receptor following washout in contrast to R,R-formoterol which shows a significant washout profile, indicating a lack of duration in this assay.

Potency and duration of action of GW642444 was also assessed using guinea pig trachea and human bronchus. GW642444 was shown to be a potent and selective beta2-receptor agonist on the guinea pig isolated superfused (electrically stimulated) trachea (pEC50 = 7.87). GW642444 was similar in potency (pEC50 = 7.68) and duration to salmeterol and around 30-fold weaker than R,R-formoterol. GW642444 has a more rapid onset than salmeterol and similar to R,R-formoterol (half onset time [Ot50] values of 6.6 minutes, 25 minutes and 13 minutes, respectively). The effects of GW642444 on guinea pig trachea were antagonised by propranolol and sotalol in a competitive manner. Reassertion studies with sotalol were consistent with CHO cell assays and support a long duration of action. Studies with GW642444 on human isolated bronchus tissues stimulated with either prostaglandin F2alpha or methacholine showed a similar potency and duration profile to that seen in guinea pig trachea.

Characterisation of GW642444 metabolites and S-enantiomer:

The beta1- and beta2-agonist activity of GW642444 (as the triphenylacetate salt, GW642444M), its S-enantiomer (GSK907117), 4 human metabolites (GW630200 [M29], GSK932009 [M33], GSK1676112 [M20] and GW875428 [M40]) and a further potential metabolite GW853734, was evaluated in TR-FRET LANCE assay measuring cAMP production in recombinant CHO cells expressing human beta1- or beta2-receptors. The GW642444 metabolites GW630200 (M29) and GSK932009 (M33) were at least 2500-fold less potent than GW642444 on the beta2-receptor, and the metabolites GW875428, GSK1676112 and GW853734 were poorly active with intrinsic activity ~30%, 70% and 50%, respectively, at beta2. The GW642444 S-enantiomer was around 60 times less potent at beta2 than GW642444. Pharmacological activity against the beta2-receptor was negligible for the other GW642444 metabolites tested. None of the metabolites tested or the S enantiomer showed any notable pharmacological activity against the beta1-receptor.

In vivo activity

The bronchoprotective effects of GW642444 over time were assessed using histamine challenge in conscious male and female guinea pigs (up to 8/sex). Airway responsiveness was measured using whole body plethysmography. GW642444 was a potent and long-acting inhibitor of histamine induced bronchospasm in the conscious guinea pig when administered by the inhaled route (nebulised aerosol). GW642444 had a similar potency to salmeterol and at an equi-effective (EC90) dose the duration of action of GW642444 was similar to salmeterol.

Repeat dosing studies (once daily/4 days at EC90) induced tachyphylaxis, manifest by a parallel rightward shift in the dose-response curve which amounted to an approximate 4-fold reduction in potency pretreated with GW642444. This tachyphylaxis was considered surmountable and was evidenced near the top of the dose-response curve. Repeated exposure to GW642444 daily for 5 days at the EC90 also caused a statistically significant decrease in the duration of action from 10 hours to <4 hours.

Umeclidinium bromide/vilanterol

No primary pharmacodynamic studies studies were performed on the fixed dose combination umeclidinium bromide/vilanterol based on the data available for each compound which was considered acceptable.

Secondary pharmacodynamic studies

Umeclidinium bromide (GSK573719)

***In vitro* studies**

The selectivity of GSK573719 (1 mcM) for a battery of 50 enzymes, receptors, ion channels and transporters was assessed in receptogram binding studies utilising radioligand binding assays (Report CH2006/00030). Any assay which gave greater than 50% inhibition was further investigated to obtain an IC_{50} and Ki value. GSK573719 inhibited radioligand binding by less than 50% at 41 of the 50 receptors, ion channels and transporters screened. The Ki values for the 5 targets that were not mAChR-1 to mAChR-4 were Kappa opioid receptor (69 nM), Sigma (non-selective) receptor (220 nM), Ca^{2+} channel (L, verapamil site) (330 nM), Na^{+} channel (Site 2) (170 nM) and dopamine transporter (780 nM).

In vivo studies

An in vivo secondary pharmacology study was conducted to determine the effect of intratracheal GSK573719 on ACh-induced bronchoconstriction and bradycardia in guinea pigs (Report CH2005/00953). The effects on bronchoconstriction are described in the in vivo pharmacology studies section above.

No consistent or dose-related effects were observed on ACh-induced bradycardia following GSK573719 treatment. The lowest dose of GSK573719 (0.025 mcg/animal) produced no significant inhibition of ACh-induced bradycardia except at the highest dose of ACh (100 mcg/kg; $p<0.05$). Using higher doses of GSK573719 (0.25 mcg or 2.5 mcg) produced only one significant effect on ACh-induced bradycardia. This effect was seen at the 2.5 mcg/animal dose of GSK573719 vs 20 mcg/kg ACh dose, but at no other doses ($p<0.05$). Tiotropium at 25 mcg/animal significantly inhibited heart rate changes at all doses of ACh ($p<0.01$). Heart rate changes (beats/min, mean ± SEM) at the highest dose of ACh (100 mcg/kg) for each group were: vehicle control = 148 ± 8.2; GSK573719 (0.025 mcg) = 123 ± 5.8; GSK573719A (0.25 mcg) = 151 ± 17.4; GSK573719 (2.5 mcg) = 136 ± 14.3; tiotropium (25 mcg) 37 ± 5.9.

Vilanterol (GW64244)

***In vitro* studies**

The selectivity of GW642444A (1 mcM) for 7-transmembrane (7TM) receptors, ion channels and transporters was assessed in radioligand binding assays.

In vivo studies

An in vivo secondary pharmacology study has been performed to assess the affect of inhaled doses of GW642444A and salmeterol on cardiovascular parameters in conscious guinea pigs.

Umeclidinium bromide/vilanterol

No secondary pharmacodynamic studies studies were performed on the fixed dose combination umeclidinium bromide/vilanterol based on the data available for each compound which was considered acceptable.

Safety pharmacology programme

Umeclidinium bromide (GSK573719)

The effects of GSK573719 on central nervous, cardiovascular and respiratory systems were assessed in several standard studies.

Table 1. Summary of safety pharmacological test results with GSK573719

Study number	Species (No. Animals/ Dosage Group)	Gender	Route of admin.	Dose (μg/kg)	Summary of results	GLP
PERIPHERAL & CENTRAL NERVOUS SYSTEM						
VD2005/00625	Rat (SD) (8)	Male	Inhalation	36, 322, 1994	36 mcg/kg: None. 322 and 1994 mcg/kg: Moderately dilated pupils between 1.25 and 9 hours after dose.	Y
RESPIRATORY						
CD2005/01385	Rat (SD) (6)	Male	Inhalation	36, 215, 2260	36 mcg/kg: None. At 215 mcg/kg, 18 to 45% increase in respiratory rate and 3 to 6% decrease in tidal volume during the 1 hour exposure. At 2260 mcg/kg, 18 to 27% increase in respiratory rate and 13 to 17% decrease in tidal volume during the 1 hour exposure.	Y
CARDIOVASCUALR						
CH2006/00029	hERG assay in HEK293 cells (Preliminary screen)	N/A	In vitro	0.3, 1, 3, 10 mcM (0.13, 0.43, 1.3, 4.3 mcg/mL)	GSK573719 was found to inhibit hERG tail current in a concentration-dependant manner. The concentration-response relationship was plotted, and the nominal IC_{25} and IC_{50} values were estimated to be 3.4 and 8.0 mcM (equivalent to 1.5 and 3.4 mcg/mL active moiety), respectively.	N
FD2005/00109	hERG assay in HEK293 cells	N/A	In vitro	1, 3, 10, 49 mcM (0.43, 1.3, 4.3, 21 mcg/mL)	GSK573719 inhibited hERG channel tail current in a concentration-dependent manner. The nominal IC_{25}, IC_{50} and IC_{75} values were estimated to be 2.65, 9.41 and 33.4 mcM (equivalent to 1.136, 4.033 and 14.315 mcg/mL active moiety), respectively.	Y
FD2005/00167	Dog (beagle) (4)	Male	I.V (infusion)	0.3, 3, 10	At 10 mcg/kg GSK573719 there was a small reduction in pulse pressure of up to 7 mmHg. Increase in heart rate to 114 bpm from a pre-dose average of 65 bpm. An increase in PR and a decrease in RR interval and AV block in 3 out of 4 dogs at 10 mcg/kg GSK573719A.	Y

There were no findings relevant to human safety at the proposed clinical dose in inhaled respiratory safety pharmacology studies with GSK573719. Single inhaled administration of GSK573719 (215 or 2260 mcg/kg) produced reversible minimal effects on ventilatory function in rats during the 1 hour pulmonary exposure. As the method of administration (1 hour exposure) differs considerably from that proposed clinically (DPI) and that a safety margin of 5.7 exists between Cmax at the NOAEL and the Cmax achieved at the maximum proposed commercial inhaled dose of 125 mcg/day, these effects are not considered relevant for human safety.

In cardiovascular safety pharmacology studies, known pharmacological responses to muscarinic antagonists including altered ion channel activities in vitro and a number of cardiovascular effects including tachycardia in vivo were observed at exposures well in excess of those achieved clinically at the highest dose. In the hERG assay, GSK573719 was a weak inhibitor of this cardiac potassium channel at a nominal IC50 value of 9.41 mcM (safety margin of 250,000).

Increases in heart rate were observed in the cardiovascular safety pharmacology study in dogs at an intravenous dose of 10 mcg/kg. At this dose, a prolongation of PR interval together with transient second degree AV block followed by a decrease of RR interval was also noted. At the NOAEL (3 mcg/kg) a safety margin of ~163 exists based on Cmax at the maximum proposed commercial dose. In addition, no evidence of QT prolongation was seen at exposures >600-fold higher than the human Cmax at the proposed commercial dose of 125 mcg.

In repeat dose inhaled toxicity studies with GSK573719 in the dog, increased pulse rates/heart rates, generally accompanied with the secondary loss of respiratory sinus arrhythmia, were observed however no additional treatment-related ECG waveform abnormalities were seen at doses up to 2254 mcg/kg/day (equating to ~388-fold safety margin).

The existence of adequate safety margins are reflected in the available clinical data. There were no clinically relevant changes from baseline in heart rate in the subjects with COPD with GSK573719/GW642444 (125/25 and 62.5/25 mcg/day, respectively) or GSK573719 (125 and 62.5 mcg/day) compared with placebo. In the thorough QT study in healthy volunteers, the maximum mean time matched change in heart rate for GSK573719 (500 mcg) compared with placebo was 2.1 bpm at 8 hours post dose (90% CI: 0.7, 3.5).

Vilanterol (GW64244)

The effects of GW642444 on central nervous, cardiovascular and respiratory systems were assessed in several studies.

CNS

Table 2. Safety pharmacology studies performed to evaluate the effects of different salts of GW642444 on CNS

Study N / GLP Compliance	Species / N / Sex / Groups	Salt form / Route / Dose (mcg/kg) /	Noteworthy findings
VD2003/00131/00 (R60372) / Yes	Rat (Sprague Dawley-CD) / 32 / Male / 4	H / Intravenous / 0, 25, 100, 400	At 25 mcg/kg: No effects observed At 100 and 400 mcg/kg: Dose-related decrease in body temperature associated with decreases in spontaneous locomotor activity and grip strength
VD2005/00527/00 (R60652) / Yes	Rat (Sprague Dawley-CD) / 32 / Male / 4	M / Inhalation / 0, 36, 612, 34399	At 36, 612 and 34399 mcg/kg: Decrease in motor activity at time points up to 9 hours following start of exposure. At 34399 mcg/kg: Decreased body temperature (up to 1.6°C) at 1.25 hours following start of exposure.

Rat

Conscious male Sprague Dawley rats were intravenously administered with single dose of vehicle or GW642444H. Animals were observed for peripheral and central nervous systems activities (e.g. motor activity, behaviour, co-ordination, somatic sensory/motor reflex responses and automatic responses such as piloerection, pupil size, lachrymation, salivation, overt cardiovascular and gastrointestinal effects) and potential effects on body temperature.

In other study also performed in conscious male Sprague Dawley CD rats, GW642444M was administered as a single dose via snout-only inhalation. Animals were subjected to neurobehavioural observations using a standard observation battery, quantitative motor activity evaluations and the recording of body temperature. Body temperature and neurobehavioural endpoints were monitored before dosing (to obtain baseline measurements), and subsequently at 1.25, 3 and 9 hours from the start of exposure while motor activity was evaluated before the dosing and at 1.25, 9 and 25 hours from the start of the exposure.

Cardiovascular System

Table 3. Safety pharmacology studies performed to evaluate the effects of different salts of GW642444 on CVS

Study N / GLP Compliance	Species/ N / Sex / Group	Salt form / Route / Dose (mcg/kg)	Noteworthy findings
FD2003/00330/00 (V24776) / Yes	HEK293 / NA / NA / NA	H / *In vitro* / 0.31, 1.02, 3.1, 10.2 and 30.7 mcM (0.15, 0.5, 1.5, 5.0 and 14.9 mcg/mL)	GW642444 inhibited hERG tail current in a concentration-dependent manner. At 30.7 mcM GW642444 inhibited hERG tail current completely. The IC_{25}, IC_{50} and IC_{75} values for GW642444 inhibition of hERG tail current were 2.0, 4.8 and 12.6 mcM (0.99, 2.3 and 6.1 mcg/mL), respectively.
FD2003/00323/01 (V24650) / Yes	Isolated dog Purkinje fibre/ NA / NA / NA	H / *In vitro* / 1, 10 and 100 mcM (0.49, 4.9 and 49 mcg/mL)	At stimulation frequencies of 0.5 and 1 Hz, exposure to GW642444 at concentrations of 1 and 10 mcM caused a concentration-dependant depolarization of RMP and decreases in UA, MRD and APD. At 100 mcM GW642444 action potentials could not be elicited in 3 of the 4 test substance treated fibres. In the remaining fibre RMP, UA and APD were further reduced compared to the effects observed at 10 mcM GW642444 (the effect on MRD was similar to the effects observed at 10 mcM) at 1 Hz. This fibre became spontaneous at 0.5 Hz. Due to these effects meaningful statistical analysis could not be performed at 0.5 and 3 Hz. These results are consistent with inhibition of cardiac potassium (IK1) and sodium channels although an additional inhibition of cardiac calcium channels cannot be ruled out.
FD2003/00275/00 (D24478) / Yes	Dog (beagle) / 4 / Male / 4	H / Intravenous / 0, 0.1, 0.3 and 1	At 1 mcg/kg, moderate increase in heart rate of approximately 60 bpm (lasting approximately 20-25 minutes along with small decreases in blood pressure, PR- and QT- intervals detected 5-minutes post dose. At 0.3 mcg/kg, smaller increase in heart rate (26 bpm), which returned back to predose levels approximately10 minutes after dosing. There were no other cardiovascular or ECG changes following treatment with GW642444H.
FD2005/00097/00 (D26014) / Yes	Dog (beagle) / 4 / Male / 4	M / Intravenous / 0, 0.1, 0.3 and 1	At 1 mcg/kg, small decrease in blood pressure of approximately 10 mmHg lasting approximately 15 minutes and an increase in heart rate of approximately 67 bpm which lasted for approximately 55 minutes. At 0.3 mcg/kg, smaller increase in heart rate of approximately 37 bpm. At both doses, 0.3 and 1 mcg/kg, reductions in PR, RR, QT and QTcL interval, attributed to the changes in heart rate. At 0.1 mcg/kg, very small prolongation of QT and QTcL interval. QTcL increased by approximately 6 msecs and returned to predose levels at approximatley 40 minutes following the end of infusion. There were no abnormal changes in ECG rhythm or waveform morphology at any dose

***In vitro* studies**

Effects on QT interval. hERG assay

The potential capacity of GW642444H to inhibit hERG tail current was evaluated by whole cell patch clamp method in HEK-293 cells stably transfected with hERG cDNA. Peak hERG tail current amplitude

was measured prior to and following exposure to GW642444H, DMSO, (vehicle) or E-4031 (0.1 mcM; an inhibitor of hERG tail current) using 4 to 5 cells/concentration.

Effect on QT interval. Purkinje fibre assay

In other *in vitro* study using beagle dog isolated Purkinje fibres, the effects of GW642444H on cardiac action potential, including action potential duration at 60 and 90% repolarization (ADP_{60} and ADP_{90}), resting membrane potential (RMP), maximum rate of depolarisation (MRD) and upstroke amplitude (UA) was examined. All mentioned parameters were measured at 1 and 0.5 Hz, except MRD that was measured at 3 Hz in the presence of vehicle or GW642444 at 100 mcM.

***In vivo* studies**

Dog

GW642444H was administered intravenously to conscious male beagle dogs to evaluate its effects on arterial pressures, heart rate, and electrocardiograph parameters. Cardiovascular function and ECG parameters were monitored via telemetry from 30 minutes prior to dosing, during the 1 minute infusion period and for 4 hours after dosing.

In conscious male beagle dog the effects of GW642444M in the cardiovascular function and ECG parameters were also evaluated. Systolic, diastolic and mean blood pressure, pulse pressure, heart rate and ECG parameters were monitored via telemetry from 30 minutes before dosing, during the 1 minute infusion period and for 4 hours after dosing. ECG waveforms were observed for any abnormal changes in rhythm or morphology.

Respiratory System

Table 4. Safety pharmacology studies performed to assess the effects of different salts of GW642444 on respiratory system.

Study N / GLP Compliance	Species / N / Sex / Group	Salt form / Route / Dose (mcg/kg)	Noteworthy findings
CD2003/00833/00 (G03140) / Yes	Rat (Sprague Dawley) / 24 / Male / 4	H / Inhalation / 0, 61, 241, 666	At 666 ug/kg: slight increases in respiratory rate during 20 to 60 minutes of exposure but this increases was not evident at 24 and 48 hours after exposure and since it was mild and had no effect on minute volume (total pulmonary ventilation) it is not considered to be an adverse effect.
CD2005/01091/00 (G05179) / Yes	Rat (Sprague Dawley) / 24 / Male / 4	M / Inhalation / 0, 36.02, 718.13, 36327.03	Statistically significant changes in respiratory rate at 15 minutes and 1 hour during exposure for 36.02 and 718.13 µg/kg groups and at 24 hours for the 36.02 and 36327.03 µg/kg groups. Since these baseline-adjusted differences were minor, isolated events, and were not dose-dependent, they are not considered to be drug-related.

The effects of GW642444H on the respiratory system were evaluated in conscious male Sprague-Dawley CD rats. T tidal volume, respiratory rate and minute volume were the respiratory parameters monitored before the dosing and at approximately 24 and 48 hours after exposure to the product.

In other study in conscious male Sprague-Dawley CD rats was also evaluate the effects of GW642444M on the respiratory. The tidal volume, respiratory rate and minute volume were respiratory parameters evaluated and measured prior to dosing, continuously during the 1 hour and for approximately 1 hour at approximately 24 hours post-exposure.

Umeclidinium bromide/vilanterol

To investigate any potential for synergistic effects on cardiovascular parameters, a dog intravenous cardiovascular safety pharmacology study was performed on GW642444 (as the triphenylacetate salt, GW642444M) and GSK573719 alone and in combination (Report FD2008/00365).

Table 5. Safety pharmacology studies performed to assess the effects of GSK573719/GW642444 on CVS

Study number	Species (No. Animals/ Dosage Group)	Gender	Route of admin.	Dose (µg/kg)	Summary of results	GLP
CARDIOVASCULAR						
FD2008/00365	Dog (Beagle) (4)	Male	I.V (bolus)	0.3/0, 0/0.3, 0.3/0.3 (GSK573719/ GW642444)	0.3/0.3 mcg/kg GW642444 (triphenylacetate salt)/GSK573719 resulted in a small increase in mean, systolic and diastolic blood pressure (between 9 to 14 mmHg), compared to vehicle, between 126 to 181 minutes. Heart rate was increased (by approximately 33 bpm) 6 minutes following the start of infusion of 0.3 mcg/kg GW642444 with GSK573719 vehicle and 0.3 mcg/kg GW642444 with 0.3 mcg/kg GSK573719.	Y

GSK573719 and GW642444 in combination produced a minimal increase in mean, systolic and diastolic blood pressure at intravenous doses of 0.3/0.3 mcg/kg/day which was not seen with the individual components in this study. These effects seen only with the combination are not explained by the available PK data as there were no notable differences in systemic exposure to GW642444 or GSK573719 as measured by either the AUC_{0-t} and/or C_{max} when dosed alone or in combination.

In 4 and 13-week inhaled combination toxicity studies (Reports FD2009/00391 and WD2010/00677), increases in femoral pulse and heart rates of a similar magnitude were observed with GSK573719/GW642444 in combination and GSK573719 or GW642444 alone. Suggesting that while an increase in heart rate was seen, this effect was not exacerbated following administration of the combination compared to the individual components alone.

There were no ECG changes that were unique to the GSK573719/GW642444 combination in either the dog cardiovascular safety pharmacology study or the inhaled combination toxicity studies.

Pharmacodynamic drug interactions

No non-clinical pharmacodynamic studies have been performed to specifically evaluate possible interactions of GSK573719 or GW642444 with other drugs that may be co-administered.

Various in vitro assays have demonstrated that GSK573719 is a potent, competitive, pan-active mAChR receptor antagonist and that GW642444 is a potent and selective beta2 receptor agonist. Secondary pharmacology studies evaluating the selectivity of GSK573719 or GW642444 using a standardized panel of receptors and channels suggested that neither compound is likely to produce biological effects unrelated to their primary activity.

Based on the high selectivity of the two compounds to their native receptors, and the low plasma concentrations within the efficacious dose range (as a consequence of the low inhaled dose and their 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 LABAs and LAMAs as human medicines is well documented and known potential drug interactions are described in the prescribing information.

2.3.3. Pharmacokinetics

Methods of analysis

Validated analytical methods utilising LC-MS/MS were employed to ensure the specific and accurate quantification of GSK573719 and GW642444 in the plasma of non-clinical species. Assays were developed and validated in mouse, rat, rabbit and dog plasma. Analytical ranges of 0.02 or 0.1 to 100 ng/mL for both compounds enabled the definition of systemic exposure across the dose ranges used throughout the nonclinical program for both compounds.

In examining the metabolic profile of GSK573719 14C labels were used and were studied using high performance liquid chromatography (HPLC) with either on-line or off-line radiochemical detection. Studies to identify the metabolites in theses samples were performed using 1H-nuclear magnetic resonance (NMR), LC-MS and LC-MS/MS. Radio-chromatographic profiles in selected extracts of human plasma samples were obtained by off-line radio-detection using Accelerator Mass Spectrometry (AMS) as a sensitive radio-detector.

For GW642444, radiolabelled metabolite profiles were generated using HPLC with either on-line or offline radiochemical detection. Off-line radio-detection generally involved eluate fractionation followed by scintillation counting. In the human ADME study low radioactivity concentrations necessitated the use of AMS as a sensitive radio-detector. Metabolites were identified (where possible) using LC-MS and LC-MS/MS and 1HNMR. For a number of metabolites, however, identification was not possible using these techniques because of the low chemical mass. The structures of some metabolites, therefore, have been assigned by comparison of chromatographic retention times with either authentic standards or metabolites identified in other studies. The sensitivity of the assays used was such that it was possible to follow the time course of GW642444 in the body and thus obtain meaningful pharmacokinetic profiles.

Absorption

Umeclidinium bromide (GSK573719)

Absorption of GSK573719 from the lung following inhalation administration was rapid in all non-clinical species with T_{max} generally at the first sample taken after the end of the inhalation period. Oral absorption of GSK573719 was very low in both rat and dog. Oral bioavailability was negligible in rats and dogs such that it could not be determined (Reports CH2006/00004 and CH2006/00001) indicating that systemic exposure from the swallowed portion of an inhaled dose in animals will be negligible. In a rat excretion study, only 0.3% of administered radioactivity was recovered in urine and bile following oral administration of ^{14}C-GSK573719. In a dog excretion study, absorption was less than 5% based on a comparison of radioactive recovery in dog urine following oral and intravenous administration of ^{14}C-GSK573719 (Report FD2005/00164).

Studies in mice and rats showed that oral bioavailability was also limited by first-pass metabolism. In mice dosed orally with ^{14}C-GSK573719, it was shown that levels of radioactive drug-related material (DRM) were lower in the systemic circulation compared to those in the hepatic portal vein (Report WD2008/00001). In rats administered GSK573719 via the hepatic portal vein, systemic concentrations of GSK573719 were much lower compared to when administered into a peripheral vein (report CH2006/00012).

Oral absorption of GSK573719 in humans, as in animals, was negligible, with no quantifiable concentrations of GSK573719 following oral administration of 1000 mcg. Similarly, the absorption of DRM was low following administration of ^{14}C-GSK573719, with the estimated oral bioavailability based on plasma radioactivity levels being approximately 5%. Absorption was less than 5% based on a comparison of radioactivity recovery in human urine following oral and intravenous administration of ^{14}C-GSK573719. The low human oral bioavailability was primarily mediated by poor absorption (studies AC4112008 and AC4112014).

Single dose:

Following intravenous administration, the pharmacokinetic parameters of GSK573719 were similar across all species investigated with a high clearance (in excess of liver blood flow, indicating extrahepatic clearance routes such as direct renal secretion) and a large volume of distribution (exceeding body water), indicating extensive distribution into tissues (Rat - Reports CH2006/00004 and WD2006/00073; Dog - Reports CH2006/00001 and WD2006/00075).

Repeat dose:

The toxicokinetics of GSK573719 were investigated in repeat dose inhalation toxicity studies in mice, rats, rabbits and dogs for up to 26, 26, 2 and 39 weeks duration, respectively (Reports 2012N131664, FD2009/00467, WD2006/03186 and FD2009/00466).

Inter-animal and inter-study variability of systemic exposure to GSK573719 was relatively high as is typical following inhalation administration. The variability was particularly notable in the dog, in which oropharyngeal tube inhalation was used to administer GSK573719 in the pivotal studies ≥13 weeks. The mean data, however, consistently showed the same trends between studies.

Systemic exposure to GSK573719 in toxicity studies was considerably greater in most cases than that in humans at the proposed doses. Generally, systemic exposure to GSK573719 following inhalation administration to mice, rats, rabbits, dogs and humans increased with increasing dose in a proportional manner. There were occasions where the increase in systemic exposure was sub- or supra-proportional between individual dose levels (two 7-day toxicity studies in the rat and a 14-day toxicity study in the dog - Reports WD2004/01556, WD2005/01063 and WD2006/03228 respectively).

There was little evidence of accumulation (greater than 2-fold) of GSK573719 on repeat administration, although increases in systemic exposure (AUC_{0-t}) were occasionally observed at higher dose levels (Reports 2011N111874, WD2006/03669 and WD2005/01423). Overall, there were no marked or consistent differences in systemic exposure between the sexes in the mouse, rat or dog. There were no marked changes in systemic exposure with time or gender following repeated administration of GSK573719 in human studies. T_{max} usually occurred immediately following the end of the inhalation dosing period in all species, indicating rapid absorption across the lung.

Replacement of cellobiose octaacetate with magnesium stearate as an excipient in the rat and dog did not result in notable changes to systemic exposure of GSK573719 (Reports WD2006/03225 and WD2006/03669).

Systemic exposure was also unchanged in dogs receiving inhalation administration and fed a wetted diet compared to a dry diet, which was a change implemented during the toxicology programme in dogs with GSK573719 (Report WD2006/03294).

Systemic exposure following subcutaneous (rat and pregnant rabbit) and intravenous (rat and dog) administration established systemic exposures greater than those achieved clinically (Reports FD2008/00339, RD2009/01098, RD2009/01099, 2011N111874, CD2009/00970 and CD2010/00235; FD2008/00365).

Two 13 week mouse oral studies were conducted with GSK573719 to assess the suitability of this route of administration for a carcinogenicity study. Given that GSK573719 has been shown to have poor oral absorption and that the systemic exposure at oral doses suitable for a lifetime study were predicted to lower than those that could be obtained following inhaled dosing, inhaled administration was chosen for use in a carcinogenicity study. At the doses used in the mouse toxicity studies, the majority of the compound would have remained unabsorbed in the gastrointestinal tract.

Vilanterol (GW642444)

Absorption of GW642444 from the lung following inhalation administration was rapid in all non-clinical species with Tmax generally at the first sample taken after the end of the inhalation period. Oral absorption of 14C-GW642444 was good in both rat and dog with at least 37% and 56% orally absorbed in BDC rats and intact dogs, respectively. Oral bioavailability of GW642444, however, was low in the rat (1.1%) and moderate in the dog (29.7%). Hepatic portal vein plasma concentrations of GW642444 in mice and rats suggest that first-pass hepatic clearance limits oral bioavailability in these species. Oral bioavailability in the rat is, therefore, limited mainly by first pass hepatic clearance as well as incomplete absorption. The higher oral bioavailability (and lower blood clearance,) in the dog suggests that a greater proportion of the swallowed component escapes first pass hepatic clearance and, as a result, the oral component in the dog is likely to make a larger contribution to systemic exposure following inhalation administration.

Oral absorption of GW642444 in human, as in animals, was good with at least 50% orally absorbed based on urinary recovery of DRM following administration of 14C-GW642444 in solution (study B2C106181). Exposure to GW642444 represented a very small percentage (in the region of <0.5%) of DRM in plasma indicating that the low human oral bioavailability (< 2%), was mediated by extensive first pass metabolism.

Differences in blood clearance of GW642444 was observed in rat, dog and human and ranged from moderate in the rat (35% of rat liver blood flow of 90 mL/min/kg), lower in the dog (26% of dog liver blood flow of 40 mL/min/kg) and high in human (> human liver blood flow). The steady state volume of distribution of GW642444 was high in the rat and human but moderate in the dog, exceeding total body water in all species.

In repeat dose inhalation studies using dry powder formulations, systemic exposure to GW642444 (AUC0-t and Cmax) increased with increasing dose in a proportional or less than dose-proportional manner; subproportionality was generally associated with higher doses. There was little evidence of accumulation of GW642444 exposure with time, although increased AUC0-t values were occasionally observed upon repeat dosing in some of the rat studies. Overall, there were no marked changes in systemic exposure between males and females in the mouse, rat or dog. There were no marked changes in systemic exposure with time or gender, following repeated administration of GW642444 in human. Tmax was generally at the first sample time after the end of the inhalation period indicating rapid absorption across the lung. Exposure to GW642444 in animal toxicity studies was considerably greater (in most cases) than following proposed dose of GW642444 to human.

Inclusion of magnesium stearate as an excipient in rat and dog vehicle formulations for inhalation studies did not result in notable changes to systemic exposure.

Systemic exposure (AUC0-t and Cmax) to GI179710 (the triphenylacetate counter-ion of GW642444M triphenylacetate salt) following inhalation administration of GW642444M increased proportionally with dose in rats and dogs but less than proportionally in the mouse. In the rat, there was some evidence for accumulation on repeat dosing but not in the mouse or dog. Overall, in the majority of studies, there were no differences in systemic exposure between genders.

In repeat dose clinical studies where asthma and COPD patients were administered at doses of up to 50 mcg GW642444M, concentrations of GI179710 were below the limits of quantification (1 ng/mL) in the majority of subjects. Cmax concentrations of GI179710 on repeat dose inhalation toxicity studies (mean of males/females over whole study at the highest dose level administered) were > 1000 ng/mL in the mouse and rat and > 200 ng/mL in the dog and pregnant rabbit. Large systemic exposure ratios for GI179710, relative to human, have, therefore been established in toxicology studies.

Systemic exposure (AUC0-t and Cmax) to Human metabolites GW630200 (M29) and GSK932009 (M33) generally increased with increasing dose in either a proportional or less than dose-proportional manner. Mice, rats and dogs were all exposed to both metabolites with metabolite:parent ratios (based on AUC0-t) of 0.002 to 0.01 for GW630200 (M29) and 0.02 to 0.08 for GSK932009 (M33). No consistent difference in exposure to metabolites was observed between males and females.

In repeat dose clinical studies where asthma and COPD patients were administered doses of up to 50 mcg GW642444M by the inhalation route, concentrations of GW630200 (M29) and GSK932009 (M33) were below the limits of quantification (0.09 and 0.18 ng/mL, respectively) in the majority (99.8%) of subjects. Cmax concentrations of GW630200 (M29) and GSK932009 (M33) observed in non-clinical repeat dose inhalation toxicity studies (at the highest dose level administered as recommended in ICH M3(R2) were > 0.7 ng/mL for GW630200 (M29) and > 3 ng/mL for GSK932009 (M33) in the rat, mouse and dog. Mice, rat and dogs have, therefore, been exposed to higher concentrations of these metabolites compared to human.

Umeclidinium bromide/vilanterol

Inhalation:

The toxicokinetics of GSK573719 and GW642444 have been investigated following repeated inhalation administration of GSK573719 and GW642444 (triphenylacetate salt) in combination to Sprague Dawley rats for 4 weeks (Report FD2009/00392) and beagle dogs for 4 and 13 weeks (Reports FD2009/00391; 2010N109790 and WD2010/00677 respectively). The combination of GSK573719 and GW642444 was administered as a dry powder formulation in lactose mostly including magnesium stearate as an excipient to aid stability which represents the proposed clinical formulation.

In rats (12/sex/group), GSK573719 was generally quantifiable in plasma up to 24 hours from the start of exposure. GW642444 was generally quantifiable in plasma up to 9 and 24 hours, respectively, at estimated achieved doses of 60.7 and 1040 mcg/kg/day. There were very limited quantifiable concentrations of GW642444 at the lowest dose (4.37 mcg/kg/day) and therefore it was not possible to define the systemic exposure in these rats. For both compounds, T_{max} generally occurred within 30 minutes following the 1 hour dosing period. Generally, there was no notable difference (>2-fold) in systemic exposure (as measured by $DNAUC_{0-t}$ and DNC_{max}) for GSK573719 when administered alone or in combination with GW642444. However, there was a trend for systemic exposure of GW642444 to be lower when administered in combination with GSK573719. Systemic exposure to GW642444 increased in approximate proportion with increasing dose between 60.7 and 1040 mcg/kg/day when co-administered with GSK573719. There was no notable difference in systemic exposure for either GSK573719 or GW642444 across the duration of the study between Day 1 and Week 4 or between the sexes.

Systemic exposure to GSK573719 or GW642444 (AUC_{0-t} and C_{max}) was not markedly different when dosed in combination compared to when dosed alone by the inhalation route to dogs. In a 4-week inhalation toxicity study in dogs (3/sex/group), GSK573719 and GW642444 were generally quantifiable in plasma over the sampling period up to 24 hours from start of exposure. For both compounds, T_{max} generally occurred immediately after the end of the dosing period at 10 minutes. Generally, there was no notable difference (2-fold) in systemic exposure (as measured by $DNAUC_{0-t}$ and DNC_{max}) for either

GSK573719 or GW642444 when administered in the presence or absence of the other compound. Overall, there was no obvious consistent trend, suggesting a difference in systemic exposure (as measured by $DNAUC_{0-t}$ and DNC_{max}) for either GSK573719 or GW642444 across the duration of the study between Day 1 and Week 4 or between the sexes in any of the dose groups.

In a second 4-week inhalation toxicity study in dogs (3/sex/group) conducted to compare two different dosing regimens with or without a 3 day pre-adaptive phase at a lower dose of GW642444 (Report 2010N109790), GSK573719 and GW642444 were generally quantifiable in plasma up to at least 24 hours and 8 hours from the start of dosing, respectively. For both compounds, T_{max} generally occurred immediately after the end of the dosing period at 10 minutes. There was notable variability in the systemic exposure to both GSK573719 and GW642444 between dogs receiving the same dose as shown with the range of $DNAUC_{0-t}$ and DNC_{max} values on both sampling occasions. There was generally no consistent difference in systemic exposure (as measured by $DNAUC_{0-t}$ and DNC_{max}) to GW642444 or GSK573719 when administered without or with the 3 day GW642444 tolerance dosing phase. Generally, there was no consistent difference in the mean systemic exposure (as measured by DNAUC0-t and DNCmax) to either GSK573719 or GW642444 across the study or between the sexes in either dose group, with the range of values overlapping.

In a 13-week inhalation toxicity study in dogs (4/sex/group) (Report WD2010/00677) GSK573719 was generally quantifiable in plasma up to 24 hours following a daily administration of GSK573719 at achieved doses of 60 mcg/kg/day and above. In dogs receiving an achieved dose of 23.3 mcg/kg/day GSK573719, there were sparse data with quantifiable concentrations up to 2 hours only. For both compounds, T_{max} generally occurred immediately after the end of the dosing period at 10 minutes. GW642444 was generally quantifiable in plasma up to 24 hours from start of exposure. Although there was notable variability in the systemic exposure to both GSK573719 and GW642444 within dogs receiving the same dose, generally the mean systemic exposure to both GSK573719 and GW642444, in terms of $DNAUC_{0-t}$ and DNC_{max}, increased in approximate proportion with increasing dose. Generally, there was no consistent difference in systemic exposure to either GSK573719 or GW642444 across the study or between the sexes for either GSK573719 or GW642444. Furthermore, there was generally no consistent difference in systemic exposure to GSK573719 or GW642444 when administered in the presence or absence of the other compound.

Subcutaneous:

The toxicokinetics of GSK573719 and GW642444 (triphenylacetate salt) in combination were investigated in a dose-ranging embryofetal study in New Zealand White rabbits (4/F/group) administered on Days 7 to 19 pc via the subcutaneous route (Report CD2009/00970).

GSK573719 was quantifiable in plasma up to at least 4 hours after a dose of 20 mcg/kg/day and up to 24 hours after doses of 100 to 1500 mcg/kg/day. The C_{max} was generally observed at 0.25 hours, which was the first sampling occasion, at all doses. Systemic exposure (as determined by AUC_{0-t} and C_{max}) to GSK573719 increased in approximate proportion with dose across the dose range. There was no notable difference in systemic exposure to GSK573719 when administered alone or in combination with GW642444. GW642444 was quantifiable in plasma up to 24 hours.

Intravenous:

In the dog (4/M/group) safety pharmacology study (Report FD2008/00365), GSK573719 was only quantifiable to between 1 and 5 minutes after dosing whilst GW642444 was quantifiable for up to 30 minutes after dosing. T_{max} for GSK573719 and GW642444 occurred at 1 minute, which was the first sampling occasion after administration. It was not possible to determine AUC_{0-t} for GSK573719 due to there being only sparse data. There were no notable differences in systemic exposure to GSK573719

or GW642444, as measured by either the AUC_{0-t} and/or C_{max}, when either was dosed alone or in combination.

Distribution

Umeclidinium bromide (GSK573719)

In vitro

Plasma protein binding

The in vitro plasma protein binding of GSK573719 (5, 25, 200 ng/mL) was studied in mouse, rat, rabbit, dog and human plasma (Report WD2008/00503) using equilibrium dialysis. The concentration of GSK573719 in the spiked plasma and dialysate was determined by HPLC-MS/MS. The plasma protein binding (87.6%, 85.6%, 76.4%, 80.2% and 87.9% in the mouse, rat, rabbit, dog and human, respectively) was moderate in all species and independent of concentration.

In a second study, the plasma protein binding of GSK573719 (2 ng/mL) was investigated in plasma obtained from healthy subjects (male and female), severe renally impaired subjects and severe hepatically impaired subjects (Report 2012N144582). In addition, the protein binding of GSK573719 (1 ng/mL) was also investigated in incubations with individual human plasma proteins: human serum albumin (40 mg/mL), α-acid glycoprotein (0.8 mg/mL) and γ-globulin (7 mg/mL) dissolved in phosphate buffered saline. The concentration of GSK573719 in respective dialysates and original incubations were determined using solid phase extraction by HPLC-MS/MS. Protein binding of GSK573719 was similar in incubations of plasma obtained from healthy male and female subjects as well as the renally and hepatically impaired human subjects ranging from 87.5 to 95.9% bound. GSK573719 was moderately bound to human serum albumin (67.2%), γ-globulin (64.6%) α-acid glycoprotein (84.9%), although the binding was slightly higher to α-acid glycoprotein.

Blood cell association

The in vitro blood cell association of ^{14}C-GSK573719 (50, 200, 500 ng/mL) was investigated in mouse, rat, rabbit, dog and human blood (Report WD2008/00503). The blood to plasma ratios (0.755, 0.682, 0.736, 0.525 and 0.551 in the mouse, rat, rabbit, dog and human, respectively) were low and independent of the concentrations in all species examined. The corresponding mean percentage blood cell association values were 28.4%, 26.5%, 7.62%, 2.96% and 7.05% for mouse, rat, rabbit, dog and human, respectively.

Distribution of DRM into blood cells was slightly higher with blood to plasma ratios of between approximately 1 and 2.7 as observed in ex-vivo samples taken following an intravenous infusion of 14C-GSK573719 to rats and dogs (Reports FD2005/00208 and FD2005/00164).

P-glycoprotein transport and membrane permeability

The potential for human P-glycoprotein (P-gp) to transport ^{14}C-GSK573719 was investigated using stable transfected Madin-Darby canine kidney II cell line transfected with human MDR1 gene (MDCKII-MDR1) cells (Report WD2006/02657).

Directional transport was determined by measurement of apical to basolateral ([A→B]) and basolateral to apical ([B→A]) rates of transport using 3 mcM ^{14}C-GSK573719 in the absence and presence of 2 mcM GF120918, a potent P-gp inhibitor. The passive membrane permeability of ^{14}C-GSK573719 was determined in the presence of GF120918 over pH range of 5.5 to 7.4 with samples being analysed for radioactivity. GSK573719 was a substrate of human P-gp, with an apical efflux ratio ranging from 7 to 17 and 0.8 in the absence and presence of inhibitor, respectively. GSK573719 was determined to have low passive membrane permeability (average pH7.4) of 2.4 ± 0.8 nm/s. The passive membrane permeability of GSK573719 was not affected over the pH range investigated. The mass balance for

14C-GSK573719 was 76% for one plate (B→A direction only), however, this did not affect the conclusion that GSK573719 is a substrate for P-gp.

Inhibition of P-glycoprotein

The ability of GSK573719 to inhibit human P-gp-mediated transport of [^{3}H]-digoxin was assessed using stable transfected MDCKII-MDR1 cells (Report WD2006/02596). GSK573719 did not inhibit transport of digoxin via human P-gp in vitro at concentrations up to 100 mcM.

Organic cation transporters

An assessment of ^{14}C-GSK573719 as a substrate of human organic cation transporters was performed using a human embryonic kidney (HEK293) cell line stably transfected with OCT1, OCT2, OCT3, OCTN1 or OCTN2 genes (Report WD2010/00669). GSK573719 (which is cationic) was found to be a substrate for the human organic cation transporters OCT1 and OCT2, but not OCT3, OCTN1 or OCTN2. Kinetic parameters were derived for OCT1 and OCT2, for OCT1 K_m and V_{max} were 4.42 mcM and 476 pmol/mg/protein/3 minutes, respectively, whilst for OCT2 the values were 0.157 mcM and 61 pmol/mg/protein/15 minutes, respectively. Uptake of GSK573719 by OCT1 and OCT2 was shown to be inhibited by both MPP+ and cimetidine with IC50 values of 105 mcM and 1.4 mcM, respectively, for OCT1, and 535 mcM and 103 mcM, respectively, for OCT2. OCT1 and OCT2 are predominantly located in the liver and kidney, respectively. These data suggest that active transport mediates the distribution of GSK573719 in vivo as it has a low passive permeability in MDCKII-MDR1 cell lines (Report WD2006/02657), although their contribution to overall systemic clearance of GSK573719 is unclear.

In vivo

P-glycoprotein transport

A pharmacokinetic study was performed to determine the influence of P-gp on the absorption of ^{14}C-GSK573719 (as the trifluoroacetate salt) following a single oral or intravenous administration of ^{14}C-GSK573719 to male FVBn (wildtype WT) and male mdr1a/1b (-/-, P-gp knockout KO) mice (Report WD2008/00001). ^{14}C-GSK573719 was administered as a solution in saline (0.9% w/v) to KO and WT mice as a single intravenous bolus administration (9/group) or oral gavage (15/group) at a target dose level of 40 mcg/kg.

The levels of radioactivity (as determined by AUC_{0-t} and C_{max}) in the hepatic portal vein and systemic plasma increased between 13- and 20-fold in the KO mice compared with WT mice, indicating that following oral administration P-gp plays a role in the absorption of GSK573719 in the mouse. Bioavailability of GSK573719 radioactive drug-related material increased in WT mice compared to KO mice, from 1 to 14%. These data are consistent with the poor absorption of GSK573719 and P-gp having a role in the absorption process.

Blood, plasma, liver and lung and GI tract concentrations

Mouse: A study was performed to estimate the lung retention and systemic exposure of GSK573719 (target dose level of 2000 mcg/kg) in the mouse (20 M) following intranasal administration (Report CH2006/00002). Concentrations of GSK573719 in the lung were considerably higher than those observed in the plasma from 15 minutes to 24 hours post dose (12915 ng/g vs 191 ng/mL at 15 min, 10612 ng/g vs 72 ng/mL at 60 min, and 2771 ng/g vs 5 ng/mL at 24 hr, in lung vs plasma, respectively).

In an excretion study, the levels of radioactivity in plasma and liver were determined following administration of a single intravenous dose of ^{14}C-GSK573719 (1000 mcg/kg) to CD-1 mice (3/M/group) (Report 2010N105743). There was a notable decrease in the level of radioactivity between 0.25 and 24 hours post dose in both the plasma and liver, with decreases of approximately

150-fold and 55-fold, respectively. There was no notable accumulation of DRM in the liver of the mouse, with approximately 0.4% of the dose being recovered in the liver at 24 hours post dose.

Rat: In an excretion study, the levels of radioactivity in blood, plasma, lungs and liver was determined following administration of a single intravenous or single oral dose of ^{14}C-GSK573719 (1000 mcg/kg) to Sprague Dawley rats (3/M/group) (Report FD2005/00208). Following intravenous administration, the mean blood:plasma ratios increased from 0.9 to 2.7 between 0.5 to 2 hours, indicating an increased association with the cellular fraction with time. The highest levels of radioactivity were observed in blood and plasma at 0.5 hours. The levels of DRM in the plasma declined at a faster rate than those in the liver or lung. Between 0.5 and 2 hours the liver to plasma and lung to plasma ratios of DRM increased from 18 to 92 and 2.1 to 41, respectively. Following oral administration, levels of radioactivity in the liver and lungs were quantifiable up to 2 hours and 0.5 hours, respectively, with a highest level being 0.003 mcg equivalents/g. Mean levels of DRM in the blood and plasma were below the limit of quantification.

Dog: In an excretion study, the level of radioactivity in blood and plasma was determined following administration of a single intravenous or oral dose of ^{14}C-GSK573719 (1000 mcg/kg) to male beagle dogs (3/sex/group) (Report FD2005/00164). Following intravenous administration, the mean blood:plasma ratios increased from 1.0 to 2.1 between 1 (end of infusion) to 3 hours, indicating an increased association with the cellular fraction with time. The highest levels of DRM were observed in blood and plasma at 1 hour and were non-quantifiable in plasma by 96 hours.

Following oral administration, mean levels of radioactivity in blood and plasma were low or below the limit of quantification at all time points.

In another excretion study, the level of radioactivity in blood and plasma was determined following the administration of a single intravenous dose of ^{14}C-GSK573719 (as the trifluoroacetate salt) in male BDC beagle dogs (n=2) (Report WD2007/01907). Following the slow bolus administration, quantifiable concentrations of radioactivity in plasma and blood were only observed at the early time points (1 and 3 minutes post dose), whilst following infusion administration at the higher dose level, quantifiable concentrations were observed at all time points investigated (latest time point was 9 hours post dose).

CNS penetration

A study was performed to determine the CNS penetration of GSK573719 following the intravenous infusion to achieve steady state plasma concentrations in the conscious rat (3/M/group) (Report CH2006/00013). GSK573719 was administered as a solution in 20% aqueous Cavitron™ (pH = 5.0) containing 1% DMSO as a continuous 24 hours infusion at estimated achieved dose of 24300 mcg/kg. Plasma and brain homogenate concentrations of GSK573719 were quantified by LC/MS/MS (LLQ = 1 ng/mL for plasma and 5 ng/mL for brain homogenate, equivalent to 15 ng/g of brain tissue). GSK573719 was shown to be present in the brain at the systemic exposure levels achieved in this study, with brain:plasma ratio of around 1.1 at approximate steady state in the rat.

Tissue distribution

Quantitative whole body autoradiography (QWBA) in rats (Report FD2005/00236) was conducted following IV and oral administration.

Pigmented (Lister Hooded) rats (6/M/group) received a single intravenous infusion over 30 minutes of ^{14}C-GSK573719 at a target dose level of 1000 mcg/kg. DRM was rapidly and widely distributed, with highest concentrations occurring in the majority of the tissues analysed at 30 minutes or 1.5 hours after the start of infusion (the first or second sample time point). The highest levels of radioactivity were in the excretory organs, with highest levels in the liver and kidney, these being 6.94 mcg equiv/g and greater than the upper limit of quantification (>7.03 mcg equiv/g), respectively. In the various

components of the CNS and the testes, levels of radioactivity were only just above the limit of quantification. In approximately half the tissues investigated the highest levels of radioactivity were observed immediately post dose, and by 35 days post dose, quantifiable levels of radioactivity were only present in the kidney medulla, mucous gland, muscle, tongue and uveal tract (choroid, iris and ciliary body)/retina. The presence of DRM in the uveal tract/retina at this time suggests its association with melanin.

Pigmented (Lister Hooded) male rats (6/M/group) received a single oral gavage administration of ^{14}C-GSK573719 at a target dose level of 1000 mcg/kg. Levels of radioactivity were below the limit of quantification in most tissues, indicating that GSK573719 was poorly absorbed in the rat following oral dosing. Excluding components of the gastrointestinal tract, quantifiable levels of radioactivity were only observed in the bone surface and marrow at the first sampling time (0.5 hours post dose). Levels in all tissues were below the lower limit of quantification (<0.007 mcg equiv/g) by 3 days post dose.

Milk transfer

In a pre-post-natal development study, female rats (dams) were administered GSK573719 (10, 60 and 180 mcg/kg) by the subcutaneous route and plasma concentrations of GSK573719 were measured in suckling pups (Report 2011N118595). GSK573719 was quantifiable in plasma in 2 out of 54 pups, and below the limit of quantification (0.02 ng/mL) in the remaining pups. Despite the low incidence of quantifiable GSK573719 concentrations in pups, transfer of GSK573719 via lactation cannot be ruled out.

Vilanterol (GW64244)

Plasma Binding:

In vitro plasma protein binding of GW642444 (parent form) was studied in rat, guinea pig, dog and human plasma using equilibrium dialysis. Plasma samples were incubated with 0.05 and 0.1 mcg/mL GW642444. The dialysates and remaining plasma samples were analysed for GW642444 by HPLC-MS. Binding of GW642444 to plasma proteins was moderately high in rats (84%), guinea pigs (92%), dog (98%) and human plasma (94%).

In a second study, plasma protein binding of GW642444 (as the α-phenylcinnamate salt, GW642444H) was investigated at concentrations of 0.005, 0.025, 0.125 or 0.625 mcg/mL in mouse, rat, guinea pig, female rabbit, dog and human plasma by equilibrium dialysis. The concentration of GW642444 in the dialysate and dialysed plasma, along with the original (non-dialysed) plasma sample, was determined by HPLC-MS/MS. The extent of plasma protein binding was moderately high at levels >90%, and appeared to be consistent across the concentration range within all species investigated. The mean plasma protein binding of GW642444 was 94.3, 92.3, 98.9, 93.4, 98.7 and 97.2% in the mouse, rat, guinea pig, female rabbit, dog and human, respectively.

Finally, protein binding of GW642444 (2 ng/mL as the triphenylacetate salt, GW642444M) was investigated by ultrafiltration in incubations with human serum albumin (40 mg/mL), α-acid glycoprotein (0.8 mg/mL) and γ-globlin (7 mg/mL) dissolved individually in phosphate buffered saline (Report 2011N118910_00). GW642444 was moderately bound to human serum albumin (60.3%) and α-acid glycoprotein (60.8%), whereas the extent of binding to γ-globlin was low (7.9%).

A study was also performed to examine the in vitro protein binding of 14C-GI179710 (the counter ion of GW642444M triphenylacetate salt - 0.05, 0.2 and 0.5 mcg/mL) in mouse, rat, rabbit, dog and human plasma using equilibrium dialysis. The mean plasma protein binding of 14C-GI179710 was 95.0, 96.5, >99, 97.1 and 97.7% in the mouse, rat, rabbit, dog and human, respectively. Extent of binding was high and appeared to be consistent across the concentration range investigated within each species.

Whole Blood Distribution

In an in vitro blood cell distribution study, GW642444 (0.1 mcg/mL) was shown to have a low moderate association with the cellular fraction of rat and human blood (58 to 63% in rat; 35 to 36% in human). The blood:plasma ratio following 30 minutes incubation was 1.5:1 and 0.85:1 for rat and human, respectively.

Similarly in a definitive study conducted during drug development, the blood cell association of 14C-GW642444 (parent form) was investigated at concentrations of 0.05, 0.2 and 0.5 mcg/mL in mouse, rat, guinea pig, female rabbit, dog and human plasma. The extent of blood cell association was low to moderate and there was no evidence of any concentration-dependence on association. The mean blood to plasma ratios of 14C-GW642444 were 1.0, 1.1, 0.73, 1.0, 0.50 and 0.76 in the mouse, rat, guinea pig, female rabbit, dog and human, respectively. The corresponding mean blood cell association values were 41.3, 55.9, 15.6, 41.4, 10.7 and 36.1%, respectively.

For the counter ion of GW642444M triphenylacetate salt (0.05, 0.2 and 0.5 mcg/mL), mean blood to plasma ratios were 0.70, 0.63, 0.66, 0.49 and 0.60 in the mouse, rat, rabbit, dog and human, respectively. The corresponding mean percentage blood cell association values were 16.8, 14.5, <1, 7.4 and 4.4%, respectively. Blood cell association of 14C-GI179710 was low and there was no evidence for any concentration-dependence on association.

P-glycoprotein transport and membrane permeability:

GW642444 was screened in Madin-Darby canine kidney II cell line transfected with human MDR1 gene (MDCKII-MDR1) cells to assess whether it was a substrate for human P-gp. The bidirectional permeability of GW642444 (5 and 10 mcM), from basolateral to apical (B→A) and apical to basolateral (A→B), was measured in the presence and absence of GF120918, a known inhibitor of P-gp. GW642444 was determined to be a substrate of human P-gp with B→A/A→B efflux ratios of 33.5 to 53.7 and 1.4 to1.5 in the absence and presence of GF120918, respectively.

In a second definitive study, the potential for human P-gp to transport GW642444 (as the α-phenylcinnamate salt, GW642444H - 0.5 mcM.) was investigated using stable transfected MDCKII-MDR1 cells in the absence and presence of a potent P-gp inhibitor. GW642444 was a substrate of human P-gp (apical efflux ratio of GW642444 determined as ≥25.7 and 0.5 in the absence and presence of GF120918A, respectively). The passive membrane permeability of GW642444 (average P7.4) was of 34 ± 13 nm/s. A passive permeability of 34 nm/s is currently classified as a moderate permeability, although at the time of the study, it was classified as being low passive permeability. Poor mass balance was observed for GW642444 and results from the assay should be interpreted with caution.

P-glycoprotein inhibition:

A study was performed to assess the ability of GW642444 (as the triphenylacetate salt, GW642444M) to inhibit human P-gp mediated transport of 3H-digoxin using stable transfected MDCKII-MDR1 cell. GW642444 inhibited the transport of digoxin via human P-gp in vitro by 26% at the highest concentration tested (100 mcM). There was no evidence of inhibition at 30 mcM or below. As a result IC50 values could not be calculated but would be >100 mcM based on the data from this study.

In vivo distribution studies:

P-glycoprotein transport:

In a pharmacokinetic study designed to provide information on the role of P-gp in attenuating CNS penetration and oral absorption of GW642444, a single oral dose of GW642444 (as the

triphenylacetate salt, GW642444M) at a target dose level of 1000 mcg/kg was administered to 21 male mdr1a/1b (knockout, KO) and 21 male FVBn (wildtype, WT) mice.

GW642444 exposures (based upon AUC0-t values) in hepatic portal vein (HPV) plasma were generally similar between KO and WT mice. Systemic concentrations of GW642444 and GSK932009 (M33) were higher in KO compared to WT mice (AUC0-t increases of 1.8- and 3-fold, respectively). In addition, the liver exposure to GW642444 was higher in KO mice versus WT mice (2.5-fold). In brain homogenate there was at least a 7.4-fold increase in the AUC0-t value of GW642444 in KO mice compared to WT mice. In conclusion, P-gp attenuated the CNS penetration of GW642444, but did not appear to play a major role in limiting its absorption. The role of P-gp in the biliary elimination of GW642444 and/or its metabolites was thought unlikely to be of biological importance.

Blood, plasma, liver and lung and GI tract concentration

As part of the excretion studies performed with 14C- GW642444 (as the α-phenylcinnamate salt, GW642444H- 350 mcg/kg) via i.v or oral route in male Sprague Dawley rats, total radioactivity in blood, plasma, lungs and liver were determined for up to 96 hours post dose. The mean blood:plasma concentration ratios of total DRM ranged from 0.8 to 1.1 following intravenous dosing and from 0.4 to 0.7 following oral administration. These data indicate that radioactivity was predominantly associated with the plasma fraction. The mean liver:plasma ratios of DRM ranged from 17 to 21 following intravenous dosing and from 3 to 11 following oral administration. Similarly, lung:plasma ratios ranged from 4 to 22 and 0.6 to 2 following intravenous and oral dosing, respectively. These data demonstrate a greater uptake of systemic DRM into the liver compared to lung.

In another excretion study, the concentrations of total radioactivity in blood, plasma and liver were determined at a single sample time (48 hours post dose) following administration of a single intravenous or oral dose of 14C-GW642444 (1000 mcg/kg, nominal) to male BDC Sprague Dawley rats (n=3/group). Mean blood:plasma concentration ratios of DRM were 0.7 (intravenous) and 0.9 (oral) corresponding to a blood cell association of 15% (intravenous) and 42% (oral), respectively. The mean liver:plasma concentration ratios of DRM for each dosing route were similar, approximately 12 (intravenous) and 8 (oral).

Likewise, the concentration of total radioactivity in blood, plasma, lungs and liver was determined in an excretion study following administration of a single intravenous or single oral dose of 14C-GI179710 (counter ion of GW642444M triphenylacetate salt) at 500 and 1000 mcg/kg, respectively, to groups of male Sprague Dawley rats (n=3/group). The mean blood:plasma concentration ratios of DRM ranged from 0.5 to 0.8 for both routes of administration. These data indicate that DRM was predominantly associated with the plasma fraction. Similarly, mean liver:plasma and lung:plasma ratios ranged from 6 to 27 and 0.5 to 0.9, respectively. These data demonstrate uptake of systemic DRM into the liver was greater than for the lung.

Whole body distribution

Whole body distribution was examined in rats and dogs following iv and oral administration of 14C-GW642444.

Pigmented (Lister Hooded) male rats (n=6/group) received a single intravenous (over 30 seconds) administration of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) at a nominal dose of 350 mcg/kg. Following intravenous dosing, rats were killed (n=1) at 15 minutes, 6 hours, and 1, 3, 10 and 35 days post dose, and QWBA performed. DRM was widely distributed into tissues at 15 minutes post dose, with the highest observed concentrations for the vast majority of tissues occurring at this time. The vast majority of tissues contained concentrations greater than that observed in blood. Highest concentrations of DRM at 15 minutes post dose were observed in the kidney, adrenals, choroid plexus and thyroid. The highest observed concentrations for some tissues, including the Harderian

gland, brown and white fat, preputial gland, seminal vesicles and pancreas, did not occur until 6 hours after dosing. DRM was also distributed into melanin containing tissues such as the eye and pigmented skin. Distribution into the brain or CNS was low following intravenous administration. Concentrations of DRM declined from the earlier time points and at 35 days only the uveal tract/retina and testis contained quantifiable radioactivity.

After Pigmented (Lister Hooded) male rats (n=6/group) received a single oral (gavage) administration of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) at a nominal dose of 350 mcg/kg, only a limited number of tissues contained quantifiable concentrations of radioactivity at any time point. Those that did included the kidney (cortex and medulla), liver, adrenal, salivary glands, brown fat, lung, uveal tract and the mucosae of the gastrointestinal tract. Other than the gastrointestinal tract, no tissue contained quantifiable levels after 3 days.

For the 14C-GI179710 counter ion (500 mcg/kg), DRM was widely distributed in Pigmented (Lister Hooded) male rats with the highest concentrations observed in the vast majority of tissues at the first sampling time (5 minutes) following iv administration. Highest concentrations were observed in the liver, tongue, kidney cortex, myocardium, pineal body, lung and bulbo-urethral gland. With the exception of various components of the gastrointestinal tract, all tissues attained their highest observed concentrations of DRM at 5 minutes after dosing. Tissue concentrations of DRM declined rapidly such that by 3 days post dose, concentrations in all tissues were generally below or close to the limit of quantification (0.003 mcg equivalents of GI179710/g). There was no evidence of association of DRM with melanin containing tissues, with no tissue containing a quantifiable concentration of radioactivity at 35 days post dose.

Following oral dosing (gavage) of the 14C-GI179710 counter ion (500 mcg/kg) DRM was widely distributed, with highest concentrations of radioactivity observed in the vast majority of tissues at the first sampling time (30 minutes). The tissues containing the highest concentrations of DRM at this time (excluding components of the gastrointestinal tract) were the liver, kidney cortex, tooth pulp, pancreas and tongue. Tissue concentrations of DRM declined rapidly such that by 3 days post dose, concentrations in all tissues were generally below or close to the limit of quantification (0.003 mcg equivalents of GI179710/g). There was no evidence of association of DRM with melanin containing tissues, with no tissue containing a quantifiable concentration of radioactivity at 35 days post dose.

Umeclidinium bromide/vilanterol

No distribution studies have been performed on the fixed dose combination umeclidinium bromide/vilanterol based on the data available for each compound which was considered acceptable by the CHMP.

Metabolism

Umeclidinium bromide (GSK573719)

In vitro

In vitro studies were performed using hepatic microsomes (rat, dog and human), hepatocytes (rat, mouse, rabbit, dog, and human) and cytochrome P450 (CYP) screen.

In vitro clearance

The in vitro intrinsic clearance of GSK573719 was determined in fresh, suspended rat, dog and human hepatocytes (Report CH2006/00011). Intrinsic clearance was similar across the species. GSK573719 was stable over the incubation period in rat (0.84 mL/minute/g liver), dog (1.80 mL/minute/g liver) and human hepatocytes (1.08 mL/minute/g liver).

The in vitro intrinsic clearance of GSK573719 was also determined in rat, dog and human liver microsomes (Report CH2006/00016). The in vitro clearance of GSK573719 was higher in the rat (15.582 mL/min/g liver) and dog (15.572 mL/min/g liver) than in human (2.142 mL/min/g liver).

In vitro metabolism

A study was performed to investigate the in vitro metabolism of ^{14}C-GSK573719 (10 and 50 mcM) in human, rat and dog using hepatocytes (Report WD2006/00147). The metabolism of GSK573719 across species was compared using radio-HPLC and HPLC-MS analyses.

The results suggest the main routes of metabolism in human are likely to be O-dealkylation (20% of the total metabolism via M14, GSK339067) and hydroxylation (23% of the total metabolism via M33, GSK1761002 and M34, which co-eluted). Other routes are conjugation with glutathione and methylation and/or glucuronidation of the hydroxylated metabolites. The major routes of metabolism in human hepatocytes were also present in either or both rat, with metabolism via M14 and minor amounts of M33 present, and in dog with metabolism via M14 and M33/M34. All of the metabolites identified in human hepatocytes were also present in either or both of the nonclinical species, with the exception of M45 (a glutathione conjugate) and M49 (a sulphate conjugate). However, there were several minor unidentified components in some of the human hepatocyte preparations which appeared to be absent from rat and dog hepatocytes. The extent of metabolism of GSK573719 in human hepatocytes was variable ranging from 19 to 84% turnover (average 43%). The metabolic turnover of GSK573719 in rat and dog hepatocytes was lower at 26% and 28%, respectively.

In addition, ^{14}C-GSK573719 (0.01, 0.1 and 1 mcM), was incubated with human liver microsomes to determine the potential for metabolic activation in the absence or presence of a NADPH regenerating co-factor solution. Some binding of drug-related material was observed in human liver microsomes, which was predominantly co-factor-dependent. The metabolic activation for GSK573719 (114 pmoles/mg protein/hour) was similar to that observed for acetaminophen (122 pmoles/mg protein/hour).

A further in vitro study to compare the metabolism of ^{14}C-GSK573719 (10 and 50 mcM) using radio-HPLC and HPLC-MS analysis was performed in human, male mouse and female rabbit hepatocytes (Report WD2007/01370). The metabolic turnover of GSK573719 was low (around 13%) in the human hepatocyte preparation used in this study, but higher (>84%) in rabbit and mouse hepatocytes. The main routes of metabolism of GSK573719 in human hepatocytes were O-dealkylation (M14), hydroxylation (M33) and methoxylation (M34 via M33). O-dealkylation and hydroxylation (as observed in human) were major pathways in the mouse but minor pathways in the rabbit (M64/M1 and M37, respectively). Methoxylation (to M34 in human) was a minor pathway in rabbit (to M22, a glucuronide of M34) but absent in the mouse. The major routes of metabolism in rabbit hepatocytes were hydroxylation (M37) followed by glucuronide conjugation (M27). The major routes of metabolism in mouse hepatocytes were O-dealkylation (M14), hydroxylation followed by glucuronide conjugation (M21, M26, M27 and M29) and formation of a hydrated glutathione conjugate (M13 and M45).

CYP450 metabolism

A preliminary study was performed to provide information on the human cytochrome P450 enzymes involved in the oxidative metabolism of GSK573719 (0.075 mcM) in vitro (Report WD2006/03367). ^{14}C-GSK573719 was incubated with human liver microsomes and with microsomes expressing the individual cytochrome P450 enzymes (CYP): CYP1A1, 1A2, 2A13, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 and 3A5. Further incubations with human liver microsomes were performed in the presence and absence of selective CYP450 inhibitors; furafylline (CYP1A2), montelukast (CYP2C8), sulphaphenazole (CYP2C9), benzylnirvanol (CYP2C19), quinidine (CYP2D6) and azamulin (CYP3A4). The quantifiable in vitro metabolism of GSK573719 in human liver microsomes is mediated primarily by CYP2D6, with some contribution from CYP3A4. GSK573719 is also metabolised by the CYP450 enzyme CYP1A1, which is

known to be expressed extrahepatically. The major metabolite routes of metabolism observed in human liver microsomes were O-dealkylation to M14 (GSK339067) and hydroxylation to M33 (GSK1761002). There was further hydroxylation to yield low levels of M56 and M61.

Metabolism studies in the isolated perfused liver

A study was performed to provide data on the major metabolites of GSK573719 (10000 mcg/kg) in male and female rat bile, perfusate and liver produced by an isolated perfused rat liver (IPRL) (Report WD2005/01195). Elimination of ^{14}C-GSK573719 in the isolated perfused rat liver was by both direct biliary secretion of parent and metabolism, with 11% and 36% of the radioactivity being recovered in bile from the male and female rat liver, respectively. Metabolism in the isolated perfused rat liver was complex with 33 metabolites being identified and many metabolites having multiple sites of metabolism. Routes of metabolism included oxidation (M33, M34, M35, M37, M38, M41) and O-dealkylation (M14 and M18), sometimes combined with glucuronide (M22, M21, M27, M20, M26), sulphate (M3, M4), methyl thiol conjugation (M11, M13) and hydration (M9). The metabolic profiles in liver and perfusate supernatant extracts were similar to those in bile. There were no notable differences in routes of metabolism between the male and female liver preparations.

Cytochrome P450 inhibition by GSK573719

A study was performed to determine the in vitro concentration-dependent inhibition of human cytochrome P450 enzymes by GSK573719 (concentration range 0.03 to 33 mcM) (Report CH2005/00950). GSK573719 was demonstrated to be an inhibitor of CYP2D6 (IC50 = 0.1 mcM) and CYP3A4 (IC50 = 0.1 mcM using diethoxyfluorescein and 8.0 mcM using 7-benzoquinoline as probe substrates). GSK573719 did not demonstrate inhibition of CYP1A2, CYP2C19 and CYP2C9.

In Vivo Studies

Mouse:

Following a single intravenous administration of ^{14}C-GSK573719 in male CD-1 mice (n=18) (Report 2010N105743) the major route of elimination was excretion of GSK573719 and metabolites in the faeces and urine (49% and 8% of the administered dose, respectively). GSK573719 was excreted unchanged (34% of dose) or via metabolism (21% of the dose). The major circulating component was parent GSK573719, accounting for 24% and 48% of the radioactivity in the 15 and 60 minutes plasma sample extracts, respectively. A hydroxylated glucuronide (M21), a methoxy, hydroxy O-glucuronide (M22) and a hydrated glutathione conjugate (M13) being the major circulating metabolites, with M21 and M22 accounting for 20% of the radioactivity in the 15 and 60 minutes plasma sample extracts, respectively. These same metabolites were observed in extract of liver homogenate.

The major routes of metabolism, as observed by metabolites in excreta, in the mouse were hydroxylation (8% of the dose to M33), methylation (4% of the dose to M34) and conjugation with glucuronic acid (M21/M22). Numerous minor metabolites accounted for the remaining 10% of excreted dose. These included products of hydroxylation, methylation, O-dealkylation and conjugation with glucuronide (M27, M44, M67, M69 and M70), glutathione (M13) and cysteine (M53) conjugation, and combinations thereof. GSK573719 was the major component in liver homogenate, urine and faeces.

Rat:

Following intravenous administration of 1^{4}C-GSK573719 to intact Sprague-Dawley rats (3/group) (Report FD2005/00208), the main route of elimination of GSK573719 was primarily by secretion of parent into the faeces (53% of the dose) and direct renal secretion (14% of the dose). Metabolism was a minor route of elimination, accounting for 4.4% dose with the major routes of metabolism being O-dealkylation (2.5% of the dose to M14) and hydroxylation (1.9% of the dose to M33, M34 and M37). The major DRM in rat plasma, lung and liver extracts was GSK573719. The only other notable

radiolabelled component observed in liver samples collected at 0.5 and 2 hours post dosing was a hydroxylated metabolite (M37) which accounted for approximately 4% and 9% of the sample radioactivity, respectively.

Following oral administration of 1^4C-GSK573719 to intact Sprague-Dawley rats (3/group) (Report FD2005/00208) approximately 95% and 87% of the administered dose was accounted as unchanged GSK573719 in the 0 to 24 hours faeces pool in intact and BDC rats, respectively. This material probably reflected, at least in part, unabsorbed parent compound. The only detected, but non-quantifiable, metabolite following oral administration was M14 in the faeces. There was insufficient radioactivity in lung, liver and plasma samples obtained following oral dosing to allow analysis. The metabolites present in bile were not investigated as the absorption of GSK573719 following oral administration was established to be very low.

Dog:

Following intravenous administration of ^{14}C-GSK573719 to Beagle dogs (3/M/group), elimination of GSK573719 was both by metabolism and as unchanged drug (a total of 14% of the dose in urine and faeces) with metabolites secreted in urine (approximately 6% of the dose) and faeces (approximately 29% of the dose). The major routes of metabolism were O-dealkylation (15.3% of the dose to M14) and oxidation (9% of the dose to M33 and M37). Other notable metabolites were dihydrodiol (4.4% via M51) and methyl catechol (2.8% of the dose to M34). Additional metabolites, detectable using mass spectrometry, but not quantifiable, were M57, M56 and M58. Unchanged GSK573719 was the major component in plasma samples at 1 and 3 hours after dosing, M14, M33, M34 and M51 being present, but non-quantifiable.

In another study, ^{14}C-GSK573719 as the trifluoroacetate salt (10 mcg/kg (slow bolus), 200 mcg/kg (60 minutes infusion) and 200 mcg/kg (10 minutes infusion)) was administered to BDC beagle dogs (2/M/group). GSK573719 was eliminated in both the urine (14% of dose) and the bile (56% of dose) with unchanged drug representing between 6 to 8% of the dose excreted in urine and bile. Metabolites were secreted in both the urine and bile with the major routes of metabolism being O-dealkylation and hydroxylation. Other pathways included formation of dihydrodiols or O-methylated catechol products and hydrated glycyl cysteine conjugates. Qualitatively the metabolite profiles in bile, urine and plasma did not significantly change with dose level or infusion time. The only quantifiable DRM component in plasma was GSK573719 with concentrations being highest following intravenous infusion at 200 mcg/kg over 10 minutes.

In a further study, following oral administration of ^{14}C-GSK573719 (1000 mcg/kg) to dogs (3/M/group) (Report FD2005/00164), elimination of radioactive DRM was predominantly via faeces accounting for 95% of the dose with approximately 78% of the administered dose being accounted for as unchanged GSK573719. This probably reflected, at least in part, unabsorbed parent compound. The only metabolite identified was the O-dealkylation product (M14) which accounted for 3.1% of the recovered dose in the 0 to 48 hour faeces pool.

Human

Following repeated-inhalation dosing of GSK573719 (1000 mcg) to healthy subjects (n=8) and in a healthy population of CYP2D6 poor metabolisers (n=6) for 7 days (Report WD2009/00030) unchanged GSK573719 and GSK339067 (M14, an O-dealkylated metabolite) were the only GSK573719-related components detected in human plasma extracts and urine. There was evidence for a 2-fold decrease in the proportion of GSK339067 relative to GSK573719 in plasma from CYP2D6 poor metabolisers compared to healthy normal metabolisers. There was no evidence for a change in the proportion of GSK339067 to GSK573719 in urine collected from CYP2D6 poor metabolisers compared to healthy

normal metabolisers. It is possible that other metabolites may have been present in plasma but were not detected under the conditions used.

In another study, a single intravenous or oral administration of ^{14}C-GSK573719 (65 mcg or 1000 mcg) was administered to 6 healthy male subjects (Report 2011N128400). Following intravenous administration elimination of GSK573719 was through a combination of direct elimination of parent and by metabolism followed by excretion in faeces, or to a lesser extent, urine. Following oral dosing, very little DRM was observed in the plasma or urine, with the vast majority in the faeces being unchanged GSK573719, indicating low oral absorption. The main routes of metabolism across the matrices studied were O-dealkylation (M14) and hydroxylation (M33).
The major circulating component in plasma samples following intravenous administration was unchanged GSK573719. The circulating metabolites observed were identified as from O-dealkylated (M14) and hydroxylation (M33) routes. A third component in plasma was tentatively assigned by chromatographic retention time as a hydroxylated metabolite (M61). Elimination of unchanged GSK573719 was the major route observed in humans dosed intravenously and was the major component seen in the bile, faeces and urine. Other metabolites observed were M14, M33 with other metabolites not being unassigned structures.

Vilanterol (GW64244)

In vitro studies:

In vitro studies were performed using hepatic and lung microsomes, hepatocytes and cytochrome P450 (CYP) screen. In microsomes from rats, dogs and humans, and lung microsomes from humans the in vitro clearance of GW642444 was high in rat (19 to 31 mL/min/g liver) and human liver microsomes (30 to 49 mL/min/g liver) and moderate in dog liver microsomes (8 mL/min/g liver). Characterisation of human microsomal drug-related products by HPLC-MS indicated that the most abundant human microsomal metabolite was GW630200 (subsequently referred to as M29). GW642444 was stable when incubated with human lung microsomes. Similarly, intrinsic clearance of GW642444 (as the triphenylacetate salt, GW642444M) by human liver microsomes was rapid, with a mean calculated intrinsic clearance value of 111 mL/min/g liver. Intrinsic clearance of GW642444 in human intestinal microsomes was approximately 4.5-fold lower than observed for liver microsomes, and GW642444 was metabolically stable using human lung microsomes.

Metabolism of 14C-GW642444 by human liver microsomes and microsomes expressing individual CYP isoenzymes, showed that turnover of 14C-GW642444 was high (48%) in human liver microsomes producing 4 major metabolites; M29 (GW630200) and M31 formed following O-dealkylation, M20 formed following N-dealkylation and M40 resulting from amine hydrolysis. Other minor metabolites, M47, M26, M16 and M32, were also detected by LC/MS^n only. The production of M29 (GW630200), M31 and M20 was predominantly mediated by CYP3A4 with minor contributions from CYP2D6. M40 was thought likely to be a further metabolite of M20 which is not mediated by cytochrome P450 but may be due to amine oxidase. In human liver microsomes the predominant route of metabolism was O-dealkylation to M29 (GW630200). The in vitro metabolism of GW642444 was primarily mediated by CYP3A4 with minor contributions by CYP2D6.

The in vitro turnover of GW642444 in human hepatocytes in 2 hours was 95% (1 mcM) and 81% (12.5 mcM). At a concentration of 1 mcM the intrinsic clearance of GW642444 was 0.021 mL/min/106 cells (~2.5 mL/min/g liver). The major metabolite of GW642444 in human liver hepatocytes was identified as a carboxylic acid derivative of GW630200 (M29) - subsequently referred to as GSK932009 or M33. The extent of metabolism in human liver hepatocytes varied between the different preparations and ranged between 42 to 64% turnover at 4 hours. The major route of metabolism in each human liver hepatocyte sample studied was O-dealkylation to M33 (GSK932009) and M29 (GW630200) which represented means of approximately 12 and 24% of the total metabolism, respectively. These

metabolites were also detected in rat and dog. Other minor metabolites were detected which represented approximately 7% or less of the total metabolism and were generally, also, the result of dealkylation metabolism. The major metabolite identified in rat liver hepatocytes was M12, an O-glucuronide conjugate, which represented approximately 40% of the metabolites assigned. The major metabolite identified in dog liver hepatocytes was M26 (C-dealkylation or oxidative loss of the salicyl alcohol) which represented approximately 43% of the metabolites assigned. Numerous other metabolites were identified in the rat and dog which included a range of O-dealkylated metabolites.

The main route of metabolism of GI179710 in human hepatocytes was acyl glucuronidation, representing approximately 95% of the total metabolism. Other metabolites resulted from para-hydroxylation/acyl glucuronidation and acyl glucose conjugation which represented 5% or less of the total metabolism. Acyl glucuronidation was prevalent in all non-clinical species (mouse, rat, female rabbit and dog) investigated (78 to 94% of the total metabolism). In general, metabolic profiles in non-clinical and human hepatocytes were qualitatively similar. The extent of metabolism of 14C-GI179710 was high in all species investigated.

A study was performed to assess the potential for chiral conversion of GW642444 (R-enantiomer) to GSK907117 (S-enantiomer) in control human plasma and in rat and dog ex-vivo plasma obtained from separate studies. Using chiral HPLC separation with MS detection to detect interconversion of GW642444 and its enantiomer GSK907117, no evidence of chiral conversion (>10%) of GW642444 to GSK907117 in plasma obtained following inhaled administration of GW642444M to the rat or dog or in incubations of GW642444 in control human plasma was observed.

Finally, in a cytochrome P450 inhibition screen, the mean IC50 values for GW642444 were >100, >23, >70 and 12 mcM for CYP450 1A2, 2C9, 2C19 and 2D6, respectively. The inhibition potential of GW642444 for CYP3A4 was determined against two CYP3A4 substrates: diethoxyfluorescein (DEF) and 7- benzoquinoline (7BQ). The mean IC50 values were 4.2 and 11 mcM, respectively.

In vivo studies:

Following intravenous administration of 14C-GW642444 (α-phenylcinnamate salt) at 350 mcg/kg in male Sprague Dawley rats, the main routes of elimination of DRM were via the faeces (69% of the administered dose) and urine (19% of the administered dose). Elimination was largely by metabolism with the main routes being dealkylation (13% dose via M7, M26, M1, M3/30, M9), oxidation (22% dose via M34, M7, M30, M1, M9) and glucuronide conjugation (5% dose via M1, M3). A further 13% of the administered dose was excreted as unchanged GW642444 in the faeces potentially resulting from either direct secretion of GW642444 or hydrolysis of the corresponding glucuronide. The principal radiolabelled components observed in plasma following intravenous dosing were unchanged parent and an unidentified component. Similarly, in male BDC Sprague Dawley rat using single intravenous (500 mcg/kg) doses of 14C-GW642444, the main routes of elimination of DRM were via the bile (45% of the dose) and urine (32% of the dose). Metabolite quantification in both urine and bile was difficult due to the complexity of the profiles and the low concentration of radioactivity in the samples. The main metabolites were by glucuronidation (to M12 representing 8% of the dose in bile) and by O-dealkylation/oxidation (to M7, M9 and M30 representing 5, 5 and 3% of the dose, respectively, in urine). Faecal elimination was a minor route (6% of the dose) and contained mainly unchanged GW642444 (4% of the dose), possibly resulting from direct gut secretion.

Following intravenous administration of 14C-GI179710 to rats, the principal radiolabelled components in plasma, liver and lung samples at the selected time points were unchanged GI179710 and M18. GI179710 represented 35 to 65% plasma radioactivity whilst M18 represented 16 to 28% of plasma radioactivity.

Following oral administration of 14C-GW642444 (α-phenylcinnamate salt) at 350 mcg/kg in male Sprague Dawley rats, elimination was was largely via faeces (86% of the administered dose) which mainly constituted unchanged parent (at least 77% of the administered dose). Unchanged GW642444 in rat faeces is potentially due to incomplete absorption, hydrolysis of one or more glucuronide conjugates or direct GI secretion. Rat urine contained a further 4.7% of the dose which was almost exclusively made up of metabolites with unchanged GW642444 being unquantifiable. Consistent with intravenous administration, the main urinary metabolites resulted from dealkylation (M7, M26, M1, M3, M30, M9), oxidation (M7, M26, M30, M9) or glucuronide conjugation (M1, M3). No metabolites could be detected by LC-MSn where the 14C-label of GW642444 was lost due to O-dealkylation. Plasma obtained following oral administration was not analysed due to insufficient radioactivity. Furthermore, in male BDC Sprague Dawley rat using single oral (1000 mcg/kg) doses of 14C-GW642444, faecal, biliary and urinary excretion accounted for 54.6, 28.3 and 8.8% of the dose, respectively. Faecal radioactivity contained predominantly unchanged GW642444 (49% administered dose) which is most likely unabsorbed drug although a proportion may be a result from direct gut secretion. The main routes of metabolism of GW642444 in the BDC rat following oral dosing were by glucuronidation (to M12 which represented 25% of the dose in bile) or by O-dealkylation, oxidation and O-glucuronide conjugation (to M1 which represented 4.5% of the dose in urine).

Following oral administration of 14C-GI179710 to rats, the principal radiolabelled components in plasma, liver and lung samples at the selected time points were unchanged GI179710 (33 to 55% plasma radioactivity) and the acyl glucuronide (17 to 32% of plasma radioactivity).

Major metabolites were also examined in male beagle dogs dosed with a single intravenous or single oral doses of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) at 50 and 100 mcg/kg, respectively. Following intravenous administration of 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) to the dog, elimination of DRM was via both the faeces and urine (48 and 39% of the administered dose, respectively). Elimination was almost completely by metabolism with the main routes being dealkylation (30% dose via M30, M7, M33 and M9) and oxidation (45% dose via M30, M7, M16 and M9). The proportion of dose excreted as unchanged GW642444 was negligible. No metabolites could be detected by HPLC-MS where the 14C-label had been lost. Unchanged GW642444 was the only major component observed in dog plasma following intravenous dosing. A high proportion of DRM in dog plasma and faeces was unextractable. Elimination of 14C-GW642444 DRM following oral administration was via both faeces and urine (56 and 22% of the administered dose, respectively). Unchanged GW642444 represented only 16% of the administered dose in dog faeces and is probably a reflection of either moderate or good absorption of the 14C-GW642444 α-phenylcinnamate salt. The main routes of metabolism in the dog (as for intravenous administration) were via dealkylation (to M30, M7, M33, M9 and M26) and oxidation (to M30, M7, M16), representing a combined 23% and 19% of the administered dose, respectively. Two principal radiolabelled components were detected in dog plasma (1 hour post dose) and were identified as unchanged GW642444 (44% plasma radioactivity) and M26 (a metabolite resulting from C-dealkylation and representing 30% plasma radioactivity). A large proportion of DRM in dog plasma was unextractable.

Following intravenous administration of 14C-GI179710 (500 mcg/kg) to the dog, elimination of DRM was mainly via faeces (88% administered dose) but also via urine (11% administered dose). Elimination was largely by excretion of unchanged GI179710 (73% administered dose), of which 72% and 1% administered dose was in the faeces and urine, respectively. Unchanged GI179710 in faecal extracts may have (at least in part) resulted from hydrolysis of the corresponding acyl glucuronides. A further 13% of the administered dose was eliminated via acyl glucuronidation (comprising 9% dose in urine and 4% in faeces). The principal radiolabelled components in the plasma samples at the selected time points were unchanged GI179710 (16 to 70% plasma radioactivity) and the acyl glucuronides (17 to 57%). An acyl glucose conjugate represented 3 to 17% plasma radioactivity. Following oral

administration of 14C-GI179710 (1000 mcg/kg) to the dog (Report FD2005/00186/00), elimination of radioactive DRM in the dog was predominantly via the faeces (76% dose) with urine representing approximately 17% of dose. Unchanged GI179710 was the largest component in dog faeces representing 57% of the administered dose which may have resulted from either incomplete absorption or hydrolysis of the corresponding acyl glucuronides. The similarity between the elimination data in urine and faeces from dogs dosed orally and intravenously, however, would tend to indicate that oral absorption was good. Approximately 15% of the administered dose was eliminated via acyl glucuronidation (comprising 12% and 3% dose in urine and faeces, respectively). The principal radiolabelled components in plasma samples at the selected time points were unchanged GI179710 (25 to 52% plasma radioactivity) and acyl glucuronides (38 to 52%). An acyl glucose conjugate represented 6 to 10% plasma radioactivity.

In humans, information on metabolism was obtained from human plasma on Day 7 following repeated inhalation dosing of GW642444 (as the α-phenylcinnamate salt, GW642444H) at 200 mcg/kg to asthmatic subjects. GW642444 was detected in all the samples analysed. M33 (GSK932009, O-dealkylation with oxidation) was detected in pooled 0 to 12 hour plasma and in individual plasma samples taken at 1 hour post dose from all 9 subjects. M29 (GW630200, O-dealkylation) was detected in the plasma of one out of nine subjects taken at 1 hour post dose. It is possible that other metabolites may have been present in plasma but were not detected under the conditions used.

Metabolism of GW642444 was also studied in six healthy male volunteers following a single oral administration of 14C-GW642444 (200 mcg). Elimination of GW642444 was mainly by metabolism followed by excretion of metabolites in urine, or to a lesser extent, faeces. The main routes of metabolism were assigned as various O-dealkylation pathways which accounted for up to 78% of the recovered radioactive dose (combined for urine and faeces). Metabolism via C- or N-dealkylation accounted for a further 5% of the recovered radioactive dose. Unchanged GW642444 was a small component in faeces (5% of the recovered radioactive dose), representing either unabsorbed material or unchanged GW642444 (or conjugate) secreted directly into the GI tract or via human bile. The residual 12% of the recovered radioactive dose constituted a mixture of small unassigned components. Human circulating plasma metabolites were also mainly the products of O- or C-dealkylation.

Umeclidinium bromide/vilanterol

No metabolism PK studies were performed on the fixed dose combination umeclidinium bromide/vilanterol which was considered acceptable by the CHMP, based on the data provided for the individual compounds.

Excretion

Umeclidinium bromide (GSK573719)

Mouse

Following a single intravenous administration of ^{14}C-GSK573719 to CD-1 mice (18/M/group) (Report 2010N105743) the total recovery was 91%, of which 49% was recovered in the faeces with a further 8% recovered in the urine. Approximately 28% of the dose was recovered in carcass digests, indicating that elimination of DRM was incomplete within the 24 hour period post dose. No cage washings were performed in this study and this may have affected the total amount of radioactivity recovered. There was a notable decrease in the levels of radioactivity between 15 minutes and 24 hours in the plasma and liver, with decreases of approximately 150-fold and 55-fold, respectively.

Rat

Following a single intravenous administration of ^{14}C-GSK573719 to intact and BDC rats (3/group) (Report FD2005/00208), radioactivity was predominantly excreted in the faeces (mean of 65.3% of the

dose) with urinary elimination accounting for a mean of 16.9% of the dose. The elimination of radioactivity was initially relatively rapid with a mean of 78.8% of the dose being recovered by 48 hours post dose. However, the remainder of the dose was excreted relatively slowly and the overall elimination was incomplete by 96 hours post dose, with a mean of 11.0% of the dose remaining in the carcass (mean of 10.1% of the dose) and tissues (mean of 0.9% of the dose). The mean total recovery of radioactivity was 93.9% of the dose.

Following a single oral administration of ^{14}C-GSK573719 to intact and BDC rats (3/group) (Report FD2005/00208) the major route of elimination was via the faeces (mean of 96.4% of the dose) and urinary elimination was minimal (mean of 0.1% of the dose). In BDC rats, the major route of elimination was via the faeces (mean of 92.9% of the dose). Urinary and biliary elimination were minor, accounting for on average no more than 0.2% of the dose. The mean total recovery of radioactivity in intact and BDC rats was 96.5% and 93.8% of the dose, respectively. Elimination of DRM was rapid in both intact and BDC rats with greater than 90% of the dose recovered by 24 hours post dose. Absorption of DRM was negligible based on the radioactivity in urine, bile and the residual carcass.

Dog

Following a single oral administration of ^{14}C-GSK573719 to beagle dogs (2M) (Report FD2005/00164), the major route of elimination of radioactivity was via the faeces (mean of 95.1% of the dose) with urinary excretion being minor (mean of 0.4% of the dose). Absorption of DRM, as judged by radioactivity in the urine, appeared to be minimal. The mean total recovery of radioactivity (including cage washes) was 96.5% of the dose. Elimination of radioactivity was rapid with the majority of the administered dose recovered within 48 hours post dose.

Following a single intravenous administration of ^{14}C-GSK573719 to beagle dogs (3M) (Report FD2005/00164), the major route of elimination of radioactivity was via the faeces (mean of 61.8% of the dose) with urinary excretion accounting for a mean of 11.9% of the dose. The elimination was protracted with approximately 1% of the dose being eliminated during each of the 24 hour periods between 96 and 168 hours post dose. This protracted elimination probably accounts for the low total recovery of radioactivity (74.5% of the dose).

In another study, administration of a single intravenous dose of ^{14}C-GSK573719 (as the trifluoroacetate salt at 10 mcg/kg (slow bolus) or 200 mcg/kg (10 minute and 60 minute infusion)) to BDC beagle dogs (2/M/goup) (Report WD2007/01907) the major route of elimination of radioactivity was via bile (mean of 57% of the dose), with majority of the elimination occurring within the first 8 hours post dose for all 3 dosing regimens. The urinary elimination accounted for a mean of approximately 14% of the dose and excretion in faeces was a minor elimination pathway accounting for no more than 4% of the dose. Total recoveries of radioactivity (including cage washes) ranged between means of 70% and 74% of the dose. The low recoveries were probably due to the short collection period (0 to 48 hours) as there was evidence that elimination was still occurring at 48 hours. Overall, the elimination of the majority of the dose was rapid, with between 58% and 66% recovered in the urine, faeces, bile and cage washes by 24 hours post dose. For all 3 dosing regimens, the rate of bile production decreased following dosing, followed generally by a recovery within 1 to 3 hours post dose, and thereafter remained relatively constant over the remaining period up to 48 hours post dose. Over the entire 48 hours study period, the overall bile production was generally similar for all 3 regimens. The highest mean concentration of radioactivity in the bile generally occurred within 60 minutes of completion of dose administration, and declined thereafter.

Vilanterol (GW64244)

Rat:

Following a single oral 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) (350 mcg/kg) in male Sprague Dawley rats, the major route of elimination observed was via the faeces (mean of 86.1% of the dose), with urinary elimination accounting for a mean of 4.7% of the dose. Elimination of radioactivity was rapid with a mean of approximately 86% of the dose being eliminated during 0 to 24 hours post dose. A mean total of 0.2% of the dose was present in the gastrointestinal tracts, residual carcasses and livers at 96 hours. At least 5% of the dose was absorbed as judged by DRM in the urine and residual carcass following oral administration. A comparison of radioactivity eliminated in urine following oral (4.7%) and intravenous (18.6%) administrations would indicate that absorption was probably as high as approximately 25%. The mean total recovery of radioactivity (including cage washes) was 91.8% of the dose.

Following a single intravenous dosing in the same study (350 mcg/kg slow bolus over 30 minutes), the major route of elimination of radioactive DRM was via the faeces (mean of 69.2% of the dose), with urinary elimination accounting for a mean 18.6% of the dose (see table below). Elimination of radioactivity was fairly rapid with a mean of approximately 73% of the dose eliminated in the urine and faeces during 0 to 24 hours post dose. A mean total of approximately 2% of the dose was present in the gastrointestinal tracts, residual carcasses and livers at 96 hours. The mean total recovery of radioactivity (including cage washes) was 93.3% of the dose.

Following a single oral dose of 14C-GI179710 (triphenylacteic acid, the counter ion of GW642444M triphenylacetate salt) (1000 mcg/kg) to male Sprague Dawley rats, the major route of elimination of the radioactive DRM, the major route of elimination of DRM was via the faeces (mean 84.4% of the dose). Urinary elimination accounted for a mean 3.6% of the dose. Elimination of radioactivity was relatively rapid, with a mean of 85% of the dose being recovered in the urine, faeces and cage washes by 48 hours post dose. At least 4% of the dose was absorbed as judged by DRM in the urine and residual carcass and tissues following oral administration. A comparison of radioactivity eliminated in urine following oral (3.6%) and intravenous (4.2%) administrations would indicate that actual absorption was probably higher than this. The mean total recovery of radioactivity (including cage washes) was 88.7% of the dose.

Following a single intravenous dosing in the same study (500 mcg/kg slow bolus over 30 minutes), the major route of elimination of DRM was via the faeces (mean of 84.8% of the dose). Urinary elimination accounted for a mean of 4.2% of the dose. Elimination of radioactivity was relatively rapid, with at least 87% of the dose being recovered in the urine, faeces and cage washes by 48 hours post dose. A mean total of 0.4% of the dose was recovered in the liver, lungs, gastrointestinal tract and residual carcass. The mean total recovery of radioactivity (including cage washes) was 90% of the dose.

To gain information on the extent of biliary excretion and metabolism of GW642444, male BDC Sprague Dawley rats were given a single intravenous or oral dose of 14C-GW642444 (parent form) (500 mcg/kg). The major routes of elimination of DRM following intravenous administration were via the bile and urine (means of 45% and 32% of the dose, respectively). Approximately 6% of the dose was recovered in the faeces. Mean total recovery (including cage washings, livers and carcasses) was 94% at 48 hours post dose. The major routes of elimination of DRM following oral administration were also via the faeces and bile (means of 55% and 28% of the dose, respectively), a further 9% was eliminated via the urine. A mean of at least 37% of the dose was orally absorbed, as judged by the amounts of DRM in bile and urine. Mean total recovery (including cage washings, livers and carcasses) was 95% at 48 hours post dose. Elimination of radioactivity was rapid following both intravenous and oral administration, with the majority of the dose being recovered by 24 hours post dose.

Dog:

Following a single oral 14C-GW642444 (as the α-phenylcinnamate salt, GW642444H) to male beagle dogs, the major route of elimination observed via the faeces (a mean of 56% of the dose), with urinary

excretion accounting for a mean of 22% of the dose. Initial elimination of radioactivity was relatively rapid, with a mean of approximately 70% of the dose eliminated in the urine and faeces during the period of 0 to 24 hours post dose. At least approximately 22% of the dose was absorbed as judged by DRM in the urine following oral administration. A comparison of radioactivity eliminated in urine following oral (22% dose) and intravenous (39% dose) administration would indicate that absorption was probably as high as approximately 56%. The mean total recovery of radioactivity (including cage washes) was 79% of the dose. Following a single intravenous dosing in the same study, the major route of elimination observed was again via the faeces (a mean of 47.9% of the dose), with urinary excretion accounting for a mean of 38.8% of the dose. Elimination of radioactivity was relatively rapid with a mean of approximately 70% of the dose eliminated in the urine and faeces during the period 0 to 24 hours post dose. The mean total recovery of radioactivity (including cage washes) was 88.8% of the dose.

Following a single oral dose of 14C-GI179710 (triphenylacteic acid, the counter ion of GW642444M triphenylacetate salt) (1000 mcg/kg), the major route of elimination of radioactivity was via the faeces (a mean of 56% of the dose), with urinary excretion accounting for a mean of 22% of the dose. Initial elimination of radioactivity was relatively rapid, with a mean of approximately 70% of the dose eliminated in the urine and faeces during the period of 0 to 24 hours post dose. At least approximately 22% of the dose was absorbed as judged by DRM in the urine following oral administration. A comparison of radioactivity eliminated in urine following oral (22% dose) and intravenous (39% dose) administration would indicate that absorption was probably as high as approximately 56%. The mean total recovery of radioactivity (including cage washes) was 79% of the dose. When dosed intravenously (500 mcg/kg slow bolus over one minute), the major route of elimination observed via the faeces (mean of 88.4% of the dose). Urinary excretion accounted for a mean of 11.1% of the dose. Elimination of DRM was prolonged, with a mean of 5.2% of the dose eliminated during 96 to 168 hours post dose. The mean total recovery of radioactivity (including cage washes) was 100.6% of the dose.

Umeclidinium bromide/vilanterol

No excretion PK studies were performed on the fixed dose combination umeclidinium bromide/vilanterol which was considered acceptable.

Pharmacokinetic drug interactions

Umeclidinium bromide (GSK573719)

Cytochrome P450 induction by GSK573719 in animals

The effects of GSK573719 (0, 26.1, 243 and 1829 mcg/kg/day) on the mRNA levels of liver CYP450 genes was investigated in Sprague Dawley rats (3/sex/group) following nose-only inhalation exposure (60 minutes/day) for 28 days in a toxicology study (Report WD2005/01627; WD2005/01422). GSK573719 did not cause any increase in the levels of mRNA of the following CYPs: CYP1A1 (in male animals only), CYP1A2, CYP2B1, CYP2B2, CYP2E1, CYP3A2, CYP3A23 and CYP4A1 (in female animals only). A small increase was observed in the levels of CYP1A1 mRNA (to a mean ratio of treated over control of 8) in the female livers at 2000 mcg/kg/day, although this mean increase is due to result from one rat. Increases in the levels of CYP4A1 mRNA were observed (to a mean ratio of treated over control of 2 and 4) in the male livers at 30 and 200 mcg/kg/day dose groups. A decrease in the expression of all the CYP mRNA was observed (<50% of control value) in the male livers at the 2000 mcg/kg/day dose group, despite the housekeeping gene GAPDH being within normal parameters.

Victim interaction potential

The major routes of metabolism for GSK573719 in vitro in human derived systems are mediated primarily by CYP2D6 (Report WD2006/03367). GSK573719 was shown to be a substrate of human P-

gp in transfected MDCKII-MDR1 cell lines (Report WD2006/02657) and in mdr1a/b (P-gp knockout) mice (Report WD2008/00001). Systemic exposure to total DRM increased 18-fold in the P-gp knockout mice compared to wildtype which is consistent with the poor absorption of GSK573719 and P-gp having a role in the absorption process. GSK573719 has a low passive membrane permeability which will also contribute to poor absorption (Report WD2006/02657).

GSK573719 is an in vitro substrate for the organic cation uptake transporters OCT1 and OCT2, which are expressed in human liver and kidney, respectively. The contribution of the OCTs to the overall systemic clearance of GSK573719 is unclear. Inhibition of CYP2D6 and P-gp on the pharmacokinetics of GSK573719 was investigated in two clinical interaction studies.

Perpetrator interaction potential

GSK573719 is an in vitro inhibitor of CYP3A4 (lowest mean IC_{50} of 1 mcM following duplicate determinations using two different probes) and CYP2D6 (IC_{50} of 0.1 mcM) (Report CH2005/00950). GSK573719 does not inhibit P-gp at concentrations up to 100 mcM (Report WD2006/02596). The C_{max} of GSK573719 at its maximum proposed commercial dose of 125 mcg/day (<0.2 ng/mL or 0.5 nM) is at least 200-fold lower than the lowest IC_{50} for CYP2D6 inhibition (0.1 mcM or 100 nM) as a worst case. In line with relevant guidance a Ki value has been calculated based on a C_{max} of GSK573719 (<0.5 nM) and a free concentration of <0.07 nM (assuming protein binding of 86%). The estimated Ki for CYP2D6 as a worse case (50 nM) is 710-fold higher than the unbound C_{max} and does not therefore warrant further clinical investigation (threshold of concern is <50-fold higher).

Small changes in mRNA expression for CYP1A1 and CYP4A1 were observed following inhaled administration of GSK573719 to the rat for up to 4 weeks at doses up to 2000 mcg/kg/day over control rats (Report WD2005/01627). However, as described above, these are small changes and were variable between individual animals and not thought to be biologically significant.

The inhibition and induction potential of GSK573719 at proposed inhaled commercial dose (125 mcg/day) is considered negligible.

Vilanterol (GW642444)

Cytochrome P450 induction by GW642444 in animals

Four studies were performed in rats to investigate the potential for GW642444 to induce the cytochrome P450 enzymes following repeat inhalation doses of GW642444 as the α-phenylcinnamate salt, GW642444H or as a triphenulate salt, significant, but weak induction of CYP2B1 mRNA at doses greater than 890 mcg/kg/day was seen only in male rats dosed for 7 days. No other notable changes were observed. Minor increases in the levels of CYP2B2 gene expression (to approximately 7-, 6- and 6-fold the control values) were observed from all dose groups (0, 45.1, 261.1 or 708.7 mcg/kg/day) in the female rats dosed for 4 weeks. No other notable changes were seen in males or females thereafter.

No notable changes in either the mean concentrations of microsomal protein or total CYP450 up to7087 mcg/kg/day for 4 weeks. In male rats, there was evidence of a small increase in CYP2E activity to a maximum of approximately twice the control. Evidence of a marked increase in the production of an unknown metabolite of testosterone was observed in all male dose groups. The identity and biological significance of this metabolite is unknown. In addition, a small dose-dependent increase in the activity of testosterone 7-alpha hydroxylase (up to approximately3 times the mean control activity) was observed in the male only. The biological consequence is unknown.

Finally, following daily dosing of GW642444 to Sprague Dawley rats for 14 days at doses of up to 34422 mcg/kg/day, there was no unequivocal evidence of a dose-dependent increase in the levels of mRNA for CYP1A1, 1A2, 2B1, 2B2, 2E1, 3A2 (males only, as it is a male specific gene), 3A23 and 4A1.

No other non-clinical studies have been performed to specifically investigate the potential for GW642444 to undergo pharmacokinetic drug interactions when administered concomitantly with other drugs or foods. In toxicology studies investigating the combination of GW642444 with the corticosteroid, GW685698, there was little evidence, in any study, for increased exposure (AUC0-t and Cmax) to either GW685698 or GW642444 (>2- to 3-fold) when dosed in combination compared to when dosed alone, suggesting that neither molecule interferes with the systemic clearance of the other. Likewise, toxicokinetics of GW642444 were generally unaffected following co-administration with LAMAs (GSK233705 or GSK573719, two developmental GSK compounds).

Umeclidinium bromide/vilanterol

No non-clinical studies have been performed to specifically investigate the potential for GW573719 or GW642444 to undergo pharmacokinetic drug interactions when administered concomitantly with other drugs or foods. In toxicology studies investigating the combination of GW573719 and GW642444, the toxicokinetics of GW642444 and GSK573719 were generally unaffected following co-administration.

2.3.4. Toxicology

GSK573719 and GW642444H or M salt have undergone separate comprehensive non-clinical toxicological evaluation in mice, rats, dogs and rabbits to support their longterm clinical use.

The toxicity of umeclidinium bromide and of vilanterol have been evaluated in an extensive non-clinical program. The toxicology program included single-dose and repeat-dose toxicity studies in four species (mice, rats, dogs and rabbits) via four routes of administration (oral, subcutaneous, intravenous and inhalation), in vivo and in vitro genotoxicity studies, reproduction and developmental toxicity studies and carcinogenicity studies. Repeat-dose toxicity and reproduction toxicity studies were conducted with the FDC umeclidinium bromide/vilanterol. This is in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).

Single dose toxicity

Umeclidinium bromide (GSK573719)

The toxicity profile of GSK573719 has been defined in single dose studies in rats and mice.

No single dose inhaled toxicity studies have been conducted with GSK573719. A summary of acute toxicity data from dose escalation/dose range finding studies/in vivo genotoxicity and inhalation safety pharmacology studies in the rat have been presented.

Vilanterol (GW642444)

Single dose acute toxicity studies have not been performed with GW642444, except for one study designed to assess the tolerability of GW642444 (as the α-phenyl cinnamate salt) administered as a 5% dry powder blend in lactose by inhaled administration in beagle dogs.

In this study, it was observed that the administration of GW642444 resulted in vasodilation and increases in pulse rate. Pulse rates were elevated until 12 hours after dosing in both the male and female but were similar to pre-dosing values at 24 hours after completion of dosing. Serum cTnI levels were increased in the male, with peak levels being attained 8 hours after dosing.

Umeclidinium bromide/vilanterol

No single dose toxicity studies were performed on the fixed dose combination umeclidinium bromide/vilanteol which was considered acceptable by the CHMP, based on the data available for each compound.

Repeat dose toxicity

Umeclidinium bromide (GSK573719)

Repeat dose toxicity studies investigating the effects of repeated administration of GSK573719 doses have been performed in CD-1 mice, Sprague Dawley rats and beagle dogs. To support the long term therapeutic use of GSK573719 by the inhaled route, studies were performed using this route of administration for periods up to 26 weeks in the rat and 39 weeks in the dog. Repeat dose bridging studies in the rat and dog (of 14 days duration) have also been performed to compare dry powder formulation in lactose with and without the excipient magnesium stearate in order to support the clinical formulation.

Mouse

13 week inhalation toxicity study (Report WD2007/01600)

GSK573719 was administered by snout only inhalation for 1 hour per day to CD-1 mice (12/sex/group) at estimated achieved doses of 0, 92, 287, 1060 or 2850 mcg/kg/day. An additional 18 animals/sex for each GSK573719-treated group and 3 animals/sex in the control group were included for toxicokinetic evaluation performed during week 13.

In the nasal turbinates, test article-related changes were seen in the olfactory and respiratory regions of animals dosed at 1060 or 2850 mcg/kg/day, generally with evidence of dose relationship in incidence and/or degree. In the nasopharynx, epithelial degeneration/regeneration was seen in a few males and females dosed at 2850 mcg/kg/day and in two females dosed at 1060 mcg/kg/day. Epithelial eosinophilic inclusions, dose-related in incidence and severity, were seen in males and females dosed at 1060 or 2850 mcg/kg/day.

In the larynx, test article-related changes were seen in animals of all groups given GSK573719, generally with evidence of a dose relationship in incidence and/or degree. Females were affected to a slightly greater extent than males. At the tracheal bifurcation, minor changes (minimal epithelial hyperplasia or loss of cilia) at the tracheal or bronchial bifurcation were seen in a small number of animals, including a single female control. A marginal increase in incidence was seen in males and females dosed at 2850 mcg/kg/day, compared with controls.

In the spleen, a decreased incidence and severity of extramedullary haemopoiesis was seen in males and, to a lesser extent, in females dosed at 2850 mcg/kg/day. Reduced weight gain over the 13 week period was seen in both sexes dosed at 1060 or 2850 mcg/kg/day with a lesser effect in females dosed at 287 mcg/kg/day. Food consumed by females dosed at 1060 or 2850 mcg/kg/day was generally lower throughout the study.

Increased white cell numbers (principally lymphocytes) were seen in both sexes dosed at 92, 287 and 1060 mcg/kg/day. No effect was seen in either sex dosed at 2850 mcg/kg/day.

Based on the histopathological findings the NOAEL was 287 mcg/kg/day. At the NOAEL, the mean DNAUC0-t and DNCmax values were 5.70 ng.h/mL and 2.3 ng/mL, respectively (males and females combined).

13 week oral toxicity studies (Report WD2010/00349 & Report WD2010/00556)

GSK573719 as a suspension was administered to groups of CD-1 mice (12/sex/group) at doses of 0 (vehicle), 100, 300 or 1000 mg/kg/day, once daily for up to 13 weeks by oral gavage.

Seven animals (main study and toxicokinetic) given 300 mg/kg/day and one animal given 100 mg/kg/day were killed for welfare reasons on Day 6 of the treatment period. Concern over the prognosis for surviving animals at 300 mg/kg/day led to their early termination on Day 6/7. In addition, there was one unscheduled death at 30 mg/kg/day and 9 deaths at 100 mg/kg/day. All but

one of the unscheduled deaths in all groups were considered probably related to test article administration. The remaining animal (a male given 100 mg/kg/day) was killed due to penis mutilation/ventral abdomen ulceration and this death was considered incidental to treatment.

Noisy breathing/râles were evident in several animals of the 300 mg/kg/day group at the pre-dose examination on Day 6. Piloerection was observed at the completion of dosing and into the early evening on Day 6 and was apparent in surviving animals at the pre-dose observation on Day 7. Abdominal distension was apparent 1 to 2 hours after dosing and persisted to the early evening. Reduced body temperature, abnormally elevated gait, hunched/flat posture, dull eyes, gasping and pallor were apparent in individuals of this group during the working day and early evening, necessitating their premature termination. The remaining animals of this dose group were terminated on Day 7.

The most significant macroscopic changes at necropsy were distension of the abdomen, abnormal contents and thickening of one or more areas of the gastrointestinal tract. In nearly all decedents, necrosis/inflammation of the epithelium, sometimes accompanied by the presence of fluid or exudate, was observed in the nasal turbinates. This change would have caused blockage of the nasal passages, leading to breathing difficulties and the poor clinical condition of the animals. Fundic degeneration in the stomach, dilatation of various segments of the intestines, glandular degeneration in the duodenum, erosions in the jejunum, erosions, abscess and inflammatory infiltrate in the caecum and epithelial hyperplasia and erosions of the colon were also present; these were likely due either directly to the test article or indirectly due to gastrointestinal distension caused by the test article.

Noisy respiration/râles and piloerection were commonly seen during the remainder of the treatment period in animals given 30 or 100 mg/kg/day. Isolated incidences of abdominal distension, flat posture, repetitive movements, underactivity, fast, gasping or irregular breathing were noted in other individuals given 100 mg/kg/day. Two males at 30 mg/kg/day were noted with hunched posture on one occasion. Dose-related, small or moderate reductions in overall mean body weight gains were seen in males and females given 30 or 100 mg/kg/day.

Haematology investigations during Week 13 revealed markedly reduced overall white blood cell counts for males and females receiving 100 mg/kg/day, due primarily to low lymphocyte counts; large unstained cell counts were also lower than control in males and females given 100 mg/kg/day. Red cell distribution width was slightly low in males given 30 or 100 mg/kg/day. Similar changes were seen on Day 6/7 in animals, males in particular, given 300 mg/kg/day. There were no associated histopathological changes. Mean body weight relative kidney weights were slightly higher than control in females given 30 or 100 mg/kg/day. Mean unadjusted spleen weights were lower than control in males and females given 100 mg/kg/day. There were no histopathological correlates for any of these organ weight differences.

At necropsy of animals killed after 13 weeks of treatment, elongation of the caecum was noted in 2 males and 2 females given 100 mg/kg/day.

A NOAEL was not identified in this study. At 30 mg/kg/day the mean AUC0-t was 9.82 ng.h/mL and Cmax was 3.45 ng/mL (males and females combined).

As a NOAEL was not identified in the previous 13 week study, an additional 13 week oral repeat dose study was performed to investigate the toxicity and toxicokinetics of GSK573719 at lower doses. GSK573719 was given to groups of CD-1 mice (12/sex/group) at 0 (vehicle), 3, and 10 mg/kg/day once daily for 13 weeks by oral gavage. A further 21 animals/sex were added at each treated dose level, and 6 animals/sex received the vehicle, for toxicokinetic evaluation. GSK573719 was formulated as a suspension administered to mice at a dose volume of 5 mL/kg.

There were no deaths. Fast respiration was seen in males and females given 3 or 10 mg/kg/day, transiently after dosing, intermittently from Week 5 onwards. Noisy breathing/râles was apparent on isolated occasions in 3 different females receiving 10 mg/kg/day.

Only stomach and nasal turbinates were examined microscopically since a NOAEL for findings in these tissues was not established in the previous 13 week study at higher doses. Test article-related changes were present in the nasal turbinates at 10 mg/kg/day; changes were more severe in the female than in the male animals. These changes were consistent with findings in the previous study. There were no microscopic changes in the stomach.

On the basis that the severity of the changes in the nasal turbinates were graded marked in one animal at 10 mg/kg/day, 3 mg/kg/day was considered to be the NOAEL. There was no quantifiable systemic exposure at this dose. At 10 mg/kg/day overall mean AUC0-t was 0.817 ng.h/mL and Cmax was 0.361 ng/mL (males and females combined).

Rat

4 week inhalation repeat dose toxicity study (Report WD2005/01244)

GSK573719 was administered by snout only inhalation for 1 hour per day to Sprague Dawley rats (10/sex/group) at estimated achieved doses of 0 (vehicle) or 26.1, 243 or 1829 mcg/kg/day. An additional 3 animals/sex were included at each dose level for toxicokinetic evaluation.

A decrease in group mean body weights was noted in all treated animals, with values on Day 28 being up to 9.8% less in males and 9.2% less in females when compared to controls. In males, body weight gain was decreased by 37%, 34% and 80% for animals receiving 26.1, 243 and 1829 mcg/kg/day, respectively, when compared to controls. In females, body weight gain was decreased by 30% and 59% for animals receiving 26.1 and 243 mcg/kg/day, respectively, when compared to controls. Females at 1829 mcg/kg/day showed a 3% loss of body weight on Day 28 when compared to Day 1.

There were slight increases in mean serum sodium and chloride levels in males (2 and 2% respectively) and females (4 and 5%, respectively) receiving ≥243 mcg/kg/day GSK573719.

In the larynx, minimal to moderate epithelial hyperplasia/squamous metaplasia and minimal or slight subacute and/or chronic inflammation of the submucosa of the ventral region of the larynx was seen at all doses.

In the nasal cavities, minimal to marked degeneration of the olfactory epithelium and minimal to moderate degeneration/regeneration of the respiratory epithelium was seen in all animals given 1829 mcg/kg/day. In animals given 243 mcg/kg/day, the only change seen was a minimal increase in the incidence of goblet cell hyperplasia of the respiratory epithelium.

In the nasopharynx, minimal to slight degeneration/regeneration of the respiratory epithelium and hyperplasia of the goblet cells was present in the nasopharynx of animals given 1829 mcg/kg/day. At the tracheal bifurcation, minimal degeneration/regeneration of the epithelium was present at the carina of males given 243 and both sexes given 1829 mcg/kg/day.

The NOAEL was 243 mcg/kg/day and is based on the severity of the microscopic changes seen in the larynx and nasal cavity in animals receiving 1829 mcg/kg/day. At the NOAEL, mean systemic exposure values (DNAUC0-t and DNCmax) were 19.9 ng.h/mL and 6.69 ng/mL, respectively (males and females combined).

14 day inhalation excipient bridging study (Report WD2006/03225)

The potential toxicity and toxicokinetics of GSK573719 were evaluated when blended in lactose monohydrate containing magnesium stearate during daily nose-only inhalation exposure (duration 60 minutes) to the Sprague Dawley rat for a minimum of 14 consecutive days with that observed when

blended with lactose monohydrate only or lactose monohydrate with COA. Groups of rats (10/sex/group) were given daily doses of either lactose monohydrate only, 1% w/w magnesium stearate in lactose monohydrate or estimated achieved doses of 1509, 1498 or 1381 mcg/kg/day of micronized GSK573719 blended with 8% cellobiose octaacetate in lactose monohydrate, 1% w/w magnesium stearate in lactose monohydrate or lactose monohydrate only, respectively, at a nominal concentration of 4% w/w. A further 6 animals/sex were included at each dose to provide samples for toxicokinetic evaluation.

One female rat receiving GSK573719 with the excipient cellobiose octaacetate in lactose monohydrate was found dead after dosing in the home cage on Study Day 1. This rat had acute erosions/ulceration within the nasal cavity, the larynx (with exudate) and the nasopharynx, however, these changes were not considered to be severe enough to have contributed directly to the death of this rat and the cause of death could not be determined.

Lower group mean body weights and body weight gains were evident in all groups receiving GSK573719 when compared to controls. The changes in body weight gain were as follows (the changes in group mean body weight were comparable): administration of GSK573719 with cellobiose octaacetate /lactose monohydrate, magnesium stearate/lactose monohydrate or lactose monohydrate only resulted in a similarly lower body weight gain when compared to the respective controls. The effects were less marked in animals receiving the test article in lactose monohydrate alone (0.31X to 0.42X) than with cellobiose octaacetate or magnesium stearate (0.19X to -0.34X). The difference in body weight response in the different groups was reflective of the differences in systemic exposure.

Microscopic findings attributed to the administration of GSK573719 were observed in the nasal cavities, nasopharynx, larynx and trachea/tracheal bifurcation. Minimal to moderate erosion/ulceration and minimal to slight squamous metaplasia of the olfactory epithelium and minimal to slight erosion of the respiratory epithelium was observed in the nasal cavity of animals receiving GSK573719. Minimal to moderate degeneration of the olfactory epithelium was also noted, however, this was also observed in the GSK573719 with lactose monohydrate blend, albeit only minimally (milder changes were seen in the epithelia although the vomeronasal organ was still significantly affected).

Minimal to moderate hyperplasia/squamous metaplasia, subacute inflammation and necrosis (of the ventral pouch cartilage) were observed in the larynx along with minimal to slight exudates. In the tracheal bifurcation, minimal degeneration/regeneration of the epithelium was observed.

The incidence of microscopic observations observed in the larynx, nasal cavities, nasopharynx and tracheal bifurcation in animals receiving GSK573719 in lactose monohydrate were generally notably less than the same findings seen in animals receiving GSK573719 in either cellobiose octaacetate/lactose monohydrate or magnesium stearate/lactose monohydrate. This is likely due to the at least 2-fold increase in systemic exposure in the groups containing the excipients and also reflection of the slightly increased chamber concentration (and therefore the local concentrations) of GSK573719 compared to GSK573719/lactose monohydrate.

On Day 14, mean DNAUC0-t values were 186.5, 233 and 79.8 ng.h/mL for the cellobiose octaacetate/lactose monohydrate, magnesium stearate/lactose monohydrate or lactose monohydrate alone formulations (males and females combined).

13 week inhalation toxicity study (Report WD2007/02012)

The toxicity and toxicokinetics of GSK573719 were evaluated in a 13 week repeat dose study, with a 4 week recovery period, in Sprague Dawley rats given once daily, 60 minute doses by nose-only inhalation from a powder aerosol formulation. Groups of rats (12/sex/group) were given estimated achieved doses of micronized GSK573719 at 0 (vehicle, lactose monohydrate with 1% w/w magnesium stearate) or 38, 102, 288 or 924 mcg/kg/day, with test article formulations containing 25% w/w

GSK573719. An additional 3 animals/sex were included at each dose level for toxicokinetic evaluation and 6 animals/sex were added to the 0 (control) and 924 mcg/kg/day dose groups for recovery evaluations.

The cause of death of two main study rats (102 and 288 mcg/kg/day groups) found dead on study Days 74 and 27, respectively, could not be determined histopathologically. As there was no mortality in the 924 mcg/kg/day group, they were not thought to be related to test article.

Administration of GSK573719 by nose-only inhalation to male and female rats for 13 weeks resulted in changes in the upper respiratory tract in male and female rats from all treated groups. The changes in the larynx and nasal cavities/sinuses were generally consistent with local irritation to GSK573719. Changes in the larynx consisting of squamous metaplasia and necrosis of the ventral pouch cartilage were seen in all dose groups and there was a clear dose response in their incidence and/or severity

Hyperplasia/hypertrophy of goblet cells were seen at all dose levels (except 38 mcg/kg/day females). Inflammation and/or exudate were sporadically seen at ≥102 mcg/kg/day. The degeneration/regeneration in the respiratory epithelium seen at 924 mcg/kg/day at the moderate grade in one male and one female was considered the only adverse finding in this study.

Following a 4 week recovery period, persistence of GSK573719-related findings were found in male and female rats at 924 mcg/kg/day in the larynx (squamous metaplasia ventrolateral and submucosal glands, necrosis and inflammation) and nasal cavity/sinuses (degeneration/regeneration respiratory/olfactory epithelium), but in a lower degree in incidence and/or severity compared to those observed in animals killed at the end of treatment.

In males at doses of ≥102 mcg/kg/day and females at 924 mcg/kg/day, body weight gain was reduced throughout the main phase of the study. This generally correlated with a reduction of food consumption throughout the main phase of the study. In recovery, body weight gains returned to normal.

Minimal decreases in reticulocytes were observed in females given GSK573719 at a dose of 924 mcg/kg/day. These changes were of low amplitude, had no microscopic correlate and were not observed at the end of the recovery period.

The NOAEL was 288 mcg/kg/day [mean DNAUC0-t was 16.2 ng.h/mL and mean DNCmax was 3.79 ng/mL (males and females combined)].

26 week inhalation toxicity study (Report FD2009/00467)

The toxicity and toxicokinetics of GSK573719 were assessed in a 26 week repeat dose study, with a 6 week recovery period, in Sprague Dawley rats given once daily, 60 minute doses by nose-only inhalation from a powder aerosol formulation. Groups of rats (12/sex/group) were given estimated achieved doses of micronized GSK573719 at 0 (vehicle, lactose monohydrate with 1% w/w magnesium stearate) or 87.1, 289 or 987 mcg/kg/day. The test article formulations contained either 2.5% w/w GSK573719 (87.1 and 289 mcg/kg/day) or 25% w/w GSK573719 (987 mcg/kg/day). An additional 3 animals/sex were included at each dose level for toxicokinetic evaluation and 6 animals/sex were added to the 0 (vehicle) and 987 mcg/kg/day dose groups for recovery evaluations.

There were 4 pre-terminal deaths during the treatment period. On Day 81, one male control animal, assigned to the recovery phase, was found dead during unloading from the inhalation chamber following exposure. On Day 86, one female control animal, also assigned to the recovery phase, was found dead following bleeding procedures. On Day 28, one toxicokinetic female given 289 mcg/kg/day was found dead following blood collection. Following blood collection on Day 85, the condition of one toxicology male given 987 mcg/kg/day deteriorated and it was subsequently found dead on Day 90. With the exception of the male given 987 mcg/kg/day, there were no adverse clinical observations

reported prior to the animals being found dead. Although the cause of death was not determined histopathologically for any of these animals, they are considered not to have been test article-related, but rather related to procedures.

Microscopic changes were observed in the nasal cavity/sinuses (≥87.1 mcg/kg/day), nasopharynx (987 mcg/kg/day), larynx (≥87.1 mcg/kg/day), tracheal bifurcation (≥289 mcg/kg/day) and lungs (≥87.1 mcg/kg/day) in male and female rats given the test article and were partially or completely reversible following cessation of treatment for a 6 week period.

Minimal squamous metaplasia was seen in the tracheal bifurcation of males and females given ≥289 mcg/kg/day.

Lungs of males and females from all groups given the test article, including control animals, had minimal to slight macrophage accumulation, with an increase in incidence and severity in males given 987 mcg/kg/day. This finding correlated with pale areas of the lung noted macroscopically.

Following a 6 week off-dose period, the changes in the nasal cavity/sinuses, nasopharynx, larynx and lungs were still present, but in general with a reduced incidence and severity. Additionally, in two treated males there was regeneration of the laryngeal ventral cartilage.

Throughout the treatment period, minimal increases in group mean neutrophil count (1.32X to 1.4X mean control) were observed in males given 87.1 and 289 mcg/kg/day (at Weeks 4 and 13), and mild increases (1.24X to 1.74X mean control) in males given 987 mcg/kg/day (at Weeks 4, 13 and 26). The decrease in magnitude of the changes (from 1.74X to 1.51X to 1.24X control) seen in animals given 987 mcg/kg/day over the course of the study reflected increases in the group mean absolute neutrophil counts in concurrent controls over the duration of the study. This change persisted at the end of the recovery period in males (1.21X control) that had previously been given 987 mcg/kg/day, however, individual absolute values were decreased compared to respective values measured at the end of the treatment period.

Minimal increases in serum urea in males given 987 mcg/kg/day in Weeks 13 (1.11X control) and 26 (1.13X control) were noted. Values were comparable to controls at the end of the recovery period.

In animals given ≥87.1 mcg/kg/day, dose-related, mild reductions in mean overall body weight gain were observed (up to 0.79X controls for males, up to 0.72X controls for females). During the off-dose period, the mean overall weight gain of animals previously given 987 mcg/kg/day increased compared to that of the controls (1.2X for males and 1.3X for females), indicating reversibility.

Due to the adverse findings in the larynx the NOAEL was considered to be 87.1 mcg/kg/day [mean DNAUC0-t 8.08 ng.h/mL; mean DNCmax 1.55 ng/mL (males and females combined)].

Dog

4 week inhalation toxicity study (Report WD2005/01423)

GSK573719 blended in lactose monohydrate at a nominal concentration of 4% w/w with a nominal 8% w/w micronized cellobiose octaacetate, was administered to groups of dogs (3/sex/group) once daily for 60 minutes. The estimated achieved doses were 0 (vehicle), 16.2, 208 or 2758 mcg/kg/day.

There was a treatment-related decrease in absolute overall body weight gains with males at 208 mcg/kg/day gaining 0.10 kg versus a gain of 0.50 kg in the controls. Males receiving 2758 mcg/kg/day lost 0.17 kg on average. Likewise, females at 208 mcg/kg/day gained 0.13 kg versus a gain of 0.40 kg in the controls. Females receiving 2758 mcg/kg/day lost 0.13 kg on average.

Food consumption was consistently decreased over the course of the study in females given 208 mcg/kg/day (-9.6%) and 2758 mcg/kg/day (-8.6%) when compared with pre-treatment values. In the males this decrease was noted at 2758 mcg/kg/day in Weeks 1 (-13.8%) and 2 (-5.0%) only.

GSK573719 did not appear to have any effects on ECG recordings with the exception of a mild positive chronotropic effect observed at 2758 mcg/kg/day during Week 4. On Day 1, marked treatment-related increases in heart rates (47% for males and 62% for females compared to pre-dose values) were seen in animals receiving 2758 mcg/kg/day with heart rates not returning to their pre-dose values up to 23 hours after dosing. On Days 2 to 7, heart rates of animals treated at 2758 mcg/kg/day continued to be elevated with the average of post dose heart rates being increased by 45% for males and by 62% for females compared to controls. On Day 28, pre-dose heart rates were increased by 25% or 20% for males and females, respectively, treated at 208 mcg/kg/day and by 25% or 58% for males and females, respectively, treated at 2758 mcg/kg/day compared to Day 1 pre-dose heart rates.

GSK573719-related changes were observed in the nasal cavity, larynx, trachea, lungs and thymus.

Minimal to moderate lymphoid atrophy was noted in the thymus at all doses with increased severity at 208 and 2758 mcg/kg/day. A small thymus was noted in one female at 2758 mcg/kg/day.

Seminiferous tubules were evaluated with respect to their stage in the spermatogenic cycle and the integrity of the various cell types present within the different stages. No cell- or stage-specific abnormalities were noted.

Based on the microscopic changes in the nasal cavities, larynx and trachea at 2758 mcg/kg/day the NOAEL would be 208 mcg/kg/day, however, in view of the adverse inflammatory findings in the lungs an overall NOAEL for this study could not be determined.

Mean systemic exposure at an estimated achieved dose of 2758 mcg/kg/day resulted in a combined calculated DNAUC0-t of 195 ng.h/mL and combined calculated DNCmax of 83.7 ng/mL for GSK573719 based on Day 28 values. The toxicokinetic parameters were not reported for the other doses due to high variability.

4 week inhalation study investigating feeding regimen (Report WD2006/03294)

In an effort to investigate the effect of feeding modifications designed to reduce the possibility of particules inhalation, on the formation of granulomas in the lung seen in the previous 4 week inhalation toxicity study in the dog, groups of dogs (3/sex/group) were given estimated achieved doses of 0 (vehicle), 22, 2254 (new feeding regime) or 1835 (old feeding regime) mcg/kg/day GSK573719 once daily for 60 minutes via oropharyngeal inhalation. One group of dogs given a dose of 1835 mcg/kg/day was given dry pelleted diet prior to dosing for approximately 6 hours (commencing in the morning), and removed generally during dosing or up to 40 minutes following the completion of dosing (identified as old feeding regimen). The feeding regimen for 3 groups of dogs given the test article at doses of 0 (vehicle), 22 or 2254 mcg/kg/day was modified to provide pelleted diet mixed with water 3 hours after completion of dosing for a period of 2 hours (identified as new feeding regimen).

Treatment-related clinical signs included dry mouth (i.e. dry muzzle and dry gums) and dry eyes observed at doses ≥22 mcg/kg/day, with the incidence more prevalent in dogs given 1835 mcg/kg/day/old feeding regimen and 2254 mcg/kg/day/new feeding regimen.

Overall body weight loss was noted at the end of the treatment period in animals given 1835 mcg/kg/day/old feeding regimen (up to 0.95X Day 1 body weight). Food consumption was generally decreased during Weeks 1 and 2 of the study in both males and females given 1835 mcg/kg/day/old feeding regimen when compared with Week -1 pre-treatment values (Week 1 = 0.56X and 0.63X; Week 2 = 0.76X and 0.94X).

The Schirmer tear test revealed that moisture content of the eyes of dogs given 2254 mcg/kg/day/new feeding regimen and dogs given 1835 mcg/kg/day/old feeding regimen were reduced in Weeks 1 and 4 (up to 0.06X and 0.07X control mean, respectively) when compared to control values. Unilateral conjunctival hyperemia and mucoid discharge was noted in one dog of each of the 2254

mcg/kg/day/new feeding regimen and 1835 mcg/kg/day/old feeding regimen doses, and was accompanied by slight corneal edema and vascularization in one eye (one female animal at 1835 mcg/kg/day/old feeding regimen). While these findings were considered not to represent a direct effect of the test article on the eyes, they were considered to be a secondary response to tear deficiency and were considered adverse.

Heart rate (measured by stethoscope) was increased for dogs given 1835 mcg/kg/day/old feeding regimen and 2254 mcg/kg/day/new feeding regimen on Day 1 (up to 2.94X pre-dose), with peak heart rates generally noted within 1 hour of completion of dosing. Heart rates remained elevated at 23 hours after completion of dosing. There was no change in heart rate following dosing on Day 25, although pre-dose values were higher on Day 25 when compared with Day 1 pre-dose values (up to 1.47X). Mild to moderate increases in heart rate were also noted at 2254 mcg/kg/day/new feeding regimen and 1835 mcg/kg/day/old feeding regimen during Week 4 (Day 27) ECG evaluation.

There was a mild increase in serum triglycerides in males given GSK573719 at 2254 mcg/kg/day/new feeding regimen.

Microscopic findings considered to be related to the old feeding regimen were seen in the lungs. Microscopic findings considered to be related to GSK573719 were seen in the nasal cavity/sinuses, larynx, trachea and bronchi. The larynx had similar changes from irritation that consisted of epithelial degeneration/necrosis, acute inflammation and/or exudate. Tracheal findings consisted of acute inflammation, epithelial degeneration/regeneration, epithelial necrosis and exudate. Bronchi had sporadic and infrequent minimal epithelial degeneration/regeneration and/or acute inflammation in dogs receiving 2254 mcg/kg/day/new feeding regimen as well as small bronchi within the lungs in one 2254 mcg/kg/day/new feeding regimen and 1835 mcg/kg/day/old feeding regimen female. One 22 mcg/kg/day/new feeding regimen male had minimal acute inflammation of the bronchi.

Mean systemic exposure (DNAUC0-t) was 278 ng.h/mL at doses of 2254 mcg/kg/day for the new feeding regimen and 284 ng.h/mL at a dose of 1835 mcg/kg/day for the old feeding regimen. Systemic exposure at a dose of 22 mcg/kg/day/new feeding regimen group was not be reported due to the variability of the data.

13 week inhalation toxicity study (Report WD2007/01512)

Groups of beagle dogs (4 dogs/sex/group with an additional 2 dogs/sex in the vehicle and high dose group held for recovery evaluation) were exposed to dry powder formulations of micronized GSK573719 in lactose monohydrate at a nominal concentration of 40% w/w with a nominal 1% w/w magnesium stearate by inhalation administration via oropharyngeal tube at estimated achieved doses of 0 (vehicle), 40.7, 187 or 1070 mcg/kg/day.

Dry mouth was seen at a higher incidence in all groups given GSK573719 immediately following and up to 1 hour post dose when compared to controls. Excessive salivation was seen in all groups (including controls) during dosing and mainly immediately post dose, but was noted at a higher incidence in animals given 1070 mcg/kg/day. Dry mouth and excessive salivation were not observed in individual animals on the same occasion. Dry nose was noted during dosing, immediately post dosing in animals given the test article and was not present in controls. Swollen neck was observed during dosing and at a higher incidence immediately post dose, starting during Week 10 in groups given GSK573719. Changes noted during the treatment period resolved during the recovery period.

In Week 13, at pre-dose, 3/6 males and 4/6 females given 1070 mcg/kg/day showed no respiratory sinus arrhythmia (RSA) (expressed by decreased RR interval variability) and all dogs given 1070 mcg/kg/day had increased heart rates (up to 1.8X pre-test individual values). Immediately following a dose of 1070 mcg/kg/day, no RSA was noted in 4/6 males and 4/6 females, which was associated with further increases in heart rates (up to 2.1X pre-dose individual values) in 2/6 males and 3/6 females.

The changes in most animals were returned to pre-test values, but RSA was not observed in females during the recovery phase.

In Week 1, a test article-related decrease in tear production was noted in animals given GSK573719 (0.2 to 0.9X pre-test mean values). In Weeks 4 and 13 (pre- and post dose), a decrease in tear production was noted in animals given 1070 mcg/kg/day (0.2 to 0.7X pre-test mean values), in Week 13 (pre- and post dose), decreased tear production was noted in animals given 187 mcg/kg/day (0.6 to 0.8X pre-test mean values). At the end of the recovery phase, tear production was comparable to pre-test values for animals given 1070 mcg/kg/day.

There were minimal to mildly higher serum cTnI concentrations at 3, 7 and/or 24 hours, peaking at 7 hours (0.189 and 0.171 mcg/L) on Day 1 for one male and one female animal, respectively, given 1070 mcg/kg/day when compared to their pre-dose values and concurrent controls. By Week 13 and at the end of the recovery period, the serum cTnI concentrations were comparable to pre-dose and concurrent controls.

Moderate amounts of black/granular material noted in the gall bladder of one male given 1070 mcg/kg/day at the end of treatment was not associated with any microscopic changes in the gall bladder itself or present in any animal at the end of recovery. The relationship to treatment is uncertain.

None of the changes seen in this study were considered to be adverse, therefore, the NOAEL was 1070 mcg/kg/day [mean DNAUC0-t 22.5 ng.h/mL, mean DNCmax 14.6 ng/mL (for males and females based on Week 13 values)].

39 week inhalation toxicity study (Report FD2009/00466)

Micronized GSK573719 was administered as a dry powder formulation blended in lactose monohydrate at a nominal concentration of 35% w/w with a nominal 1.0% w/w magnesium stearate. Groups of beagle dogs (4 dogs/sex/group with an additional 2 dogs/sex in the vehicle and high dose group held for recovery evaluation) were exposed at estimated achieved doses of 0 (vehicle), 109, 421 or 1002 mcg/kg/day daily.

Moderate subacute inflammation of the extramural coronary arteries was seen in one male given 421 mcg/kg/day and one female given 1002 mcg/kg/day. In addition, there was mild intimal thickening with minimal areas of mixed inflammatory cell infiltrate in an arteriole in the lung in one female given 1002 mcg/kg/day. These changes were not seen following the 6 week recovery period. A definite relationship to the test article could not be established owing to the low incidence of changes and the lack of systemic exposure relationship. These changes are consistent with a manifestation of a latent spontaneous disease precipitated by treatment. However, in the absence of similar vascular changes in concurrent controls or in the background data from this laboratory, the NOAEL for this change is conservatively set at 109 mcg/kg/day.

Test article-related changes were seen in the upper respiratory tract (minimal to slight erosion/ulceration of the mucosal epithelium and slight inflammation of the mucosal gland/hyperplasia of the squamous epithelium in the larynx and squamous metaplasia of the respiratory epithelium of the nasal turbinates) in animals given ≥421 mcg/kg/day.

These changes were consistent with a local irritant effect of the test article and were found to be reversible in animals previously given 1002 mcg/kg/day at the end of a 6 week off-dose recovery period. Changes in the nasal cavity and larynx in animals given ≥421 mcg/kg/day at the end of the dosing period were considered to be a local irritant response to the test article and non-adverse.

Dry mouth was observed immediately after dosing in all groups, including controls. Bilateral swelling of the neck and excessive salivation observed during and immediately after dosing were also seen in all

groups. The incidence and frequency of these observations were greater in animals given GSK573719 and were dose-related. Though the swelling generally persisted until the end of the day, it was only measurable (up to 40 mm in diameter) up to 4.5 hours after the completion of dosing. Radiographs of the swollen areas and cytological examination of the fluid collected from these areas, the latter of which only confirmed the presence of salivary gland cells, did not reveal any information on the mechanism of the swelling. The frequency of abnormal stool findings (unformed, watery and/or with mucus) was decreased in animals given GSK573719 when compared to controls. This reduction in occurrence was more apparent and also dose related in males. These observations were no longer evident during the recovery period.

Increased femoral pulse rates (up to 1.51 and 1.53X in males and females, respectively) were noted in both sexes given ≥109 mcg/kg/day at all intervals commencing immediately after the completion of dosing, which is also generally when peak exposure values occurred. Pulse rates returned to baseline levels between 1 and 3 hours after the completion of dosing. In both sexes, the effect on pulse rates diminished at Week 39 when compared to previous intervals. ECGs taken prior to and immediately after dosing during Week 39 confirmed the increased heart rates (up to 1.50 and 1.61X in males and females, respectively).

Minimal increases in group mean serum cTnI concentrations were noted in the majority of females given ≥421 mcg/kg/day at 4 and 8 hours after the start of dosing on Day 1 (up to 11.6X and 7.4X pre-dose, respectively). A near complete return to baseline was achieved by 24 hours after the start of the previous day's dose. A male given 421 mcg/kg/day demonstrated an increased serum cTnI concentration at 4 and 8 hours after the start of dosing, with partial return to baseline levels seen at 24 hours. The change in this single male is of uncertain relationship to the test article owing to a raised baseline value for the animal and the isolation of this finding in males.

Decreased tear production (up to 0.11X pre-test for both sexes) was noted during Weeks 1, 4, 13, 26 and 39 in animals given GSK573719. While reductions were apparent prior to dosing, their magnitude was even greater after dosing. At the end of the recovery phase, tear production was comparable to pre-test and control values for animals previously given 1002 mcg/kg/day.

Lower thymus weights (up to 0.54X controls) were seen in males given 1002 mcg/kg/day. After 6 weeks of recovery, thymus weight was still slightly lower than controls in one male previously given 1002 mcg/kg/day (0.46X). There was no histopathological correlate with this finding.

Slight decreases in haemoglobin, hematocrit and red blood cell count (up to 0.91X controls) were seen in males given ≥109 mcg/kg/day at Week 39. At the end of the recovery period, these parameters were still slightly lower than controls (0.91X).

Slight increases in blood urea nitrogen (BUN) during Weeks 26 and 39 were seen in both sexes given 1002 mcg/kg/day (1.38X and 1.27X controls in males and females, respectively), which were no longer evident after 6 weeks of recovery.

A definitive relationship to the test article could not be established for the inflammatory changes seen in the extramural coronary arteries of the heart in a male given 421 and a female given 1002 mcg/kg/day and in the pulmonary arteriole of another female given 1002 mcg/kg/day owing to the low incidence of these findings and absence of systemic exposure relationship. Although the changes are consistent with a manifestation of latent spontaneous disease precipitated by treatment, a conservative approach has been taken during assessment of these changes in the absence of similar findings in concurrent controls or in the historical data base at this laboratory. Based on the occurrence of the vascular lesions in the heart or lungs in dogs given 421 or 1002 mcg/kg/day, the NOAEL is considered to be 109 mcg/kg/day. At the NOAEL, mean DNCmax and DNAUC0-t values were 7.65 ng/mL and 11.2 ng.hr/mL, respectively (males and females combined).

Vilanterol (GW642444)

The toxicity profile of GW642444 has been investigated adequately in repeat dose inhaled toxicity studies of up to 13 weeks in mice, 26 weeks in rats and 39 weeks in dogs. Identified NOAELs ocurred generally at doses achieving systemic exposures at large multiples of those seen in human patients at the proposed commercial dose of 25 mcg/day (13 week mice study NOAEL=38200 mcg/kg/day (4500 (Cmax) or 2210-fold (AUC)); 26 week female rats study NOAEL=57.7 mcg/kg/day (31 (Cmax) or 20-fold (AUC)); 26 week male rats study NOAEL=10253 mcg/kg/day (5680 (Cmax) or 2630-fold (AUC)); 39 week toxicity dogs study NOAEL=62.5 mcg/kg/day (305 (Cmax) or 124-fold (AUC)). Toxicological findings in these studies were mostly associated with the primary pharmacology and seen with other marketed beta2 agonists. These findings are described below.

The principal toxicity of GW642444 was in the heart and cardiovascular system. GW642444 caused tachycardia, vasodilation, heart lesions in dogs. Microscopic changes (predominantly myocardial fibrosis) in the papillary muscle of the heart which correlated with increase in heart-rate were seen in most studies. In the 13 and 39 week studies in dogs, NOAELs for papillary muscle changes were identified as 9.3 and 62.5 mcg/kg/day, respectively (systemic exposures 26- or 124-times those achieved in humans at the proposed commercial dose). However, the dose of 0.953 mcg/kg/day with and without GW685698 in the 4 week combination toxicity study, produced myocardial fibrosis of the interventricular septum. In addition, increases in serum cTnI were noted in some dogs. Cardiovascular responses in the dog were expected effects in dogs experiencing beta2-agonist peripheral vasodilatation and reflex tachycardia. Such lesions could not be relevant to the use in humans at the proposed commercial dose because tachycardia occurred at exposure 44-fold the human exposure at the proposed commercial dose.

In the upper respiratory tract, GW642444 produced irritancy in mice, rats and dogs. In rats, minimal to marked microscopic changes in nasal cavity / sinuses, nasopharynx and larynx at ≥10253 mcg/kg/day were observed in the 13 or 26 week toxicity studies. In mice, this finding which was its principal toxicity was noted at ≥ 1020 mcg/kg/day in the 13 week study, with nasal turbinates and larynx being the primary sites, as well as an increased of luminal inflammatory cells/cell debris in the nasal cavity from females at all doses and olfactory degenerative changes at ≥62 mcg/kg/day in the mouse carcinogenicity study. In dogs, this finding was observed in the 39 week inhaled toxicity study, in the respiratory epithelium of all treated groups and in the squamous and transitional epithelia of a single male given 510 mcg/kg/day. In addition, minimal to moderate lymphoid cell infiltrate in the lamina propria of the olfactory epithelium was seen in animals given ≥62.5mcg/kg/day. The upper respiratory tract irritancy determined the NOAEL in the 13 week study in rat and was the main test article-related finding in the 13 week study in mouse. The findings observed in rats and mice are considered not to predict unacceptable irritancy in humans, as the larynx is a particularly sensitive area of the respiratory tract in rodents and since GW642444 was given for an extended period of time which contrasts sharply with the oral inhalation method in humans. The changes in the nasal cavities of dogs are also not of concern as they were only seen at high doses administered by oronasal facemask over a 30 or 60 minute period each day.

In the lung, it was observed greater incidence of focal pulmonary haemorrhage in rats dosed up to 4 weeks duration. However, this effect is not considered to be of relevance to humans because it was limited to the rat, resulted from deposited lung doses 37-fold to 25800-fold the proposed commercial dose of GW642444 and was seen with similar incidence in control rats.

Metabolic effects produced by GW642444 included increased weight gain in mice, rats and dogs at most dose levels within the majority of studies, which is a result from an alteration in the distribution of fat, enhanced protein synthesis and a reduction in protein degradation in muscle; variable changes in serum or plasma protein, albumin, urea and /or creatinine concentrations in mouse, rat and/or dog

after 13 and or 26/39 weeks treatment which are secondary to the changes in muscle mass and do not represent a toxic event. These effects are considered not to represent a hazard to human health since there have been no consequences with other beta2 agonists in clinical use. Reduction in plasma glucose concentrations in rats at all doses in the 13 and 26 week studies have also been observed, which may be due to an overcompensation of insulin response to an acute rise in glucose; decrease in triglyceride levels in rats at ≥657.9 mcg/kg/day which is likely to be related to the beta-adrenergic stimulation of lipolysis; changes in electrolytes in rats at all doses which have been suggested to be due to increased tissue uptake or a secondary effect resulting from an increase in insulin.

In addition, minimal increase in serum alkaline phosphatase activity and bilirubin concentration and a decrease in serum alanine aminotransferase activity in rats at doses ≥658 mcg/kg/day have been observed in the 13 week toxicity study. These changes are considered not to represent a hazard to human since none were noted during the rat 26 week study at doses achieving AUC0-t exposures up to 2500-fold greater than those in humans at the proposed commercial dose.

Changes produced by GW642444 in hepatocyte rarefaction were seen in the 13 and/or 39 weeks study in dogs at doses ≥9.3 mcg/kg/day (<21-fold human exposure) and in mice at doses ≥6490 mcg/kg/day (312-fold human exposure). It was showed that these changes in rarefaction were due to alterations in glycogen distribution which were fully reversible.

Haematology changes in dogs included increase in platelet count at the highest dose tested (2010 to 571 mcg/kg/day) in the 4 week study, increase in white blood cell count, primarily due to neutrophils and monocytes, at 501 mcg/kg in the 13 week study, slight reduction in haemoglobin in female given 510 mcg/kg/day during the 39 week study. In rats, increase in neutrophil and/or monocyte counts, along with very small reductions in erythrocyte parameters were noted at 34422 mcg/kg/day with an increase in reticulocyte count apparent at ≥625 mcg/kg/day in the 14 day study, and reversible reductions in platelet counts at ≥56.2 mcg/kg/day (13 weeks) or ≥537 mcg/kg/day (26 weeks). At the NOEL for haematological changes in the 26 week study in rats (57.7mcg/kg/day) and the 39-week study in dogs (62.5 mcg/kg/day), AUC0-t was 20- or 124-fold greater, respectively, than human AUC0-t at the proposed commercial dose, thus these findings are considered not relevant for human safety at this dose.

In the thymus, GW642444 was associated with increase of thymic involution/atrophy in dogs at doses of ≥137, ≥64.2, ≥9.3 and 510 mcg/kg/day administered for 14 days or 4, 13 or 39 weeks, respectively. In dogs, although seen at all doses in the 13 week study in which AUC0-t was ≥26-fold greater than that at the proposed human commercial dose, in the 39 week study at the NOEL (62.5 mcg/kg/day), AUC0-t was 124-fold greater than human. Furthermore, involution/atrophy of the thymus is a normal age-related change in dogs which is often further advanced with experimental stress and is considered not relevant for humans.

In the female reproductive tract, GW642444 was associated with dose-related myometrial hypertrophy seen at doses ≥1020 mcg/kg/day in mouse in the 13 week study and at ≥62 mcg/kg/day in the mouse carcinogenicity study. The fact that no myometrial hypertrophy in the 13 week mouse study at 58.6 mcg/kg/day (35-fold human exposure) have been observed suggests the uterine changes have no relevance to human use at the proposed commercial dose. There was also an increase of cystic endometrial hyperplasia in all treated groups in the mouse carcinogenicity study which will be discussed in the carcinogenicity part.

In rats, reversible decrease of recent corpora lutea, increase of dilated or cystic follicles in the ovary and increase of females in a proestrus or estrus state in the 26 weeks study at ≥537 mcg/kg/day have been observed. At the same doses in the mammary gland of rats, non-reversible increase of acinar development and secretory activity, as well as incidences of lobular hyperplasia with atypia and/or mammary adenoma have been observed. The NOAEL for these effects in rats is 57.7 mcg/kg/day (20-

fold human exposure), which determined of the rat 26 week study. In addition in the 104 week carcinogenicity study in rats, increase of serum estradiol concentrations in females but not males, increase of ovarian cysts at all dose levels, increase of mesovarian ligament smooth muscle hyperplasia/hypertrophy and leiomyomata at ≥84.4/28.2 mcg/kg/day have been observed. The absence of these changes in males in the 26 week study suggests that GW642444 may be acting at a local level in the female reproductive tract in the rat rather than through any perturbation of the hypothalamic-pituitary axis.

In mice, the incidence of development of ovarian cysts was increased at ≥62.0 mcg/kg/day, but not at 6.40 mcg/kg/day at which AUC0-t was 30-fold the clinical exposure at the proposed commercial dose. In the rat carcinogenicity study the incidence of ovarian cysts was increased at all doses. These ovarian changes are considered to be rodent-specific and are of no relevance to humans because a similar beta2 related mechanism for cyst formation had not been identified over many patient years of clinical use with other beta2 agonists. These changes were not seen in dogs receiving GW642444 at doses of up to 510 mcg/kg/day for 39 weeks.

The benign neoplastic changes in the mammary glands (mammary adenoma; lobular hyperplasia with atypia) of rats dosed for 26 weeks were restricted to 2/18 animals at 2670 mcg/kg/day where the mean exposure was >1000 times higher than in humans at the proposed commercial dose. GW642444 is not genotoxic and the NOAEL for this finding (537 mcg/kg/day) was 135 times greater than that in humans at the proposed commercial dose and therefore indicates no clinical concern. There were no GW642444-related mammary findings in the carcinogenicity study in rats in which doses up to 657 mcg/kg/day were administered for up to 104 weeks.

Table 6. A summary of principal toxicological findings in rats, mice and dogs following inhaled administration of GW642444 together with exposure ratios

	Rat			Dog			Mouse		
Effect	Lowest Effect Dose (mcg/kg	No Effect Dose (mcg/kg)	Multiple to Clinical Exposure[b]	Lowest Effect Dose (mcg/kg	No Effect Dose (mcg/kg)	Multiple to Clinical Exposure[b]	Lowest Effect Dose (mcg/kg	No Effect Dose (mcg/kg)	Multiple to Clinical Exposure[b]
26 Week Rat, 39 Week Dog & 13 Week Mouse Studies									
General Condition and Clinical Signs	NO	NO[R]	-	NO	NO[D]	-	63600[a]	38200	2210-fold
Heart / Cardiovascular System Tachycardia Papillary muscle fibrosis	NO	NO[R]	-	 62.5 510	 9.55 62.5	 44-fold[+] 124-fold	NO	NO[M]	-
Upper respiratory tract / Nasal Cavity Irritancy Lymphoid cell infiltration of the olfactory epithelium	10253 NO	2674 NO[R]	NA NA	9.55 62.5	<9.55 9.55	NA NA	1020 NO	58.6 NO[M]	NA NA
Increased body weight gain	57.7	<57.7	<20-fold	9.55	<9.55	<21-fold	58.6	<58.6	<35-fold
Liver – Altered hepatocellular rarefaction	NO	NO[R]	-	9.55	<9.55	<21-fold	6420	1020[c]	312-fold
Increased food consumption	57.7	<57.7	<20-fold	NO	NO[D]	–	NO	NO[M]	-
Thymus – Involution/atrophy	NO	NO[R]		510	62.5	124-fold	NO	NO[M]	-
Ovary – Ovarian cysts and decreased corpora lutea	537	57.7	20-fold	NO	NO[D]	-	NO	NO[M]	-
Mammary gland - Increased acinar development, adenoma and atypia	537	57.7	20-fold	NO	NO[D]	-	NO	NO[M]	-
Uterus - Myometrial hypertrophy	NO	NO[R]	-	NO	NO[D]	-	1020	58.6	32-fold
Other findings not seen in pivotal chronic studies or seen at lower doses in shorter studies									
Skeletal muscle - Myofibre degeneration/ inflammation [WD2007/00766/00]	6.29	<6.29	NC						
Thymus – Involution/atrophy [WD2006/01711/00]				9.3	<9.3	<26-fold			
Lung - Focal pulmonary haemorrhage [WD2006/02926/00]	503	NI[d]							
Heart: Myocardial fibrosis or mineralisation [WD2007/00765/00; WD2005/00845/00]				0.953 10.1	<0.953 <10.1	NC NC			

Key: Doses are estimated achieved doses (based on a 100% deposition fraction) calculated for the whole duration of the study.
a = Initial high dose, reduced to 38200 mcg/kg/day on Day 8 of study.
b = Comparison of AUC data in animals at No Effect Dose or Lowest Effect Dose with AUC_{0-t} (geometric mean AUC_{0-t} following administration of 25 mcg GW642444 (alone or in combination with GW685698) in subjects with COPD – see m2.7.2, Summary of Clinical Pharmacology.) except where indicated: $+C_{max}$ (Model predicted geometric mean following administration of 25 mcg GW642444 (alone or in combination withGW685698) in subjects with asthma - see m2.7.2, Summary of Clinical Pharmacology.)
c = One animal affected at 58.6 mcg/kg/kg.
d = Not identified since only one dose level was used on study
NO^R = Not seen at highest dose in 26 week rat study (10253 mcg/kg/day) achieving multiple to clinical exposure (AUC) 2500-fold
NO^D = Not seen at highest dose in 39 week dog study (510 mcg/kg/day) achieving multiple to clinical exposure (AUC) 1177-fold
NO^M = Not seen at highest dose in 13 week mouse study (38200 mcg/kg/day) achieving multiple to clinical exposure (AUC) 2210-fold
NI = Not identified (1 dose level only used in study); NC = Not calculated (insufficient data at this dose); NA = Not appropriate (unlikely to be related to systemic exposures or deposited lung dose)

In relation to the toxicity of α-phenylcinnamate salt of GW642444, this salt showed similar significant safety findings to the triphenylacetate salt of GW642444. However, there were safety findings seen only with the triphenylacetate salt of GW642444, such as the observed changes in haematologic and biochemistry parameters. The comparison of toxicity profile of both salts of GW642444 could have been clearer in one comparative study which includes the two salts.

In relation to magnesium stearate toxicity alone, in repeat dose studies of up to 26 weeks duration in the rat and 4 weeks duration in the dog with this compound has demonstrated little to no toxicity of clinical relevance. Deposited lung doses of magnesium stearate at the NOAEL in rats (1648 mcg/kg/day for 26 weeks) or dogs (5820 mcg/kg/day for 4 weeks) were 210 or 1016-fold, respectively, the deposited lung dose in humans given an inhaled formulation containing 130 mcg magnesium stearate.

Umeclidinium bromide / vilanterol

Rat

4 week inhalation combination toxicity study (Report FD2009/00392)

GSK573719 and GW642444 (formulations containing 0, 6 or 40% w/w GSK573719, 0.2, 2 or 6% w/w GW642444 and 1% w/w magnesium stearate blended in lactose monohydrate) were given to Sprague Dawley rats (10/sex/group) by snout-only inhalation administration once daily for 60 minutes/day for 4 weeks. The estimated achieved doses of GSK573719/GW642444 were 817/4.37, 1200/60.7, 1060/1040, 757/0 and 0/869 mcg/kg/day. Twelve animals/sex were added at each dose for toxicokinetic evaluation which was performed on samples collected on Days 1, 14 and 28.

There was one unscheduled death. One male given 869 mcg/kg/day GW642444 died in the restraint tube during exposure on Day 5. This death was considered to be as a result of the dosing procedure and not related to the test article.

Test article-related histopathological findings of generally minimal and occasionally slight to moderate severity were seen in the nasal turbinates, nasopharynx, larynx and at the tracheal bifurcation in animals given GSK573719 alone or in combination with GW642444. Microscopic findings were seen in the larynx only in animals given GW642444 alone. When GSK573719 and GW642444 were administered in combination, there was evidence of exacerbation of irritancy in these respiratory tract tissues.

In the nasal turbinates, findings included minimal or slight atrophy/disorganisation of the olfactory epithelium when GSK573719 and GW642444 were given in combination at all combination doses but not when GSK573719 was given alone at 757 mcg/kg/day; minimal or slight atrophy of the olfactory nerve fibres when GSK573719 and GW642444 were given in combination at all doses but not when GSK573719 was given alone at 757 mcg/kg/day, and minimal erosion of the squamous epithelium when GSK573719 and GW642444 were given in combination doses in one male given GSK573719/GW642444 at 1200/60.7 or 1060/1040 mcg/kg/day.

GSK573719 alone at 757 mcg/kg/day (minimal severity); an increased severity when GSK573719 and GW642444 were given in combination at all doses in degeneration/regeneration of the vomeronasal organ (minimal to slight severity) compared to the severity of response in animals given GSK573719 alone at 757 mcg/kg/day (minimal severity); and an increased incidence of minimal squamous metaplasia of respiratory and olfactory epithelium of the vomeronasal organ in females given GSK573719/GW642444 at 1060/1040 mcg/kg/day (3 females affected) compared to the incidence in females given GSK573719 alone at 757 mcg/kg/day (one female affected).

In the nasopharynx, findings comprised minimal or slight degeneration of the respiratory epithelium in animals given GSK573719/GW642444 at 1060/1040 mcg/kg/day and in males given GSK573719/GW642444 at 817/4.37 mcg/kg/day. This finding was not seen in animals given GSK573719 or GW642444 alone.

In the larynx, findings included minimal epithelial keratinisation of the arytenoids in males when GSK573719 and GW642444 were given in combination at 1060/1040 mcg/kg/day but not when GSK573719 was given alone at 757 mcg/kg/day.

Body weight gain was higher in the animals given GW642444 alone at 869 mcg/kg/day (up to 1.36X control) and lower in the animals given GSK573719 alone at 757 mcg/kg/day (as low as 0.47X control). In the combination groups, higher or lower body weight reflected the relative contributions of each test article, with lower body weight gain in animals given GSK573719/GW642444 at 817/4.37 mcg/kg/day (as low as 0.57X control), similar body weight gain to controls in animals given GSK573719/GW642444 at 1200/60.7 mcg/kg/day and higher body weight gain in animals given GSK573719/GW642444 at 1060/1040 mcg/kg/day (up to 1.40X control). There was no evidence of an exacerbation of effects when GSK573719 and GW642444 were given in combination.

Red cell counts were higher in females given GSK573719/GW642444 at all combination doses (up to 1.08X control) or animals given GSK573719 at 757 mcg/kg/day. Mean cell haemoglobin and mean cell haemoglobin concentrations were lower in animals given GSK573719 at 757 mcg/kg/day or GW642444 at 869 mcg/kg/day (as low as 0.93X control). There was no evidence on exacerbation of effects when GSK573719 and GW642444 were given in combination.

Alanine aminotransferase activity was higher in animals given GSK573719/GW642444 at 1060/1040 mcg/kg/day and GW642444 alone at 869 mcg/kg/day (up to 1.26X control), and aspartate aminotransferase activity was higher in animals given GSK573719/GW642444 at 1060/1040 mcg/kg/day (up to 1.17X control), GSK573719 alone at 757 mcg/kg/day (up to 1.24X control) and GW642444 alone at 869 mcg/kg/day (up to 1.33X control). There was no evidence of an exacerbation of effects when GSK573719 and GW642444 were given in combination.

Dog

4 week inhalation combination toxicity study (Report FD2009/00391)

GSK573719 and GW642444 (formulations containing 0, 10 or 30% w/w GSK573719 and 0, 0.15 or 10% w/w GW642444, and each blend contained 1% w/w magnesium stearate in lactose monohydrate) were given to beagle dogs (3/sex/group) by oroparyngeal administration once daily for 10 minutes/day for 4 weeks. The estimated achieved doses of GSK573719/GW642444 were 0/0, 996/6.46, 190/205, 997/0, 0/174 mcg/kg/day. Prior to dosing in the 4 week phase, Group 3 (GSK573719/GW642444, 190/205) and Group 5 (0/174) received pre-treatment for 3 days (Phase 1, tolerance phase) with 42.0/48.7 mcg/kg/day or 0/47.4 mcg/kg/day, respectively, to induce tachyphylaxis of potential cardiovascular effects anticipated from GW642444 (a beta2 agonist) dosing. Toxicokinetic evaluation was performed on samples collected on Days 1, 9 and 23.

Swelling of the neck, observed immediately after dosing, and dry mouth were recorded in all groups given GSK573719 or GW642444 alone or in combination. The findings were seen at a greater

frequency in animals given GSK573719 at a target dose of 1000 mcg/kg/day, more so alone than in combination with GW642444. Decreased tear production was noted in animals given GSK573719, alone or in combination with GW642444. Generally, there were no apparent differences in tear production in animals given GSK573719 alone in comparison with those given the combination. Excessive salivation was observed during Phase 1 exposures in all males given GW642444 alone and in 1/3 females given either GW642444 alone or in combination with GSK573719. This finding, which was observed more frequently in animals given GW642444 alone, subsided by the completion of dosing.

During Phase 1, increased femoral pulse rates (up to 1.96X pre-dose) were seen commencing immediately after the completion of dosing in animals given GW642444, alone or in combination. Pulse rates generally peaked between 0.5 and 1 to 2 hours post dose, with a return to baseline between 8 and 23 hours 50 minutes post dose. Beyond Day 1 (Phase 1), the magnitude of the effect diminished in both sexes, with no effect evident on Day 3 (Phase 1), with the exception of an increase at 10 minutes after dosing. During Phase 2, increased femoral pulse rates (up to 2.22X pre-dose) were seen commencing immediately after the completion of dosing in animals given GSK573719 and GW642444, alone or in combination. There were no apparent differences between animals given the combination and those given GSK573719 or GW642444 alone.

Minimal to mild increases in serum cTnI were observed on the first day of dosing in Phase 1 and Phase 2 in all groups given GSK573719 or GW642444, alone or in combination. On both occasions, the greatest increases were noted between 4 and 8 hours after the completion of dosing. Throughout Phase 2, the most consistent changes were seen in animals given GW642444 alone (2/3 males and 1/3 female), although the number of animals affected was generally similar in all groups given GSK573719 or GW642444, alone or in combination. Partial to near recovery was noted 24 hours after dosing for all affected animals. A return to baseline levels was evident for all animals on Day 23. Changes in cTnI seen in animals given GW642444 alone at 174 mcg/kg/day or GSK573719 alone at 997 mcg/kg/day were not exacerbated in animals given the test articles in combination.

Focal fibrosis associated with mineral deposition was seen in the cardiac papillary muscle in one female given GSK573719/GW642444 at 190/205 mcg/kg/day and correlated with the increases in femoral pulse rate and serum cTnI seen in this animal on Day 1 of Phase 1 (up to 142X pre-dose) and Day 1 of Phase 2 (up to 5.6X pre-dose).

An increase in the severity of thymic involution/atrophy (slight to severe) was seen in animals given GSK573719 and GW642444, alone or in combination, when compared to controls. However, the incidence and severity of this finding was generally similar across groups given either test article, alone or in combination. This finding correlated with slight to moderately small thymus noted in some animals given GSK573719, alone or in combination with GW642444. Furthermore, in animals given GSK573719/GW642444 at 190/205 mcg/kg/day, lower thymus weight was seen (0.56X controls in males and 0.65X controls in females).

Group mean body weight gains were slightly greater in animals given GSK573719/GW642444 at 190/205 mcg/kg/day or GW642444 alone at 174 mcg/kg/day (+0.6 to 1.1 kg) compared to controls (-0.2 kg).

There was no notable difference in systemic exposure for GSK573719 and GW642444 when administered alone or in combination.

4 week inhalation combination toxicity study (Report 2010N109790)

GSK573719 and GW642444 (formulations containing 0 15% w/w GSK573719 and 15% w/w GW642444, and each blend contained 1% w/w magnesium stearate in lactose monohydrate) were given to beagle dogs (3/sex/group) by oroparyngeal administration once daily for 10 minutes/day for 4 weeks. The estimated achieved doses of GSK573719/GW642444 were 189/201 and 188/199

mcg/kg/day. Prior to dosing in the 4 week phase, Group 2 (GSK573719/GW642444, 189/201) received 42/47 mcg/kg/day of GSK573719/GW642444 for 3 days (tolerance phase) to induce tachyphylaxis of potential cardiovascular effects anticipated from GW642444 (a beta2 agonist) dosing. The other group (Group 3) was not dosed in Phase 1. As GW642444 at a target dose of 160 mcg/kg/day had not been given to dogs without previously undergoing a 3 day tolerance phase, one animal per sex per group was given doses of 160/160 mcg/kg/day of GSK573719/GW642444 for 3 days without previously undergoing a tolerance phase (prior to commencement of dosing of Group 3). Toxicokinetic evaluation was performed on samples collected on Day 1 and during Week 4.

Inhalation exposure of dogs to the combination of GSK573719 and GW642444 at 189/201 (Group 2, with tolerance phase) and 188/199 mcg/kg/day (Group 3, without a tolerance phase) resulted in increased heart rate (HR) up to 3.4X and 3.7X pre-dose, respectively, decreased heart rate variability (HRV), ventricular arrhythmias and increase in cTnI. On Days 1 and 2 of Phase 2, although the changes to HR and HRV were generally comparable between animals in both groups, the duration of the effects were more prolonged in animals that did not undergo the tolerance phase (Group 3). Changes in HR and HRV were accompanied by occasions of ventricular arrhythmia after the first dose in one animal that did not undergo the tolerance phase (Group 3), however, there were fewer ventricular premature contractions on Day 2 and no such events thereafter in this dog. The differences in cardiovascular parameters were marginal across the groups by Day 14 and during Week 4.

As expected, femoral pulse rates increased in Group 2 (with tolerance phase, up to 2.0X pre-dose) and Group 3 (without tolerance phase, up to 2.3X pre-dose), the magnitude of which was generally comparable across both groups and diminished with repeated dosing.

Group 3 animals (without tolerance phase) demonstrated minimally to moderately increased serum cTnI concentrations (up to 4.41 mcg/L; 735X baseline) on Day 1 and were mildly to moderately higher (up to 3.5X peak elevation at 8 hours) than those animals previously exposed during the tolerance phase (Group 2; up to 3.5X peak elevation at 8 hours). The administration of GSK573719/GW642444 in this tolerance phase was therefore considered to provide partial tolerance (tachyphylaxis) to the higher dose given in Phase 2, particularly in the females. Partial recovery of affected males and complete recovery of affected females was apparent at 23 hours 50 minutes after completion of dosing on both Day 1 of Phase 1 for Group 2 (with tolerance phase) and Day 1 of Phase 2 for Group 3 (without tolerance phase), with a return to baseline levels at all time points in the previously affected animals evident on Day 27 (with the exception of Group 3 female whose serum cTnI levels remained minimally but consistently higher than baseline). The pattern of cTnI elevation suggests that these increases are linked to release of cTnI from myocardium, correlated with the marked and sustained increases in HR as observed on Day 1.

Swelling of the neck, observed during and immediately after dosing, dry mouth and decreased tear production were recorded in both groups given the combination (swelling of the neck was also seen in control animals to a lesser extent). Overall, the frequency, incidence and/or severity of these findings, as appropriate, were greater in animals in Group 3 (without tolerance phase). Excessive salivation was also observed during and immediately after exposure in both groups given the combination. During the tolerance phase, lacrimation was also occasionally noted after dosing in animals given the combination. During Phase 2, mydriasis was seen after dosing, albeit infrequently, in Group 2 animals (with tolerance phase). These clinical observations have been observed previously in studies with GSK573719 and are considered due to pharmacology and/or the dosing procedure.

Slightly increased body weights (up to 1.09X pre-test), when compared to controls, were recorded in Group 2 animals (with tolerance phase).

Minimal increases in serum potassium (up to 1.20X pre-test), creatinine (up to 1.25X pre-test), blood urea nitrogen (up to 1.64X pre-test) were seen and the changes were generally similar in both groups

given the combination. A minimal decrease in chloride (0.95X pre-test) was noted in Group 3 females (without tolerance phase).

Absolute and relative heart weights were slightly lower (as low as 0.79X) than controls in Group 2 animals that were subjected to the 3 day tolerance phase. There was no evidence of any associated morphologic changes in the heart even with the use of Masson's trichrome stain.

There was generally no consistent difference in systemic exposure (as measured by AUC0-t and Cmax) to GSK573719 or GW642444 when administered with or without the 3 day tolerance dosing phase. Variability in systemic exposure to GSK573719 and GW642444 between individual dogs receiving the same dosage was observed across all the studies in which GSK573719 and/or GW642444 were administered alone or in combination by the oropharyngeal route. During Week 4, GSK573719 AUC0-t values were 17.3 and 18.6 ng.h/mL in males and 9.26 and 13.9 ng.h/mL in females, respectively, in both dose groups. For GW642444, AUC0-t values were 264 and 130 ng.h/mL in males and 84.4 and 187 ng.h/mL in females, respectively, in both dose groups.

13 week inhalation combination toxicity study (Report WD201006677)

GSK573719 and GW642444 (formulations containing 0, 3, 15 or 40% w/w GSK573719 and 0, 0.2, 3 or 15% w/w GW642444, and each blend contained 1% w/w magnesium stearate in lactose monohydrate) were given to beagle dogs (4/sex/group) by oroparyngeal administration once daily for 10 minutes/day for 13 weeks. The estimated achieved doses of GSK573719/GW642444 were 0/0, 1070/7.5, 23/29, 60/72, 177/183, 1048/0 and 0/180 mcg/kg/day. Prior to dosing in the 13 week phase, Group 5 (GSK573719/GW642444, 177/183) and Group 7 (0/180) received pre-treatment for 3 days (Phase 1, tolerance phase) with 44/47 mcg/kg/day or 0/49 mcg/kg/day, respectively, to induce tachyphylaxis of potential cardiovascular effects anticipated from GW642444 (a beta2 agonist) dosing. Toxicokinetic evaluation was performed on samples collected in Weeks 4, 8 and 13.

Swelling of the neck, observed during and immediately after dosing, was recorded in all groups given GSK573719 or GW642444, alone or in combination. Decreased tear production was noted in animals given GSK573719, alone or in combination with GW642444. Neck swelling and reduced tear production were seen at a greater frequency and severity in animals given GSK573719 at a target dose of 1000 mcg/kg/day, more so alone than in combination with GW642444.

During Phase 1, increased femoral pulse rates (up to 2.18X pre-dose) were seen commencing immediately after the completion of dosing in animals given GW642444, alone or in combination with GSK573719. Pulse rates generally peaked within 1 hour after the completion of dosing, with a return to baseline between 4 and 23 hours 50 minutes post dose. During Phase 2, increased femoral pulse rates (up to 2.23X pre-dose) were seen commencing immediately after the completion of dosing in animals given GW642444 alone or in combination with GSK573719. The greatest effect on pulse rates was seen in animals given GSK573719/GW642444 at 177/183 mcg/kg/day. The effect on pulse rates diminished (tachyphylaxis) over the duration of the study in both sexes given either test article, alone or in combination. ECG measurements taken immediately following exposure during Week 13 confirmed increased heart rates (HR) in all affected groups. In contrast with pre-test, where all animals showed respiratory sinus arrhythmia (RSA), RSA was not observed pre- or post dose during Week 13 in animals given GSK573719 at a target dose of 1000 mcg/kg/day, alone or in combination with GW642444.

The measured serum cTnI can provide indication of onset of tolerance (tachyphylaxis) to animals given GW642444 alone or in combination with GSK573719 during Phases 1 and 2. Evidence of tachyphylaxis was noted in 2 males given GW642444 at 49 then 180 mcg/kg/day during Phase 1 then 2, respectively, as demonstrated by increases in serum cTnI concentration during Phase 1, but no further response during Phase 2. However, one male who did not demonstrate an increase during Phase 1 did show an increase in cTnI concentration during Phase 2. All males remained virtually unresponsive

when given GSK573719 and GW642444 in combination during Phase 1 and 2. Evidence of tachyphylaxis seen in the females given GSK573719 and GW642444 at 44/47 mcg/kg/day during Phase 1 followed by 177/183 mcg/kg/day during Phase 2 as demonstrated by all 4 animals showing an increase in cTnI during Phase 1 but only one animal showing an increase in Phase 2. When GW642444 alone at 49 then 180 mcg/kg/day was administered to females, 2/4 showed an increase in cTnI during Phase 1 but 3 showed an increase during Phase 2 showing tachyphylaxis had not developed. More so than the males, the females appeared to be more sensitive to administration of GSK573719 in combination with GW642444. This was evidenced by the increased cTnI levels in females given GSK573719 and GW642444 at 23/29 mcg/kg/day, effects which were not seen in concurrent males. The increases in serum cTnI noted in this study were considered to reflect minimal to mild cardiomyocyte injury, a result of the pharmacology of the test articles.

Increased severity and incidence of mixed inflammatory cell infiltrates in the laryngeal mucosa was observed microscopically in males given GSK573719/GW642444 at 1070/7.5 mcg/kg/day or 177/183 mcg/kg/day, and in females given GSK573719 alone at 1040 mcg/kg/day. This change is indicative of a minor irritant effect of treatment.

Subacute to chronic inflammation of the lungs was observed in 1 of 4 males given GSK573719/GW642444 at 1070/7.5 mcg/kg/day. This change is considered to be secondary to inhaled exogenous material in this animal in which the mucociliary defence mechanism might have been compromised by the antimuscarinic effect of GSK573719.

Group mean body weight gains were slightly greater in animals given GW642444 at ≥7.5 mcg/kg/day (1.1 to 2.6 kg), alone or in combination with GSK573719, when compared to controls (0.7 to 0.8 kg). In females, this correlated with an increase in food consumption.

Transient increases in serum potassium (up to 1.21X pre-test at Week 4) and in phosphorus (males only; up to 1.19X at Week 4) were seen in animals given GW642444, alone or in combination with GSK573719. Increases in glutamate dehydrogenase (up to 1.51X controls at Week 13) and in serum blood urea nitrogen levels (up to 1.71X) were also seen in animals given GSK573719 or GW642444, alone or in combination.

Generally, there were minor differences in the magnitude of change between groups given GSK573719 or GW642444 alone and those given the test articles in combination. Decreased prostate weights were seen in males given GSK573719/GW642444 at 177/183 and 0/180 mcg/kg/day. Reductions in heart and thymus weights were noted in females given GSK573719 or GW642444, alone or in combination.

The NOAEL for the 1:1 ratio GSK573719/GW642444 combination is considered to be 177/183 mcg/kg/day GSK573719/GW642444. These doses correspond to mean DNAUCs of 9.71/192 ng.h/mL and DNCmax of 6.20/86.8 ng/mL for GSK573719 and GW642444, respectively (males and females combined). There was no notable difference in systemic exposure for GSK573719 and GW642444 when administered alone or in combination.

Genotoxicity

Umeclidinium bromide (GSK573719)

Table 7. Genotoxicity studies performed with GSK273719

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria WD2005/00750 GLP	*S. thyphimurium* strains (TA98, TA100, TA1535 & TA1537) *E.coli* strain (WP2 uvrA pkM101)	0 to 2500 (*S. thyphimurium-limited by toxicity*)/5000 (*E.coli*) mcg/plate (in DMSO) +/- S9	Negative.
Gene mutations in mammalian cells WD2005/00751 GLP	Mouse lymphoma assay L5178Y cells at the TK+/- locus	10 to 225 mcg/mL (in DMSO) +/- S9	Negative. The maximum concentration tested was limited by solubility to 200 mg/mL for the 3 hour treatment in the presence of S9-mix and toxicity to 225 and 110 mcg/mL for the 3 hour and 24 hour treatments in the absence of S9-mix, respectively.
Chromosomal aberrations in vivo WD2005/01079 GLP	Rat, micronuclei in bone marrow	10, 20 mg/kg/day Intravenous	Negative. Dilated pupils (pharmacology) were observed in males at 10 mg/kg/day and above. The highest dose tested was the maximum dose limited by solubility.

GSK573719 showed no genotoxic potential in the standard battery of in vitro and in vivo tests.

An assessment of the route of synthesis for GSK573719 (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.

Vilanterol (GW642444)

Table 8. Genotoxicity studies performed with GW642444

Type of test / study ID / GLP	Test system	Concentrations / Concentration range / Metabolising system	Results Positive / negative / equivocal
Gene mutations in bacteria WD2003/01017/00 GLP	*S. thyphimurium* strains (TA98, TA100, TA1535 & TA1537) and *E.coli* strain (WP2uvrA (pKM101))	0 to 5000 μg / plate +/- S9	Negative
Mammalian Cell Mutation Test WD2003/01463/00 GLP	L5178Y mouse lymphoma assay	0-35 mcg/mL +/- S9	Positive increase in mutation frequency observed in the presence of S9-mix
Syrian hamster embryo (SHE) cell transformation assay WD2002/00528/00 GLP	Syrian hamster embryo cells	0-32.5 mcg/kg 7 days continuous exposure	GW642444 did not induce morphological transformation in a standard 7 day continuous exposure SHE cell transformation assay. The maximum examined concentration was limited by cytotoxicity.
Micronucleus Test WD2003/01411/00 GLP	Polychromatic erythrocytes (PCE)	0-12.5 mg/kg	Mean GW642444X concentration 15 minutes after administration at 12.5 mg/kg/day = 967.5 ng/mL GW642444 produced no evidence of clastogenicity in a bone marrow micronucleus assay following intravenous doses of 7800 and 12500 mcg/kg, approximately 24

			hours apart.
Unscheduled DNA synthesis (UDS) WD2004/01713/00 GLP	Primary hepatocyte Cultures from Sprague Dawley rats	0-12.5 mg/kg/day	GW642444 did not induce UDS in the hepatocytes of male rats following two intravenous doses of 3750 or 12500 mcg/kg, 14 hours apart.
GI179710X: High Throughput fluctuation test WD2005/00325/00 GLP	Reverse mutation in bacterial cells (S. thyphimurium strains TA98 & TA100)	0, 7.81, 15.63, 31.25, 62.5, 125, 250, 500, 1000 mcg/mL	GI179710X was shown to be non-mutagenic in the absence and presence of an in vitro metabolic activation system (rat liver S9-mix).
GI179710X: L5178Y mammalian cell mutation screen WD2005/00277/00 GLP	L5178Y mouse lymphoma assay – Forward mutation in mammalian cells at the tk locus	0, 19.53, 39.06, 78.13, 80, 100, 120, 156.25 mcg/mL	GI179710X is non-mutagenic in the mouse lymphoma test system in the absence and presence of an in vitro metabolic activation system (rat liver S9-mix).

GW642444 (as the α-phenyl cinnamate salt) was not mutagenic in a bacterial mutagenicity assay at concentrations up to ≥1500 mcg/plate, as well as did not induce morphological transformation in the Syrian hamster embryo cell transformation assay up to 32.5 mcg/mL (limited by cytotoxicity) and was not genotoxic *in vivo* in either the rat micronucleus assay or the unscheduled DNA synthesis assay using rat hepatocytes at maximum tolerated intravenous doses that produced plasma concentrations >20000 times (Cmax) higher than those seen in humans. However, although GW642444 (as the α-phenyl cinnamate salt) was not genotoxic in the *in vitro* mouse lymphoma assay in the absence of S9-mix at concentrations up to 30 and 8 mcg/mL, GW642444 (as the α-phenyl cinnamate salt) did induce an equivocal, non-reproducible response in the presence of S9-mix at highly cytotoxic concentrations (≤20% Relative Total Growth). The weight of evidence from the all data indicates that GW642444 (as the α-phenyl cinnamate salt) does not represent a genotoxic hazard to humans. On the other hand, GI179710 did not cause gene mutation in a bacterial mutagenicity test or chromosomal damage in a mammalian *in vitro* assay. The concentrations of GI179710 tested alone represent considerably higher levels than would have been achieved if tested as part of GW642444 (as the triphenylacetate salt). Since both GW642444 (parent) and GI179710 (triphenylacetic acid) were not genotoxic, it is acceptable that the commercial compound GW642444M (the triphenylacetate salt of GW642444) is considered not to represent a genotoxic hazard to humans.

Umeclidinium bromide/vilanterol

No genotoxicity studies have been performed for the combination umeclidinium bromide/vilanterol which is considered acceptable by the CHMP.

Carcinogenicity

Umeclidinium bromide (GSK573719)

Mouse carcinogenicity study (Report 2012N1316646)

The carcinogenic potential of GSK573719 was assessed in a 2 year inhalation repeat dose study in which groups of CD-1 mice (75/sex/group) were administered estimated achieved doses of, for males, 0 (vehicle), 58.6, 188 or 533 mcg/kg/day once daily (60 minutes/day) for Weeks 1 to 66 and then 0 (vehicle), 32.2, 102 or 295 mcg/kg/day once daily (30 minutes/day) from Week 67 onward; and for females, 0 (vehicle), 20.8, 63.7 or 200 mcg/kg/day once daily (60 minutes/day) throughout. Fifteen animals/sex were added to the vehicle control group and 45 animals/sex were added to each of the treated groups for toxicokinetic evaluation in Weeks 4 and 26 at the initial doses (60 minutes exposure/day). An additional 9 males were added to the vehicle control group and 24 males were added to each of the treated groups for toxicokinetic evaluation following 4 weeks of dosing at the reduced doses (30 minutes exposure/day).

There were no adverse effects of GSK573719 on survival of male or female mice. At the end of Week 104 the number of animals surviving was 53, 40, 44 and 53 in males given 0, 58.6/32. 2, 188/102 and 533/295 mcg/kg/day, respectively, and 40, 59, 39 and 45 in females given 0, 20.8, 63.7 and 200 mcg/kg/day, respectively. There were no GSK573719-related neoplastic changes.

Body weight gain was lower than controls in all male groups given GSK573719 over Weeks 0 to 66 (0.93X, 0.97X and 0.76X control in males given 58.6, 188 and 533 mcg/kg/day, respectively); there may be some evidence of recovery following the lowering of the dose levels. Food consumption was lower in Week 1 in all male treated groups (0.85X, 0.85X and 0.87X control in males given 58.6, 188 and 533 mcg/kg/day, respectively), and retained lower throughout in males given 533/295 mcg/kg/day (0.94X control).

An increase in incidence but not severity of bilateral posterior lens opacity in Week 103 for males (9, 12, 15 and 27 affected in males given 0, 58.6/32.2, 188/102 and 533/295 mcg/kg/day, respectively) and females given 20.8 or 200 mcg/kg/day (35 and 27 females affected, respectively, compared to 16 in the control group) was considered unlikely to be related to treatment as the incidence was within background ranges for males and showed no dose relationship for females, and showed no correlating histopathological lesions.

GSK573719 systemic exposure (DNAUC0-t) to male mice based on combined values from Weeks 4 and 26 were 4.15, 1.64 and 12.2 ng.h/mL at 58.6, 188 and 533 mcg/kg/day, respectively (data only from Week 4 at 58.6 mcg/kg/day). GSK573719 systemic exposure (DNAUC0-t) to female mice based on combined values from Weeks 4 and 26 were 1.01, 4.31 and 8.26 at 20.8, 63.7 and 200 mcg/kg/day, respectively (data only from Week 4 at 20.8 mcg/kg/day). GSK573719 systemic exposure (DNAUC0-t) to male mice at Week 76 (4 weeks at revised doses) were 1.53, 3.28 and 8.21 ng.h/mL at 32.2, 102 and 295 mcg/kg/day, respectively.

Rat carcinogenicity study (2012N121619)

GSK573719 was given to Sprague Dawley rats (65/sex/group) by snout-only inhalation at estimated achieved doses of 0 (vehicle), 30.1, 101 or 276 mcg/kg/day once daily (60 minutes/day) for Weeks 1 to 72 and then 0 (vehicle), 14.7, 45.0 or 137 mcg/kg/day once daily (30 minutes/day) from Week 73 to 104 owing to significant dose related decreases in body weight. Nine animals/sex were added at each dose level and to the control group for toxicokinetic evaluations. An additional 9 animals/sex were added to each group for toxicokinetic evaluation following 4 weeks of dosing at the lower doses.

There were no adverse effects of GSK573719 on survival of male or female rats. Increased survival was noted for males and females given 276/137 mcg/kg/day over the 104 weeks of treatment (72% and 62% survival for males and females, respectively, compared with 58% and 38% for control males and females, respectively).

During Weeks 0 to 72, there was a statistically significant, dose-related decrease in body weight gain in males and females at all dose levels ≥30.1 mcg/kg/day (down to 0.84X control and 0.75X control at 276 mcg/kg/day for males and females, respectively). This was accompanied by a minimal (statistically significant in females in all treated groups) reduction in food consumption (down to 0.97X and 0.94X at 276 mcg/kg/day in males and females, respectively, over Weeks 1 to 72). As a result of the reduction in body weight gain, the dose levels were reduced in all treated groups from Week 73. In males, the dose reduction prevented any further reduction in body weight gain such that by the end of the study, the overall reduction in body weight gain remained similar to that at Weeks 0 to 72 (0.84X control for males at 276/137 mcg/kg/day). In females, the dose reduction had a positive influence on body weight gain such that by the end of the study, the overall reduction in body weight gain had improved for doses of 30.1/14.7 and 101/45.0 mcg/kg/day (up to 0.92X control) and had prevented any further reduction in body weight gain at 276/137 mcg/kg/day (0.78X control). Food consumption remained consistent such that by the end of the study, there remained a minimal (statistically

significant) reduction over Weeks 1 to 104 (0.97X control and 0.94X control for males and females, respectively, at 276/137 mcg/kg/day).

A higher incidence and severity of increased eosinophilic inclusions in the olfactory epithelium in the nasal turbinates were seen in males and females given 276/137 mcg/kg/day.

There were no GSK573719-related neoplastic changes. The following neoplastic lesions were statistically significant in one test (but not in others): benign granular cell tumour in the brain in males and benign basal cell tumour in the skin in females. These tumours although statistically significant in some tests were considered not to be related to treatment with GSK573719. The range and distribution of neoplastic lesions seen in this study was considered to be similar to those seen previously in this strain of rat in this laboratory.

GSK573719 systemic exposure (DNAUC0-t) to male rats based on combined values from Weeks 4 and 26 were 3.25 and 13.5 ng.h/mL at 101 and 276 mcg/kg/day, respectively (insufficient data to define AUC at 30.1 mcg/kg/day). GSK573719 systemic exposure (DNAUC0-t) to female rats based on combined values from Weeks 4 and 26 were 0.451, 84 and 13.5 ng.h/mL at 30.1, 101 and 276 mcg/kg/day, respectively.

GSK573719 systemic exposure (DNAUC0-t) to male rats at Week 76 (4 weeks at revised doses) were 0.921, 2.10 and 6.26 ng.h/mL at 14.7, 45.0 and 137 mcg/kg/day, respectively. GSK573719 systemic exposure (DNAUC0-t) to female rats at Week 76 (4 weeks at revised doses) were 0.353, 2.09 and 7.23 ng.h/mL at 14.7, 45.0 and 137 mcg/kg/day, respectively.

Vilanterol (GW642444)

Mouse carcinogenicity study

The carcinogenic potential of GW64244 was assessed in a 2 year inhalation repeat dose study in which groups of mice (60/sex/group) were administered estimated achieved doses of 0 (vehicle, 2 groups), 1.0, 3.2, 8.6 mcg/kg/day in lactose once daily (1 hour/day). The original design required 60 main study animals/sex/group and 66 toxicokinetic animals/sex/group. Due to the high mortality that occurred across all groups during the first few months of the study, when compared with historical control data, 24 toxicokinetic animals/sex/group were reassigned as main study animals; these animals had not previously been subject to any blood sampling. All data related to these animals have been combined with the main study animals and is reported together. The total group size was therefore 84 animals/sex/group in the main study and 42 animals/sex/group in the toxicokinetic study.

High mortality occurred across all groups when compared with historical control data due to swollen abdomen which was believed to be associated with the design of the restraint tube, possibly leading to air swallowing. As a result the tube end caps were changed on several occasions during the study, following which there was a marked reduction in the incidence of swollen abdomen. Despite these mortalities, a sufficient number of animals survived to the end of the study to assess the carcinogenic potential of GW642444.

The most common cause of death in both sexes was gaseous distension of the GIT (see above). Other common causes of death included lymphoreticular neoplasms (both sexes), urogenital tract infection/obstruction (primarily in males) and skin ulceration/infection, including pododermatitis and tail infection (both sexes). All conditions occurred in control and treated groups, and showed no evidence of a dose-response or clear association with GW642444 administration.

Administration of GW642444 was associated with test article-related neoplastic and non-neoplastic proliferative changes in the ovaries and uterus and non-neoplastic changes in the ovaries, uterus and vagina of females and in the nasal cavity of both sexes. In the ovary, an increased incidence of sex cord stromal hypertrophy/hyperplasia was seen at all doses and an increased incidence of tubulostromal hyperplasia, sex cord tumors and ovarian cysts (and ovarian compression due to cysts)

at ≥62 mcg/kg/day. An increased incidence of tubulostromal adenomas was seen at 29500 mcg/kg/day. In the uterus, an increased incidence and severity of cystic endometrial hyperplasia was seen at all doses, accompanied by endometrial glandular squamous metaplasia in a few females at 6150 or 29500 mcg/kg/day. Myometrial hypertrophy/hyperplasia and an increased incidence of leiomyoma and/or leiomyosarcoma were seen at ≥62 mcg/kg/day. In the vagina, a slight increased incidence of anestrus appearance (with/without mucin) was seen in at all doses. In the nasal cavity, an increased incidence and/or severity of luminal inflammatory cells/cell debris was seen in females at all doses and olfactory degenerative changes were seen in both sexes at ≥62 mcg/kg/day. The findings were minimal or slight in severity at doses up to 615 mcg/kg/day, but were more notably increased in incidence and severity in both sexes given ≥6150 mcg/kg/day.

GW642444 systemic exposure (AUC0-t) to male and female mice based on combined values from Weeks 4 and 26 were 7.93, 34.9, 135, 920 and 3591 ng.h/mL at 6.4, 62, 615, 6150 or 29500 mcg/kg/day, respectively. Following treatment with GW642666 systemic exposure was also demonstrated to GI17910 (counterion) and GSK932009 and GW630200 (the major human metabolites).

Rat carcinogenicity study

GW642444 was given to Sprague Dawley rats (60/sex/group) at estimated achieved doses of 0, 10.5, 84.4, 223 and 657 mcg/kg/day for 60 minutes once daily for 85 weeks by nose-only inhalation. Due to increased mortality dosing was stopped for females given 223 and 657 mcg/kg/day at Week 85 (26 and 23 animals surviving in these groups, respectively). These females remained on study without further treatment until group survival fell to 15 (Weeks 95 or 96, respectively) at which time they were electively killed. The doses of the remaining females were reduced from Week 86 to 3.47 (from 10.5) and 28.2 (from 84.4) mcg/kg/day by decreasing the daily exposure duration from 60 to 20 minutes for the remainder of the study. Females at 84.4/28.2 mcg/kg/day were terminated in Week 95 due to survival reaching 15. Control females and females given 10.5/3.47 mcg/kg/day were killed in Week 104. All males were electively killed in Week 101 when the number of survivors in the control group fell to less than 20.

Early mortality associated with pituitary neoplasms was observed in male rats given ≥223 mcg/kg/day GW642444 and females given ≥84.4/28.2 mcg/kg/day. In both sexes this finding was proposed to be the result of pharmacologically-mediated increased body weight gain in the early stages of the study and increased food consumption. In females hormonal imbalance resulting from pharmacologically-mediated, dose related, increase incidence and severity (size) of ovarian follicular cysts may have contributed to the reduced latency of the pituitary findings.

An increased incidence of mesovarian smooth muscle hyperplasia/hypertrophy and of mesovarian leiomyomata was seen in females given ≥84.4/28.2 mcg/kg/day. The findings were present in decedent females and those surviving to terminal kill and are considered a consequence of prolonged β2-adrenergic stimulation.

GW642444 systemic exposure (AUC0-t) to male rats based on combined values from Weeks 4 and 26 were 0.420, 8.52, 16.9 and 51.8 ng.h/mL at 10.5, 84.4, 223 and 657 mcg/kg/day, respectively. GW642444 systemic exposure (AUC0-t) to female rats based on combined values from Weeks 4 and 26 and extrapolating to lowered doses were 0.215/0.0711, 9.72/3.25, 18.7 and 55.7 ng.h/mL at 10.5/3.47, 84.4/28.2, 223 and 657 mcg/kg/day, respectively. Following treatment with GW642444, systemic exposure was also demonstrated to GI17910 (counterion) and the major human metabolites (GSK932009 and GW630200).

Umeclidinium bromide/vilanterol

The fixed dose combination of umeclidinium bromide/vilanterol contains two compounds assessed as non carcinogenic. The carcinogenic potential is thus fully assessed. Hence other studies assessing carcinogenic potential with the combination are not needed in accordance with the requirements of the

"Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products "(EMEA/CHMP/SWP/258498/2005).

Reproduction Toxicity

Fertility and early embryonic development

Umeclidinium bromide (GSK573719)

Male fertility (Report CD2010/00187)

GSK573719 was administered subcutaneously to male Sprague Dawley rats (25/group) at dose levels of 30, 60 or 180 mcg/kg/day once daily for 49 to 53 days. After 14 days of treatment, males were co-habited 1:1 with untreated females. Mated females were separated from the males and considered to be on Day 0 pc. Mated females and their litters were euthanized on Day 20 pc.

There were no GW573719-related deaths or clinical observations. Statistically significant decreases in body weight gain and food consumption were seen intermittently in the high dose group throughout the study. A statistically significant decrease in food consumption was also seen between Study Days 36 to 43 in the 30 mcg/kg/day group.

There was no effect on days needed for mating (2.0 to 3.3 days), mating incidence (100%), pregnancy incidence (96% to 100%) or organ weights at any dose. There was no GSK573719-related effect on mean numbers of corpora lutea, implantations, resorptions, pre-implantation loss, post-implantation loss, total live fetuses, percent live males, placental morphology or on uterus weight at any dose tested. There was no GSK573719-related effect on fetal body weight at any dose. There were no GSK573719-related fetal malformations or variations at any dose. Therefore, the NOAEL for mating, fertility and gonadal function in male rats was 180 mcg/kg/day.

Toxicokinetic data from the 14 day subcutaneous toxicokinetic and tolerability study in male rats shows that systemic exposure achieved at the NOAEL was 31.1 ng.h/mL and 31.4 ng/mL for AUC and C_{max} (Day 14), respectively

Female fertility and early embryonic development

GSK573719 (3.37, 29.1, 100 or 294 mcg/kg/day) was administered by snout-only inhalation to female Sprague Dawley rats (25/group) (Report WD2007/00763). Females were treated daily for 2 weeks before pairing, throughout pairing and until Day 7 after mating. Mated females and their litters were euthanized on Day 20 post coitum (pc).

There were 3 deaths during the pre-mating period, none of which was considered GSK573719-related. One female given 29.1 mcg/kg/day collapsed and died following smearing on Day 15. Two females, one each at 100 and 294 mcg/kg/day, died during exposure (related to the dosing procedure).

There were no adverse effects on body weight, food consumption, clinical signs or macroscopic necropsy findings. Mating performance (assessed on the basis of regularity of estrous cycles), pre-coital interval or fertility were unaffected by treatment. There were no adverse effects on gravid uterus, litter or fetal weights. A slightly higher mean fetal weight (1.06X control) at 294 mcg/kg/day was considered not adverse in the absence of any other changes.

Based on these findings, the NOAEL for effects on female fertility and early embryonic development was the highest dose tested (294 mcg/kg/day). Based on data from the 13 week inhalation study in (non-pregnant) female rats, exposure to GSK573719 in terms of mean $DNAUC_{0-t}$ and DNC_{max} at a similar dose (288 mcg/kg/day) was 16.2 ng.h/mL and 3.79 ng/mL, respectively (Report WD2007/02012).

GW642444

Rat

Male fertility

GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to male Sprague Dawley rats (25/group) at estimated achieved doses of 0 (vehicle), 62, 824 or 31508 mcg/kg/day (4 or 40% w/w blend in lactose) once daily for 60 minutes by nose only inhalation for 54 to 57 days. After 14 days of treatment, treated males were co-habited 1:1 with untreated females. Mated females were separated from the males and considered to be on Day 0 post coitum (pc). Mated females and their litters were euthanized on Day 20 pc.

Paternal effects were evidenced at 824 and 31508 mcg/kg/day by increased body weight gain and post dosing clinical signs (salivation, periorbital fur staining and/or wetness of the muzzle and lower jaw associated with salivation). Mating, fertility and conception rate were unaffected. Slight organ weight differences in epididymis ventral prostate and seminal vesicles at 824 and 31508 mcg/kg/day were inconsequential to mating or fertility and therefore not considered adverse effects. The NOAEL for male fertility was considered to be ≥31508 mcg/kg/day.

Female fertility and early embryonic development

The effects of GW642444 on mating and fertility and on early embryonic development to implantation were assessed in a study in Sprague Dawley rats. GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to mated females (25/group) at estimated achieved doses of 0 (vehicle), 49.4 or 664 mcg/kg/day (as a 4% blend in lactose) or 37112 mcg/kg/day (as a 40% blend in lactose) via snout only inhalation (1 hour) for 15 days before co-habitation, during co-habitation with untreated males (1 to 12 days) and on Days 0 to 6 pc. Mated females and their litters were euthanized on Day 20 pc.

Evidence of maternal effects was noted at ≥49.4 mcg/kg/day as indicated by increased body weight and body weight gains. There was no evidence of an adverse effect on female fertility or early embryonic development. Based on these results, the NOAEL for effects on female fertility and early embryonic development in this study was considered to be ≥37112 mcg/kg/day.

Umeclidinium bromide/vilanterol

No fertility and early embryonic development studies have been performed for the combination umeclidinium bromide/vilanterol which is considered acceptable by the CHMP.

Embryo-fœtal development

Umeclidinium bromide (GSK573719)

Rat

GSK573719 was administered as a dry powder formulation (0.5% w/w with 1% w/w magnesium stearate in lactose monohydrate) to mated female Sprague Dawley rats (22/group) at estimated achieved doses of 0 (vehicle), 31.7, 96.9 or 278 mcg/kg/day by snout-only inhalation (1-hour) on Days 6 to 17 pc (Report WD2007/00764). Mated females and their litters were euthanised on Day 21 pc.

GSK573719-related decreases in maternal body weight gain were evident at doses ≥96.9 mcg/kg/day. There were no adverse effects on numbers of corpora lutea, implantations, resorptions or live and dead fetuses per litter, gravid uterine weight or placental morphology. There was no test article-related effect on fetal body weight or morphology. There were no adverse effects on the pregnant female or embryofetal survival and development. The NOAEL for embryofetal development in the rat was therefore identified in this study as 278 mcg/kg/day. Based on data from the 13 week inhalation study

in (non-pregnant) female rats, exposure to GSK573719 in terms of mean $DNAUC_{0-t}$ and DNC_{max} at a similar dose (288 mcg/kg/day) was 16.2 ng.h/mL and 3.79 ng/mL, respectively (Report WD2007/02012).

Rabbit

Dose range finding and preliminary EFD study (Report WD2006/03186)

GSK573719 was administered as a dry powder formulation (40% w/w with magnesium stearate 1% w/w in lactose monohydrate) to mated and unmated female Sprague Dawley rats (5 and 4/group respectively) at estimated achieved doses of 0 (vehicle), 128, 257 or 1820 mcg/kg/day or 48.2 or 305 mcg/kg/day respectively by snout-only inhalation (1-hour) for 13 days. The unmated animals were sacrificed on Day 14; the mated animals were sacrificed on Day 29 pc.

In the unmated animals, there were no GSK573719-related clinical signs. Treatment at 1820 mcg/kg/day was associated with a treatment-related body weight loss (mean 0.18 kg) during the dosing period. There was no conclusive effect of treatment on body weight at lower doses. There were treatment-related reductions in mean food consumption in all treated groups relative to pre-dose consumption, with the reduction more marked at 1820 mcg/kg/day than at lower doses.

In the mated animals, there were no GSK573719-related clinical signs or apparent effect on maternal body weight gain. At the high dose (305 mcg/kg/day) there was a GSK573719-related decrease in mean food consumption. Macroscopic examination revealed no treatment-related findings in the dams. There was no effect of treatment on embryofetal survival, since the mean live litter size in rabbits receiving 305 mcg/kg/day was similar to controls. Mean fetal weights in the test article-treated groups were slightly lower than controls. However, review of the individual litter values did not reveal any conclusive effect of treatment. One fetus from a dam receiving 42.8 mcg/kg/day was observed to have an irregular fissure of the cranium (left), with exposed neural tissue, open eyelids (right) and a partially restricted oral cavity. However, in the absence of any fetal abnormalities in rabbits receiving 305 mcg/kg/day, these abnormalities were considered not to be related to GSK573719.

On Day 11, mean $DNAUC_{0-t}$ values were 0.668 and 16.3 ng.h/mL for GSK573719 doses of 48.2 and 305 mcg/kg/day, respectively.

Pivotal EFD studies

GSK573719 was administered as a dry powder formulation (2% w/w with 1% w/w magnesium stearate in lactose monohydrate) to mated female New Zealand white rabbits (22/group) at estimated achieved doses of 0 (control), 28.5, 88.9 or 306 mcg/kg/day by snout-only inhalation (1-hour) on Days 7 to 19 pc (Report WD2007/00762). Mated females and their litters were euthanised on Day 29 pc. There were 3 deaths, none of which were considered GSK573719-related. One female at 306 mcg/kg/day aborted her litter on Day 19 pc. One female at 88.9 mcg/kg/day was sacrificed on Day 28 pc due to poor condition. A second female at 88.9 mcg/kg/day was sacrificed on Day 28 pc due to clinical signs, indicating a possible abortion, although there was no evidence at necropsy and uterine examination of abortion. Overall mean food consumption during the treatment period was slightly lower than controls in all treated groups. There were no adverse effects on embryofetal survival, weight or development. The NOAEL for embryofetal development in the rabbit was 306 mcg/kg/day, the highest dose tested. At the NOAEL, on Day 11 mean $DNAUC_{0-t}$ and DNC_{max} values were 10.9 and 1.78 ng/mL, respectively.

GSK573719 (0, 40.0, 100 or 180 mcg/kg/day) was administered subcutaneously to female New Zealand white rabbits (22/group) once daily on Days 7 to 19 pc (Report CD2010/00253). Mated females and their litters were euthanized on Day 29 pc. There were no GSK573719-related deaths. There were GSK573719-related maternal fecal observations (soft feces and decreased fecal output at

180 mcg/kg/day, elongated feces at all doses) both during the treatment period and after treatment ceased. There were no GSK573719-related effects on maternal body weight. At 100 and 180 mcg/kg/day, there was a statistically significant decrease in maternal food consumption. There was no GSK573719-related effect on mean numbers of corpora lutea or implantations, resorptions, pre-implantation loss, post-implantation loss, total live fetuses, percent live males, placental morphology or on uterus weight at any dose tested. There was no GSK573719-related effect on fetal body weight at any dose. There were no GSK573719-related fetal malformations or variations at any dose. There were no effects on embryofetal development, therefore, the NOAEL for rabbit embryofetal development is 180 mcg/kg/day, the highest dose tested. At the NOAEL, mean AUC_{0-t} and C_{max} values were 61.4 ng.h/mL and 65.4 ng/mL, respectively.

Vilanterol (GW642444)

Rat

Embryofetal development studies

GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to mated female Sprague Dawley rats (22/group) at estimated achieved doses of 0 (vehicle), 45.4 or 613 mcg/kg/day (as a 4% blend in lactose) or 33733 mcg/kg/day (as a 40% blend in lactose) via snout only inhalation (1 hour) on Days 6 to 17 pc. Mated females and their litters were euthanized on Day 21 pc.

Maternal effects at ≥613 mcg/kg/day was evidenced by substantially increased body weight gains and increased or decreased food consumption. There was no evidence of an adverse effect on pregnancy (numbers of corpora lutea, implantation sites, live fetuses and dead fetuses, resorptions, sex ratio, and the pre and post implantation losses) or on embryofetal development (no major malformations nor minor external, visceral or skeletal anomalies). Based on these results, the developmental NOAEL on this study was considered to be >33733 mcg/kg/day.

Rabbit

Dose ranging and pivotal inhalation embryofetal development studies

A study was performed to establish tolerated doses in the non-pregnant rabbit, to assess the effects on progress and outcome of pregnancy in rabbits, and to establish suitable doses for a main embryo-fetal development study. GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation (40% (w/w) blend in lactose) to groups of non-pregnant (4/group) and pregnant (5/group) New Zealand white rabbits, at estimated achieved doses of 447, 1350, 5120, 19600 (non-pregnant) and 0, 5330 and 18800 mcg/kg/day (pregnant), via snout only inhalation (1 hour) for up to 13 days which in the pregnant animals was from Days 7 to 19 pc.

Treatment with GW642444 at doses up to 19600 mcg/kg/day was well tolerated by unmated female rabbits following snout-only inhalation administration for 1 hour per day for up to 13 days. Treatment of pregnant female rabbits from Days 7 to 19 pc at 5330 or 18800 mcg/kg/day was associated with lower group mean food consumption during the first 2 days of treatment (Days 7 to 8 pc). Unacceptable levels of intrauterine deaths were noted at 18800 mcg/kg/day. Open eyelid was evident in fetuses at 5330 and 18800 mcg/kg/day, limb, snout and palate malformations were also noted at 18800 mcg/kg/day.

Toxicokinetic evaluation on Day 5 of treatment (Day 11 post coitum) at 5330 mcg/kg/day revealed study exposure normalised AUC0-t of 244 ng.h/mL and Cmax of 110 ng/mL

In the main pivotal study, GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation (7% (w/w) blend in lactose) to mated New Zealand white rabbits (22/group)

at estimated achieved doses of 0 (vehicle), 62.7, 591 and 5740 mcg/kg/day via snout only inhalation (1 hour) from Days 7 to 19 pc. Pregnant rabbits and their litters were killed on Day 29 pc.

Mean fetal weight was low at 5740 mcg/kg/day. GW642444 at 5740 mcg/kg/day caused open/partially open eyelids/punctate opening, cleft palate and forelimb flexure/malrotation. Also, at 62.7 mcg/kg/day there were open/partially open eyelids/punctuate opening and cleft palate. A dose relationship was not established (these abnormalities were not found at 591 mcg/kg/day), suggesting the aetiology of the findings at the low dose may be multifactoral (test article and other factors). In addition, there were higher incidences of fetuses/litters with bridges of ossification/partially fused/fused sternebral centres, small misshapen interparietals, enlarged anterior/posterior fontanelle, incomplete ossification of the 5th sternebrae, epiphyses and metacarpals/phalanges and an associated costal cartilage abnormality in the 5740 mcg/kg/day group compared with controls, which may reflect the lower mean fetal weight in this group. A clear developmental no observable adverse effect level (NOAEL) for GW642444M was not identified in this study. The exposure (normalised AUC and Cmax) at the lowest dose of 62.7 mcg/kg/day were 3.76 ng.h/mL and 2.07 ng/mL, respectively.

Dose ranging and pivotal subcutaneous embryofetal development studies

Subcutaneous studies were conducted in the rabbit in order to determine whether the low incidence of developmental effects observed following inhalation administration of GW642444 could be reproduced. In a dose range finding study, GW642444 (as the triphenylacetate salt, GW642444M) was administered at doses of 20, 200 and 2000 mcg/kg/day, via subcutaneous injection (formulated as a solution in 20/80 PEG400/8% 2HPBC), to pregnant New Zealand white rabbits (4/group) from Day 7 to 11 pc. Mated females and their litters were euthanized on Day 12 pc. GW642444 produced no effects on clinical signs, body weight or food consumption and all animals were pregnant at scheduled euthanasia. At the highest tolerated dose of 2000 mcg/kg/day AUC0-t and Cmax values were 2160 mcg.h/mL and 408 mcg/mL, respectively, for GW642444.

In the main pivotal study, GW642444 (as the triphenylacetate salt, GW642444M) was administered to pregnant New Zealand white rabbits (22/group) at doses of 0 (vehicle alone), 3, 7, 30 or 300 mcg/kg/day, via subcutaneous injection (formulated as a solution in 20/80 PEG400/8% 2HPBC), from Days 7 to 19 pc. Mated females and their litters were euthanized on Day 29 pc.

Maternal body weights were increased at 30 and 300 mcg/kg/day, while food consumption was decreased at 300 mcg/kg/day at the end of the drug treatment period. Fetal body weights were reduced at 300 mcg/kg/day and fetal skeletal variations (less than the expected number of ossified forepaw metacarpals, talus bone not ossified, and cervical vertebral centrum not ossified) indicative of developmental delay were also observed at this dose level. Open eye, a malformation, observed in one fetus at 300 mcg/kg/day was considered treatment-related since it was observed at a similar plasma exposure in another study when GW642444 was administered by inhalation, and it is a common finding in rabbit fetuses when β2-agonists are administered to does by inhalation administration. The NOAEL for embryofetal development in rabbits was therefore 30 mcg/kg/day based upon the decreased fetal weights, fetal skeletal variations indicative of developmental delay and the observation of open eye at 300 mcg/kg/day. The AUC0-t values at 30 mcg/kg/day for GW642444 and its counterion GI179710 (triphenylacetate) were 22.4 and 18.4 ng.h/mL, respectively, and the Cmax values for these 2 analytes were 6.26 and 12.4 ng/mL, respectively.

Umeclidinium bromide/vilanterol

A definitive embryofetal development study with the GSK573719/GW642444 combination has not been performed.

A dose range-finding rabbit embryofetal study on GSK573719 alone and in combination with GW642444 was conducted in pregnant New Zealand while rabbits via the subcutaneous route on Days 7 to 19 pc (Report CD2009/00970).

The study was conducted in two rounds. In Round 1, timed mated rabbits (4/group) were given 0.02, 0.18 or 1.5 mg/kg/day GSK573719. In Round 2, timed mated rabbits (4/group) were given 0.1 mg/kg/day GSK573719 alone or both 0.1 mg/kg/day GSK573719 and 0.1 mg/kg/day GW642444.

All rabbits given GSK573719 produced elongated abnormally shaped feces, and in general, rabbits with decreased food consumption correlated with decrements in fecal output. There were no other GSK573719-related or GSK573719 and GW642444-related clinical findings.

In Round 1, a dose of 1.5 mg/kg/day GSK573719 was not tolerated due to excessive body weight loss (group mean body weight loss of up to 5.4% from starting Day 7 body weights) and decreased food consumption. Consequently, this dose group was terminated early on Day 16 pc with one rabbit that was more severely affected terminated on Day 14 pc. In the group receiving 0.18 mg/kg/day GSK573719, decreased body weight gain (5.2% vs 7.9% in controls between Day 7 and Day 29 pc) was observed which was accompanied by transient decreases in food consumption in some rabbits. There were no GSK573719-related effects on body weight or food consumption in rabbits given 0.02 mg/kg/day. There were no GSK573719-related effects on pregnancy and embryofetal development (only 0.02 and 0.18 mg/kg/day dose levels were examined).

In Round 2, there were no GSK573719 alone (0.1 mg/kg/day) or GSK573719 and GW642444-related (0.1/0.1 mg/kg/day) effects on body weights, food consumption or embryofetal development. The systemic exposures (AUC) achieved at these doses in the combination group were 39.4 and 130 ng.h/mL for GSK573719 and GW642444, respectively.

Prenatal and postnatal development, including maternal function

Umeclidinium bromide (GSK573719)

GSK573719 was given subcutaneously by injection at doses of 10, 60 or 180 mcg/kg/day to female Sprague Dawley rats (n= 24) from Day 6 pc through Day 20 post partum (pp) (Report 2011N118595). F0 females were allowed to deliver naturally. Mated (F0) females were euthanized on Day 21 pp. On Post-Natal Day (PND) 21, F1 males and females (2/sex/litter) were assigned to each dose group and assigned to one of two subsets. Subset 1 was selected for acoustic startle habituation (PND 45 ± 2) and reproductive performance. Mated F1 females assigned to Subset 1 were allowed to deliver naturally and the dams and F2 litters were evaluated until Day 7 pp. Subset 2 was selected for acoustic startle habituation (PND 77 ± 3), motor activity (PND 46 ± 2) and modified M-watermaze evaluations (PND 70 ± 2).

There were no F0 maternal GSK573719-related mortalities, clinical or necropsy observations during the pc or pp periods. There were slight GSK573719-related reductions in F0 maternal body weight gain in the 180 mcg/kg/day dose group during the pc dosing period (Days 6 to 21 pc) but there were no effects in the pp period, and the overall mean body weight on Day 21 pp was comparable to the control mean value. Decreases in F0 maternal food consumption occurred during the first dosing interval at ≥60 mcg/kg/day. Food consumption continued to be reduced at 180 mcg/kg/day for the remainder of the pc period and throughout the pp period as compared to the control means. There were no adverse GSK573719-related effects on the F0 maternal duration of gestation, average pup delivery time, number of liveborn pups, viability index or gestation index, mean number of live pups per litter, percentage of male pups per litter or post-natal viability at any dose.

There were no F1 GSK573719-related mortalities or clinical observations during pre- or post-weaning. During pre-weaning (PND 1 to 21), there were GSK573719-related reductions in the F1 mean body

weights from PND 7 to 21 at 180 mcg/kg/day (a dose which caused decreased maternal body weight gain and food consumption).

During the F1 generation post-weaning period, there were no GSK573719-related mortalities or clinical observations or adverse effects on the body weights, body weight gains or food consumption. There were no GSK573719-related effects on the mean day of sexual maturation or any behavioral parameter (acoustic startle habituation, motor activity or learning or retention of a spatial navigation task) at any dose. All reproductive capacity parameters for the F1 generation (mating, fertility, mating index, average number of days in co-habitation and estrous cycling) were comparable among all dose groups. The mean duration of gestation and the mean pup delivery time were comparable among all dose groups. There were no GSK573719-related effects on litter size, pup survival, clinical and necropsy observations or mean body weights in the F2 generation pups. The NOAEL for maternal (F0) reproductive function was 180 mcg/kg/day and for the pre- and post-natal development of the offspring in rats was 60 mcg/kg/day due to the decreased pre-weaning pup weight. At the NOAEL, mean AUC_{0-t} values for F0 dams were 24.9 ng.h/mL and 24.5 ng/mL, respectively.

Vilenterol (GW642444)

Rat

Pre- and post-natal development study

GW642444 (as the triphenylacetate salt, GW642444M) was given to groups of mated female Sprague Dawley rats (24/group) by oral gavage administration at doses of 0 (vehicle), 300, 3000 and 10000 mcg/kg/day beginning on Day 6 pc and continuing to Day 20 post partum (pp) as a suspension in 1.0% w/v aqueous methylcellulose. F0 females were allowed to deliver naturally. Mated (F0) females were euthanized on Day 21 pp. On Postnatal Day (PND) 21, 46 to 48 F1 males and 46 to 48 F1 females were assigned to each dose group and assigned to one of two subsets. Subset 1 was selected for PND 77 auditory startle habituation evaluation and reproductive performance. Mated F1 females assigned to Subset 1 were allowed to deliver naturally and the dams and F2 litters were evaluated until Day 7 pp. Subset 2 was selected for motor activity, PND 45 auditory startle habituation, and Morris Watermaze evaluations. F1 offspring assigned to Subset 2 were euthanized after behavior testing was completed. F1 males assigned to Subset 1 were euthanized following completion of the cohabitation period, and F1 females assigned to Subset 1 were allowed to deliver naturally, and were then euthanized with their litters (F2 offspring) on Day 7 pp.

Increases in the mean maternal F0 body weight and body weight gains throughout the post coitum and post partum periods at all dose levels with a related increase in food consumption during the post coitum period at 10 mg/kg/day and an increase in the average delivery time per pup at 10 mg/kg/day were considered to be related to the pharmacology. There were no other adverse effects on maternal (F0) pregnancy, parturition, lactation or offspring (F1) survival.

Pre- and post-weaning body weights were decreased in the 3 and 10 mg/kg/day dose groups without any adverse consequences to other measures of growth and development. There were no effects on F1 neurobehavioral or reproductive function (F1 pregnancy, parturition and lactation) or F2 survival.

The no observed adverse effect level (NOAEL) for maternal (F0) reproductive function as well as effects on pre- and post-natal development of the offspring in rats is 10 mg/kg/day; the highest group tested.

Umeclidinium bromide/vilanterol

No prenatal and post-natal development studies have been performed for the combination umeclidinium bromide/vilanterol which is considered acceptable by the CHMP based on the data available on both compounds.

Local Tolerance

Umeclidnium bromide (GSK573719)

Dermal Irritancy Local lymph node assay in the mouse (Report 2011N123962)

GSK573719 (50 mcL 25% w/w in propylene glycol) was topically applied to the dorsal surface of the ear of CBA/Ca strain mouse (5/F/group) daily for 3 days. No signs of systemic toxicity or local irritation were noted in the GSK573719-treated or control animals during the test. Body weight changes of the GSK573719-treated animals between Day 1 and Day 6 were comparable to those observed in the corresponding control group animals over the same period. GSK573719 was considered to be a non-sensitiser under the conditions of the test.

Dermal Irritancy- 7-day study in rabbits (Report 2012N139906)

GSK573719 (0 (vehicle), 0.5%, 1% or 2% as solutions in 1% propylene glycol/99% (60% ethanol/40% water)) was dermally administered to male rabbits (2/group) once daily for a period of approximately 20 hours for 7 days. Animals treated with GSK573719 had dose-responsive test article-related minimal to marked microscopic findings in the application skin sites that were consistent with irritation (dermal mixed inflammatory cell infiltrate, epidermal neutrophilic exudate, dermal edema, acanthosis multifocal ulceration and/or subcutaneous congestion). Very slight erythema was noted on the vehicle abraded skin site of one animal in the control group and on the abraded test article site of one animal in each group given 0.5%, 1% or 2% GSK573719.

Dermal irritancy - GSK573719: determination of skin irritation potential using the skinethic reconstituted human epidermal model (Report 2011N123960)

A study was performed to determine the skin irritation potential of GSK573719 (25 mg) using the SkinEthic Reconstituted Human Epidermal model (RHE, SkinEthic Laboratories, Nice, France) following treatment periods of 4 and 24 hours. A prediction of skin irritation potential of GSK573719 was made based on % viability. The relative mean viability of the GSK573719-treated tissues was 78.0% after 4 hours exposure and 23.2% after 24 hours exposure, indicating that GSK573719 was considered to be a mild-moderate irritant.

Ocular Irritancy - GSK573719: determination of eye irritation potential using an in vitro test strategy (Report 2011N123961)

A study was performed to determine the eye irritation potential of GSK573719 (30 mg) using the SkinEthic Reconstituted Human Corneal model (RHC, SkinEthic Laboratories, Nice, France) following treatment periods of 10 and 60 minutes. A prediction of the eye irritation potential of GSK573719 was made based on % viability. The relative mean viability of GSK573719-treated tissues was 80.2% after a 10 minute exposure and 10.6% after a 60 minute exposure, indicating that GSK573719 was considered to be a mild-moderate ocular irritant.

Vilanterol (GW642444)

Dermal irritancy - Local lymph node assay in the mouse

A study was performed to assess the skin sensitisation potential of the GW642444 in the CBA/Ca strain mouse following topical application to the dorsal surface of the ear. Following a preliminary screening test, a group of four animals were treated with 50 mcL (25 mcL per ear) of GW642444 at a concentration of 50% w/w in dimethyl formamide (as the triphenylacetate salt, GW642444M) daily for 3 days. A further group of four animals was treated with dimethyl formamide alone. All animals were observed twice daily on Days 1, 2 and 3 and on a daily basis on Days 4, 5 and 6.

No signs of systemic toxicity or local irritation were noted in the GW642444 treated or control animals during the test. Off white residual test material on ears and fur was noted in GW642444 treated animals post dose on Day 1 and on Days 2 to 5. Bodyweight changes of the GW642444 treated animals between Day 1 and Day 6 were comparable to those observed in the corresponding control group animals over the same period. GW642444 was considered to be a non-sensitiser under the conditions of the test.

Dermal irritancy - GW642444: determination of skin irritation potential using the skinethic reconstituted human epidermal model

A study was performed to determine the skin irritation potential of GW642444 (as the triphenylacetate salt, GW642444M) using the SkinEthic Reconstituted Human Epidermalmodel (RHE, SkinEthic Laboratories, Nice, France) following treatment periods of 4 and 24 hours. The test is based on the hypothesis that irritant chemicals are able to penetrate the stratum corneum of the SkinEthic RHE model and are sufficiently cytotoxic to cause cell death in the underlying cell layers. Triplicate SkinEthic tissues were treated with 25 mg of GW642444 and exposed for 4 hours and 24 hours. A prediction of skin irritation potential of the GW642444 was made based on % viability. The relative mean viability of the GW642444 treated tissues was 110.1% after 4 hours exposure and 93.9% after 24 hours exposure indicating that GW642444 was considered to be a non irritant.

Ocular irritancy - GW642444: determination of eye irritation potential using an in vitro test strategy

A study was performed to determine the eye irritation potential of GW642444 (as the triphenylacetate salt, GW642444M) using the SkinEthic Reconstituted Human Corneal model (RHC, SkinEthic Laboratories, Nice, France) following treatment periods of 10 and 60 minutes. The test is based on the hypothesis that irritant chemicals are able to penetrate the corneal epithelial tissue and are sufficiently cytotoxic to cause cell death. Triplicate SkinEthic tissues were treated with 30 mg of GW642444 and exposed for 10 minutes and 60 minutes. A prediction of the eye irritation potential of the GW642444 was made based on % viability. The relative mean viability of GW642444 treated tissues was 98.2% after a 10 minute exposure and 97.2% after a 60 minute exposure indicating that GW642444 was not likely to be a severe ocular irritant.

Umeclidinium bromide/vilanterol

No local toterance studies have been performed for the combination umeclidinium bromide/vilanterol which is considered acceptable by the CHMP.

Other toxicity studies

Immunotoxicity

A weight of evidence review of immunotoxicity potential for the combination of GSK573719 and GW642444 has been conducted.

Preclinical literature from knockout mice and pan mAChR antagonists (atropine and tiotropium bromide) demonstrate that mAChR antagonists have the potential to be immunomodulators and that atropine had immunosuppressive effects in mice and rats following systemic (osmotic pump, intraperitoneal or intravenous) administration. The risk of potential immunosuppression with GSK573719 is mitigated by administration via the inhalation route which minimizes systemic exposure. Furthermore, the extensive clinical safety data and post-marketing experience with inhaled Spiriva (tiotropium bromide) demonstrates no significantly increased incidence of immune-related adverse effects. In addition, there were no findings in general toxicology studies or clinical safety signals with GSK573719 alone or in combination with GW642444 that indicate immunotoxicity. Based on this assessment, additional preclinical testing to evaluate the immunotoxicity potential of GSK573719 and

GW642444 alone or in combination has not been conducted. In clinical studies, there was no evidence of a higher incidence of infections up to and including the maximum proposed human dose (125/25 mcg/day GSK573719/GW642444).

Studies on impurities

Assessments of the route of synthesis for GSK573719 and GW642444 (as the triphenylacetate salt) has been conducted to determine whether any impurities might be present which are known or suspected DNA-reactive genotoxins, and to assess the likelihood of any such impurities being present in final drug product.

Umeclidinium bromide (GSK573719)

Ames tests were performed with the following potential genotoxic impurities (GR130510X [Report 2012N146384], GR59413X [Report 2010N111625], and GW348594X [Report 2010N110596]). An Ames test was also performed on GW377650X [Report 2010N112354], a potential impurity in the starting material of synthesis GR130510X.

Impurities GR130510X, GR59413X, and GW348594X were positive for mutagenic potential in the Ames test. Consequently, these impurities are controlled at levels well below the TTC in the drug substance specification. This approach was considered acceptable.

Vilanterol (GW642444)

Genotoxicity (AMES test) for GW642444 impurities

An Ames test was conducted with GW844166X (an intermediate in the synthesis of the drug substance), using Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli strain WP2 uvrA (pKM101) . GW844166X was formulated in dimethyl sulphoxide (DMSO) and assays were conducted with concentrations in the range 50 to 5000 mcg/plate. GW844166X induced a dose-related increase in the frequency of TA1535 revertant colonies, in the presence of S9 only, from 50 mcg/plate. These increases achieved a threefold increase over the concurrent vehicle control at 50 mcg/plate rising to a 22-fold increase at 1500 mcg/plate. Revertant colony frequency increases in excess of twofold were also noted for TA100 (presence of S9 only) at 500 and 1500 mcg/plate. No significant increases in the frequency of revertant colonies were recorded for any of the remaining bacterial strains, with any dose of the test material, either with or without metabolic activation. GW844166X was considered mutagenic under the conditions of this test.

An Ames test was conducted with 2,6-dichlorobenzyl chloride (precursor used to manufacture the starting material GW842540X) using Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537 and Escherichia coli strain WP2 uvrA (pKM101). 2,6- dichlorobenzyl chloride was formulated in dimethyl sulphoxide (DMSO) and assays were conducted with concentrations in the range 1.5 to 1500 mcg/plate. 2,6- dichlorobenzyl chloride was non-mutagenic in all assays at concentrations up to 1500 mcg/plate, in the absence and presence of an in vitro metabolic activation system (rat liver S9-mix).

2.3.5. Ecotoxicity / environmental risk assessment

The Environmental Risk Assessment (ERA) submitted for Laventair was prepared in compliance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The two active substances umeclidinium bromide and vilanterol have been assessed separately. Predicted environmental concentrations were significantly below the threshold value of 0.01 µL, indicating that no a Phase II – Tier A is needed for both active substances.

Umeclidinium bromide (GSK573719)

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of umeclidinium bromide. The log K_{ow} was determined according to study OECD 107 with a value of 1.354. Based on the log K_{ow} value being below 3, umeclidinium bromide is not expected to be a bio-accumulative substance. The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSE\text{ai} \cdot F_{\text{pen}}}{WASTEW_{\text{inhab}} \cdot DILUTION}$$

The following values were used for the calculation:

*DOSE*ai = 0.125 (mg patient^{-1} d^{-1})

F_{pen} = 0.01 (patient inh^{-1})

*WASTEW*inhab = 200 (L inh^{-1} d^{-1})

DILUTION = 10 (–)

$PEC_{surfacewater}$ is 0.00063 µg/L.

The PECsurfacewater is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Table 9. Summary of main study results for umeclidinium bromide

Substance (INN/Invented Name): Umeclidinium			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	1.256	Potential PBT N
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	1.256	Not B
	BCF	n/a	n/a
Persistence	DT50 or ready biodegradability	n/a	n/a
Toxicity	NOEC or CMR	n/a	n/a
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)	0.00063	µg/L	> 0.01 threshold N
Other concerns (e.g. chemical class)			N

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 202	NOEC	**Yield** EyC50 (72 hr) = 0.25 mg/L NOEC (72 hr) = 0.0625 mg/L **Growth Rate** ErC50 (72 hr) = 0.42 mg/L NOEC (72 hr) = 0.125 mg/L	µg/L	Species: *Pseudokirchneriella subcapitata* Report not provided
Daphnia sp. Reproduction Test	OECD 211	NOEC	**Immobilisation** EC50 (21 day) >	µg/L	Report not provided

			10.00 mg/L LOEC (21day) = 10.00 mg/L NOEC (21 day) = 3.20 mg/L **Reproduction** EC50 (21day) > 10.00 mg/L LOEC (21day) = 10.00 mg/L NOEC (21day) = 3.20 mg/L		
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	**Hatching** LOEC > 10 mg/L NOEC (28 day) = 10 mg/L **Larvae Survival** LOEC > 10 mg/L NOEC (28day) = 10 mg/L **Length and Weight** LOEC > 10 mg/L NOEC (28 day) = 10 mg/L	µg/L	Species: *Pimephales promelas* Report not provided

Vilanterol (GW64244)

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of vilanterol. The log K_{ow} was determined according to study OECD 107 with a value of 1.256. Based on the log K_{ow} value being below 3, vilanterol is not expected to be a bio-accumulative substance. The environmental exposure assessment was estimated according to the formula for the calculation of the Predicted Environmental Concentration (PEC):

$$PEC_{\text{SURFACE WATER}} = \frac{DOSE\text{ai} \cdot F_{\text{pen}}}{WASTEW_{\text{inhab}} \cdot DILUTION}$$

The following values were used for the calculation:

*DOSE*ai = 0.025 (mg patient^{-1} d^{-1})

F_{pen} = 0.01 (patient inh^{-1})

*WASTEW*inhab = 200 (L inh^{-1} d^{-1})

DILUTION = 10 (–)

$PEC_{surfacewater}$ is 0.00013 µg/L.

The PECsurfacewater is below 0.01 µg/L, and thus a phase II assessment is not necessary.

Table 10. Summary of main study results for vilanterol

Substance (INN/Invented Name): GW642444M			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 …	0.092 (to pH 5) 1.354 (to pH 7) 1.390 (to pH 9)	Potential PBT (N)
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**

Bioaccumulation	log K_{ow}	0.092 (to pH 5) 1.354 (to pH 7) 1.390 (to pH 9)	not B
	BCF	ND	NA
Persistence	DT50 or ready biodegradability	ND	NA
Toxicity	NOEC or CMR	ND	NA
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)	0.00013	µg/L	> 0.01 threshold (N)
Other concerns (e.g. chemical class)	ND	NA	NA

Phase IIa Effect studies

Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/*Species*	OECD 202	NOEC	Yield (72 hr) EyC50= 910 NOEC= 95.4 Growth Rate (72 hr) ErC50 = 5910 NOEC = 977 Biomass (72 hr) EbC50 = 1080 NOEC = 95.4	µg/L	Species: *Pseudokirchneriella subcapitata* Report not provided
Daphnia sp. Reproduction Test	OECD 211	NOEC	Reproduction (21 days) EC50 > 12500 LOEC > 12500 NOEC = 12500 Reproduction (21 days) EC50 > 12500 LOEC = 12500 NOEC = 6250	µg/L	Report not provided
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	Hatching LOEC > 10000 NOEC (28 day)= 10000 Larvae Survival EC50 (28 days)> 10000 LOEC > 10000 NOEC (28 days)= 10000 Length and Weight LOEC = 1111 NOEC (28 day)= 370	µg/L	Species: *Pimephales promelas* Report not provided

2.3.6. Discussion on non-clinical aspects

Laventair is a new fixed dose combination of vilanterol, a long acting beta2-agonist and umeclidinium bromide, a novel inhaled long-acting muscarinic antagonist, intended for the once daily treatment of COPD. Separate comprehensive non-clinical packages have been conducted for both umeclidinium bromide and vilanterol which have adequately characterised the pharmacology, pharmacokinetics and toxicology of each active alone. Adequate studies with the combination evaluated cardiovascular safety

pharmacology, repeated-dose toxicity via the inhalation route for up to 13-weeks and effects on embryofetal development.

In toxicity studies with the actives alone, the effects seen were limited to known class-effects of either muscarinic receptor antagonists or beta$_2$-adrenergic agonists respectively and local irritancy. Little evidence of any exacerbation of these effects was seen on administration of the combination product in rats and dogs. The use of these classes of compound in COPD is well established and it is considered that adequate margins of safety exist between exposures at which effects were seen and exposures achieved at the clinical dose.

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, based on AUC, respectively. Umeclidinium bromide was not genotoxic in a standard battery of studies and was not carcinogenic in lifetime inhalation studies in rats or mice at exposures similar to those at the maximum proposed human dose, based on AUC. In genetic toxicity studies, vilanterol (as alpha-phenylcinnamate) and triphenylacetic acid were not genotoxic indicating that vilanterol (as trifenatate) does not represent a genotoxic hazard to humans. Consistent with findings for other beta2 agonists, in lifetime inhalation studies vilanterol trifenatate caused proliferative effects in the female rat and mouse reproductive tract and rat pituitary gland. There was no increase in tumour incidence in rats or mice at exposures 2- or 30-fold, respectively, those at the maximum recommended human dose, based on AUC.

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, based on AUC). Vilanterol was not teratogenic in rats. In inhalation studies in rabbits, vilanterol caused effects similar to those seen with other beta$_2$-adrenergic agonists (cleft palate, open eyelids, sternebral fusion and limb flexure/malrotation) at 6-times the human clinical exposure based on AUC. When given subcutaneously there were no effects at 36-times the human clinical exposure of vilanterol 22 micrograms, based on AUC.

2.3.7. Conclusion on the non-clinical aspects

The overall non-clinical development programme of the umeclidinium/vilanterol FDC was considered adequate to support the recommendation for a marketing authorisation for Laventair. The available non-clinical data including the results obtained from the repeat dose toxicity and reproduction toxicity studies with Laventair and the environmental risk assessment did not raise any particular safety issue. Based on the available non-clinical safety data with the two compounds, umeclidinium bromide and vilanterol, it is concluded that the FDC should be well tolerated when used in humans at the proposed dosage.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

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.

The CHMP was informed of significant deviations from GCP for investigator site 040688. These deviations were identified by the Applicant during the conduct of the UMEC/VI development program and the FF/VI development program (prior to un-blinding of the DB2113360 and DB2113359 studies and after un-blinding of the AC4115321, HZC102871 and HZC112207 studies). A total of 48 subjects from this site were treated in the UMEC/VI program and 25 subjects were treated in studies from the FF/VI COPD program relevant to this submission.

The CHMP was informed on the 1st July 2013 that up to a13% of tiotropium treated patients in study DB2113360 (COPD indication) were not blinded to treatment due to an incorrect coverage of the original foil supplied by an US contractor. The Applicant was requested during the evaluation to show how this issue did not impact on the final results. The Applicant provided a preliminary analysis of several important clinical endpoints (trough FEV1, 0-6 hour FEV1, SGRQ, TDI) comparing change over time in patients treated with the potentially defectively masked tiotropium to those treated with correctly masked tiotropium. However, there are several deficiencies in the analysis provided (e.g. only the results for the tiotropium and vilanterol arms were provided, the numbers per treatment arm and the dropout rate are unknown). In conclusion, considering that 87% of patients in the tiotropium arm were still blinded and that the results of the analyses of efficacy data were generally consistent, the impact of the unblinding can be considered acceptable by the CHMP as it does not change the benefit/risk of the UMEC/VI combination.

2.4.2. Pharmacokinetics

A total of 40 clinical studies have been conducted supporting the clinical pharmacology of UMEC/VI as an inhaled combination from the novel dry powder inhaler (NDPI) or with UMEC or VI (administered alone by a variety of routes). Studies conducted with UMEC alone included administration by the inhaled, intravenous, and oral routes.

Studies conducted with VI alone also included administration by the IH, intravenous, and PO routes. Clinical pharmacology studies with UMEC, VI, or UMEC/VI were conducted predominantly in healthy subjects but also included subjects with COPD, subjects with hepatic impairment, and subjects with renal impairment. In certain instances, PK and PD data for VI is taken from studies which utilized VI in combination with FF. The rationale to support the use of PK and PD data from these studies is in part due to the fact that no differences in VI PK are observed when VI is administered alone or in combination with FF.

Pharmacokinetic data for UMEC and VI was also obtained from Phase IIb studies with the individual components in subjects with COPD and Phase III studies with UMEC/VI (some of these included arms with UMEC alone and/or VI alone) in subjects with COPD.

The concentration time data from these studies have been used, where possible, to develop population pharmacokinetic models to investigate potential covariate effects such as demographics on the pharmacokinetics and to evaluate potential relationship between UMEC and VI Systemic exposure and reported AEs in the Phase IIb and Phase III.

Pharmacokinetic/Pharmacodynamic (PK/PD) analyses were conducted to describe the concentration effect relationship β2-adrenoreceptor mediated effects on heart rate and QT interval corrected for heart rate using Fridericia's formula (QTc(F)). Analyses were also conducted to describe the efficacy dose-response relationship for UMEC in Phase IIb.

Absorption

The absorption, distribution, metabolism, and excretion of UMEC and VI have been studied separately after oral and intravenous (UMEC only) administration of radiolabeled drug (studies AC4112014,

B2C106181, AC4112008 and B2C106180). UMEC and VI PK parameters were also measured when administered as a combination (see section “Dose proportionality and time dependencies” below).

Bioavailability

Umeclidinium bromide (GSK573719)

Study AC4112008 evaluated the PK of UMEC using a single PO dose (1000 mcg), a single IH dose (1000 mcg) and 3 ascending IV doses (20, 50 and 65 mcg) in a cross-over study, 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%.

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

Study AC4112014 was a mass-balance study using radiolabeled UMEC, which was administered as a single dose of a PO solution of 1000 mcg and an IV infusion of 65 mcg. Samples were taken for a minimum of 168 hours.

Plasma concentrations of unchanged UMEC following single PO dose administration of [14C]-UMEC were all not quantifiable (NQ).

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.

Vilanterol (GW64244)

Study B2C106180 was a PK study in healthy male subjects who received single IV (2.5, 20 and 55 mcg), IH (100 mcg) and PO doses (200 mcg and 500 mcg) of VI.

True estimates of oral and inhaled bioavailability could not be accurately determined from plasma due to the low number of subjects with measurable post dose plasma VI concentrations. However, results from 100 mcg IH VI and 55 mcg IV VI suggested approximately 30% IH bioavailability calculated from the ratio of AUCs to a common time point after IH and IV administrations. Consistent results were obtained from urinary excretion data which indicated approximately 26% IH bioavailability.

Following 500 mcg PO VI administrations, maximum plasma concentrations were achieved at a median time of 0.5 hours post dose. The approximate estimate of PO bioavailability was <2%, calculated from the ratio of AUCs to a common time point after PO and IV administrations.

Study BC106181 was a mass-balance study using radio-labelled VI following a single oral dose of 200 mcg solution to healthy volunteers. Samples were collected for up to 168 hours after dosing. Based on all NQ data for parent VI in 5 out of 6 subjects and sparse quantifiable data from the remaining

subject, it was concluded that VI only represented an estimated <0.5% of the circulating drug-related material in plasma. These results along with presence of one or more circulating metabolites suggested extensive first-pass metabolism of the orally absorbed VI.

Based on urinary recovery of radioactivity (study B2C106181), at least 50.4% of the VI solution oral dose was absorbed via the gut, resulting in notable exposure to drug related material. Based on the proportion of unchanged VI in human faeces (5% of the recovered dose) oral absorption is likely to be greater than this estimate. Exposure to parent VI represented a very small percentage (in the region of <0.5%) of the total drug-related material in plasma. This was indicative of extensive first-pass metabolism of orally absorbed VI and the presence of one or more circulating VI metabolites following oral dosing.

Following oral administration, maximum VI plasma concentrations were achieved at a median time of 30 minutes post-dose (study B2C106180). The low approximate estimate of VI oral bioavailability (<2%), calculated from ratio of AUCs to a common time point after oral and IV administration, suggested a minimal oral contribution to the overall inhaled pharmacokinetic profile in healthy subjects. Consequently, following inhaled administration, systemic VI exposure is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Umeclidinium bromide/vilanterol

No additional studies have been conducted for the umeclidinium bromide/vilanterol FDC which is considered acceptable by the CHMP.

Bioequivalence

No bioequivalence studies were performed with UMEC/VI since there were no changes to the formulation after the start of the Phase III studies and the PK data that is available is considered adequate.

Influence of food

The per oral (PO) bioavailability of UMEC is negligible (<1%) and VI from the swallowed portion undergoes extensive first pass metabolism resulting in <2% systemic exposure after oral administration. Therefore, even if co-administration with food were to affect the rate and/or extent of absorption of either UMEC or VI, it would not be expected to significantly impact the systemic exposure, compared with the fasted state, at the proposed clinical doses of UMEC/VI.

The oral bioavailability of UMEC and VI are small (<2%) and therefore it is acceptable that no food effect study was performed.

Distribution

Following intravenous dosing, UMEC was rapidly and extensively distributed with an average tlast of 1 hour (study AC4112014). 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 either males or females. Both plasma protein binding and blood cell binding for UMEC were independent of concentration.

Vilanterol (GW64244)

Following intravenous dosing, VI was extensively distributed (study HZA102934). The average volume of distribution at steady-state was 165 L. Blood cell association of VI had a blood-to-plasma ratio of 0.8 for man (study WD2006/02044/00). In-vitro plasma protein binding of VI in human plasma was moderately high with an average value of 93.9%. Both plasma protein binding and blood cell binding for VI were independent of concentration.

Umeclidinium bromide/vilanterol

No additional studies have been conducted for the umeclidinium bromide/vilanterol FDC which is considered acceptable by the CHMP.

Elimination

Excretion

Umeclidinium bromide

Plasma clearance following intravenous administration was on average 151 L/h (95% CI: 58.5 L/h, 390.9 L/h; study AC4112014). Following discontinuation of infusion at 30 minutes (median tmax = 30min), unchanged UMEC showed rapid disappearance from systemic circulation (median tlast = 1 hour) and an elimination half-life following intravenous administration could not be estimated. Approximately 58% of the administered radiolabelled dose (or 73% of the recovered radioactivity) was excreted in faeces by 192 hours post dose. Urinary elimination accounted for 22% of the administered radiolabelled dose by 168 hours (27% of recovered radioactivity). The excretion of the drug-related material in the faeces following intravenous dosing suggests evidence for biliary secretion. The discrepancy between administered and recovered radioactivity is most likely explained by a combination of non-specific losses during sample processing (exacerbated by the low chemical mass in excreta samples) and the slow elimination of a small proportion of the dose, with collection of excreta stopping 8 days after dosing.

Following oral administration of (14C)-UMEC to healthy male subjects in Study AC4112014, total radioactivity was excreted primarily in feces (92% of the administered radiolabeled dose or 99% of the recovered radioactivity), by 168 hours post dose. Less than 1% of the orally administered dose (1% of recovered radioactivity) was excreted in urine, suggesting negligible absorption following an oral dose.

UMEC plasma elimination half-life following IH dosing for 10 days averaged 19 hours (study DB2114635). Following IH UMEC, approximately 1%-2% and 3%-4% of the drug following single and repeat dosing, respectively, was excreted unchanged in urine. Renal clearance was on average 6 to 20 L/h suggesting elimination via glomerular filtration and possible renal tubular secretion. Urine half-life of UMEC was on average approximately 9 to 35 hours and is consistent with UMEC half-life observed in plasma.

Vilanterol (GW64244)

The intravenous pharmacokinetics of VI showed high plasma clearance (geometric mean: 108 L/h [95% CI: 86.2 L/h, 135 L/h]) (study HZA102934). The apparent terminal phase elimination half-life of VI following intravenous dosing was, on average, 2.40 h (95% CI: 1.65, 3.48). Following oral administration of [14C]VI to healthy male subjects in clinical study B2C106181 total radioactivity was excreted primarily in urine (50.4% of the administered radioactive dose or 70% of the recovered radioactivity). Faecal elimination accounted for 21.2% of the administered radioactive dose over the 168 h post-dose period (corresponding to 30% of the recovered radioactivity). Most of the urinary radioactivity (48.4% of the administered radioactive dose) was excreted within 24 hours post-dose and

most of the faecal radioactivity (20.6% of the administered radioactive dose) was excreted within 96 hour post-dose. Although only 72% of the administered radioactive dose was recovered in urine and faeces collected over 7 days post-dose, the elimination of VI drug-related material was essentially complete within 120 hour of dosing with less than 0.2% of the administered oral radioactive dose being recovered in the 120 to 144 h and 144 to 168 hour urine and faecal post-dose collections. The discrepancy between administered and recovered radioactivity is most likely due to technical consequences resulting from the analytical approaches required as a result of the low chemical and radioactive doses administered.

Umeclidinium bromide/vilanterol

No additional studies have been conducted for the FDC umeclidinium bromide/vilanterol which is considered acceptable.

Metabolism

Umeclidinium bromide

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.

Disposition of UMEC following intravenous administration was by a combination of biliary and renal secretion of unchanged UMEC and metabolism. The major routes of metabolism were via hydroxylation (M33) and O-dealkylation (M14) with metabolites being excreted in both the urine and faeces. There were low amounts of drug related material in plasma with the major component being parent. There were 3 other noteworthy components, these were GSK339067 (M14, an O-dealkylated metabolite), GSK1761002 (M33; a hydroxylated metabolite) and a further metabolite which could not be fully characterized but assigned as di-hydroxy metabolite based on retention time alone. All metabolites were less than 20% of radioactivity present and based on in vitro result; GSK339067 and GSK1761002 have negligible or equivalent pharmacological activity to UMEC, respectively.

Based on the initially proposed doses for UMEC (62.5 or 125 mcg) by the IH route, the chemical mass of drug-related material in the circulation and excreta will be low, with the likelihood of a metabolite causing unexpected toxicity also being low.

Vilanterol (GW64244)

The human metabolism of VI was investigated using faecal, urine, plasma and duodenal bile samples collected following oral administration of [14C]VI to healthy male subjects in clinical study B2C106181. Following oral administration, VI was absorbed then eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces (approximately 70% and 30% of the recovered radioactive dose, respectively). The main route of metabolism was by O-dealkylation to a range of metabolites with significantly reduced β_1- and β_2-agonist activity that included GW630200 and GSK932009. Up to 78% of the recovered dose (in all excreta) was potentially associated with O-dealkylated metabolites. Ndealkylation (to M20) and C-dealkylation (to M26) were minor pathways in human representing a combined 5% of the recovered dose. Unchanged VI in human faeces (5% of the recovered oral radioactive dose) represented either unabsorbed dose or absorbed but unchanged VI (or conjugate) secreted directly into the GI tract or via human bile. Duodenal bile collected using the exploratory EnteroTest device technique contained low levels of radioactivity. This may be a reflection of metabolites being eliminated mainly via alternative non-biliary routes (e.g. urine) or could be due to non-optimal collection of the bile samples or inefficient gall bladder emptying in the subjects.

The applicant states that three independent pieces of data support the hypothesis that human metabolites of VI make a negligible contribution to its pharmacological effect in man. Firstly, following oral administration of [14C]VI (200 mcg) in study B2C106181 plasma concentrations of VI metabolites (drug-related material) were significantly higher than VI plasma concentrations and were also likely to be considerably greater than plasma concentrations of metabolites produced after administration of the therapeutic inhaled VI dose (25 mcg). Secondly, despite the higher metabolite concentrations, there were no changes in measured vital signs or heart rate which is indicative of a lack of metabolite beta-adrenoceptor activity. Metabolites representative of the major human metabolic routes, including GW630200 and GSK932009 have been synthesised, tested and shown to have negligible pharmacological activity against both β1- and β2-receptors (study HR2008/00016/00). Lastly, in human liver microsome incubations with VI, β2-activity diminished with time in proportion with the loss of VI by metabolism indicating that the β2 activity is due to the presence of parent VI.

Umeclidinium bromide/vilanterol

No additional studies have been conducted for the FDC umeclidinium bromide/vilanterol which is considered acceptable by the CHMP.

Dose proportionality and time dependencies

Study DB2114635

Study DB2114635 provides the best available data on the PK of UMEC and VI in healthy subjects when administered as a combination as well as on dose-proportionality and time-dependency as this study included repeated dosing and different doses of the combination. This was a randomized, 4-way cross over study in healthy subjects and the administered treatments were:

- UMEC 500 mcg QD (N=76)
- UMEC/VI 125/25 mcg QD (N=78)
- UMEC/VI 500/100 mcg QD (N=74)
- Moxifloxacin 400 mg QD (N=74) and
- Placebo (N=77)

This study is discussed in detail under pharmacodynamic section as this is a thorough QTc study. However the PK parameters as ascertained from this study are provided below.

UMEC Plasma Pharmacokinetic Parameters

The selected PK parameters at Day 10 for the UMEC/VI 125/25 and UMEC/VI 500/100 treatment groups are summarized in the table below.

Table 11. Summary Statistics of Day 10 UMEC PK Parameters (DB2114635)

Parameter	Treatment	N	n	Geometric Mean	95% CI	%CVb
$AUC_{(0-\tau)}$ (h•pg/mL)	UMEC/VI 125/25 mcg	75	74	495	431, 569	65.6
	UMEC/VI 500/100 mcg	73	70	2145	1977, 2328	35.2
C_{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	334	294, 379	59.1
	UMEC/VI 500/100 mcg	73	70	1400	1285, 1525	37.1
t_{max} (h)[a]	UMEC/VI 125/25 mcg	75	74	0.10	0.08, 0.15	NA
	UMEC/VI 500/100 mcg	73	70	0.10	0.08, 0.12	NA
t_{last} (h) [a]	UMEC/VI 125/25 mcg	75	74	24.08	0.10, 24.25	NA
	UMEC/VI 500/100 mcg	73	70	24.08	24.08, 24.25	NA
$t_{½}$ (h)	UMEC/VI 125/25 mcg	75	37	19.1	12.6, 29.0	195.9
	UMEC/VI 500/100 mcg	73	36	25.2	22.4, 28.4	36.5
CL/F (L/h)	UMEC/VI 125/25 mcg	75	73	244	216, 276	56.9
	UMEC/VI 500/100 mcg	73	70	233	215, 253	35.2
V/F (L)	UMEC/VI 125/25 mcg	75	37	7858	6225, 9918	79.3
	UMEC/VI 500/100 mcg	73	36	8418	7375, 9608	40.6
λz	UMEC/VI 125/25 mcg	75	37	0.036	0.024, 0.055	195.9
	UMEC/VI 500/100 mcg	73	36	0.028	0.024, 0.031	36.5

Data Source: Study DB2114635, Table 11.2

N=number of subjects who received a specific treatment; n=the number of subjects with non-missing values (including not calculable where applicable).

a. Presented as median and range.

UMEC was rapidly absorbed with median tmax values occurring at 6 minutes post dose. The terminal phase t½ for all subjects was determined using at least 3 data points (range 3-8 points) based on visual inspection and was estimated to be on average approximately 19 to 25 hours. Systemic exposure of UMEC in terms of both AUC(0-t) and Cmax following UMEC/VI 500/100 mcg were approximately dose proportional (~4-fold higher) with systemic exposure of UMEC/VI 125/25 mcg.

The median UMEC concentration-time profile at Day 10 suggest that the PK of UMEC does not appear to be affected significantly when administered in a combination with VI.

Comparison with results from other studies indicate that Umeclidinium systemic exposure following 125 mcg was approximately twice the systemic exposure following 62.5 mcg.

VI Plasma Pharmacokinetic Parameters

Following repeat-dose administration of VI in combination with UMEC, VI was rapidly absorbed with median tmax values occurring at 6 minutes post dose. The t½ for all subjects was determined using at least 3 data points (range 3-7 points) based on visual inspection and was estimated to be on average approximately 11 to 19 hours.

VI systemic exposure in terms of both AUC(0-t) and Cmax following UMEC/VI 500/100 mcg were approximately dose proportional (~4-fold higher) with systemic exposure of UMEC/VI 125/25 mcg.

Selected VI PK parameters at Day 10 for the UMEC/VI 125/25 mcg and the UMEC/VI 500/100 mcg treatment groups are summarized in the below table.

Table 12. Summary Statistics of Day 10 VI PK Parameters (DB2114635)

Parameter	Treatment	N	n	Geometric Mean	95% CI	%CVb
$AUC_{(0-\tau)}$ (h•pg/mL)	UMEC/VI 125/25 mcg	75	74	429	379, 486	57.6
	UMEC/VI 500/100 mcg	73	70	1824	1729, 1925	22.9
C_{max} (pg/mL)	UMEC/VI 125/25 mcg	75	74	340	307, 376	45.9
	UMEC/VI 500/100 mcg	73	70	1518	1416, 1627	29.8
t_{max} (h)[a]	UMEC/VI 125/25 mcg	75	74	0.10	0.08, 0.15	NA
	UMEC/VI 500/100 mcg	73	70	0.10	0.08, 0.22	NA
t_{last} (h)[a]	UMEC/VI 125/25 mcg	75	74	16.02	0.52, 24.25	NA
	UMEC/VI 500/100 mcg	73	70	24.08	24.08, 24.25	NA
t½ (h)	UMEC/VI 125/25 mcg	75	55	10.52	8.43, 13.12	97.8
	UMEC/VI 500/100 mcg	73	62	19.22	17.68, 20.90	33.9
CL/F (L/h)	UMEC/VI 125/25 mcg	75	74	58.2	51.4, 65.9	57.6
	UMEC/VI 500/100 mcg	73	70	54.8	52.0, 57.9	22.9
V/F (L)	UMEC/VI 125/25 mcg	75	55	890	783, 1010	49.8
	UMEC/VI 500/100 mcg	73	62	1526	1383, 1684	40.2
λz	UMEC/VI 125/25 mcg	75	55	0.066	0.053, 0.082	97.8
	UMEC/VI 500/100 mcg	73	62	0.036	0.033, 0.039	33.9

Data Source: Study DB2114635, Table 11.4
N=number of subjects who received a specific treatment; n=the number of subjects with non-missing values (including not calculable where applicable).
a. Presented as median and range.

Other studies generally support the above estimates of PK parameters for UMEC and VI in healthy subjects. Although none of the studies did a formal comparison of steady state UMEC systemic exposure when UMEC was administered alone as compared to UMEC/VI, the results shown in the table below indicate that there is no significant difference.

Dose/Study/Day	UMEC/VI	UMEC	UMEC/VI	UMEC
	C_{max} (pg/mL) Geometric Mean		AUC_{tau} (pg•h/mL) Geometric Mean	
500/25 mcg QD / DB2113950 / Day 8	1233	1183	1755	1847
500/100 mcg QD / DB2114635 / Day 10	1400	1541	2145	2444

Data Source: Study DB2114635, Table 11.2; Study DB2113950, Table 12.3

A comparison of AUC(0-1) and Cmax for VI following the administration of UMEC/VI 500/50 mcg versus VI 50 mcg alone was performed.

The results of the analysis showed no evidence of a difference in VI Cmax when delivered as the UMEC/VI 500/50 mcg combination compared with VI 50 mcg administered alone. The ratio for AUC showed some evidence of higher exposure (21% (95% CI: 2% to 44%)) in the combination treatment arm compared with VI alone. Following repeat dosing of inhaled VI, steady state was achieved within 6 days with on average 2.4-fold accumulation.

Special populations

Pharmacokinetics in target population

The PK profile of UMEC in patients with COPD has been established after administration of UMEC alone and after administration of UMEC/VI.

Umeclidinium bromide (GSK573719)

UMEC systemic exposure in terms of steady state Cmax and AUC(0-15) between healthy subjects and subjects with COPD were compared. Overall, plasma data appear to show somewhat lower UMEC systemic exposure in subjects with COPD compared with healthy subjects, and UMEC Cmax and AUC appeared to increase in an approximate dose proportional manner.

Following repeat dosing, both healthy subjects and subjects with COPD showed an approximately 1.2- to 2.9-fold accumulation in UMEC systemic exposure in terms of AUC and Cmax.

Plasma elimination $t_{1/2}$ could not be measured in many healthy subjects and subjects with COPD studies due to limited sampling, a large number of NQ samples, and a flat elimination phase. Study DB2114635 showed that the geometric mean $t_{1/2}$ of UMEC in healthy subjects after inhaled dosing was 26 hours (95% CI: 24, 28 hours; n = 47) for the 500 mcg dose group and 19 hours (95% CI: 13, 29; n = 37) following UMEC/VI 125/25 mcg. In COPD patients only urine $t_{1/2}$ of UMEC could be calculated and this ranged from 6 to 12 hours.

In addition to systemic exposure, apparent clearances were estimated in both the TQT study (DB2114635) and the pop PK analysis (DB2116975). There were no differences in apparent clearance between the two populations.

Vilanterol

The pharmacokinetics of VI in subjects with COPD was well described by a three compartment model with zero-order absorption. The analysis showed that there was a decrease (27%) in inhaled clearance (CL/F) over the observed age 41 to 84 years. A reduction (47%) in CL/F is also predicted over the bodyweight range of 160 to 35 kg in subjects with COPD. The central volume (V1/F) was found to decrease (30%) with increasing age (41-84 years), to be lower (12%) in females and to be increased with smoking. Additionally, the Phase II study HZC111348 was a significant covariate on CL/F and V1/F.

As a result of lower CL/F and a smaller central volume (V1/F), the VI exposure was predicted to be higher (approximately 1.5-fold higher AUC(0-24) and 2.7-fold higher Cmax) in the small number of subjects with COPD (n=39) recruited to the Phase II study (study HZC111348) compared with the larger Phase IIIa population (n= 1052 subjects with COPD). The reason for this marked study difference is unclear. Despite the higher systemic VI exposure in HZC111348, the FF/VI dose was well tolerated and was not associated with an increase in heart rate (weighted mean 0-4 hours difference from placebo was 0.6 bpm [95% CI: -3.9 to 5.1]). Comparison of the model predicted VI systemic exposure (final model) showed no notable difference between individual component versus combination treatment.

Study DB2113120

This was phase IIa study in COPD subjects conducted to evaluate the pharmacokinetics and pharmacodynamics of UMEC/VI. The dose administered was 500/25 mcg once daily for 4 weeks. The brief study design is depicted in the below table.

Protocol No.	Type of Study	Primary Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects: Gender M/F: Mean Age (Range)	Treatment Details (Drug/ Dose/ Form/ Route/ Frequency/ Duration)
DB2113120	Safety, tolerability, PD, PK	To evaluate the safety and tolerability of the combination of inhaled UMEC (500 mcg) and VI (25 mcg) administered qd for 4 weeks in subjects with COPD	R, DB, PC, PG	Subjects with COPD with post-bronchodilator FEV_1 ≤80% of predicted & FEV_1/FVC ratio ≤0.70	Placebo: 9 7/2 59y (42y-69y) UMEC /VI 500/25 mcg QD: 42 24/18 59y (40y-83y)	UMEC/VI 500/25 mcg QD Placebo QD IH 4 weeks

Single and repeat dose administration of 500 mcg GSK573719 in combination with 25 mcg GW642444 showed rapid absorption of both drugs following which plasma concentrations quickly declined indicating rapid distribution and elimination. There were no evidences of accumulation based on both GSK573719 Cmax and AUC comparisons except Cmax comparison of Day 14 versus Day 1. The observed mean accumulation of Cmax for Day 14 versus Day 1 was 38% (90% CI: 6%, 80%). There were no evidences of accumulation based on both GW642444 Cmax and AUC comparisons except Cmax comparison of Day 14 versus Day 1. The observed mean accumulation of Cmax for Day 14 versus Day 1 was 31% (90% CI: 5%, 63%).

Based on the results from study DB2113120 and a cross-study comparison, the PK of UMEC and VI were similar when administered as a combination compared with administration as monotherapies, demonstrating a lack of a drug-drug interaction between UMEC and VI. There was modest accumulation based on both UMEC Cmax and AUC comparisons (1.4-fold higher systemic exposure at Day 14 and a 1.1- to 1.3-fold higher systemic exposure at Day 28 compared with Day 1). There was no evidence of marked accumulation based on both VI Cmax and AUC comparisons. At the proposed doses of UMEC/VI 62.5/25 and 125/25 mcg, UMEC systemic exposure was dose proportional in subjects with COPD. None of the subject demographic or baseline characteristics (age, weight, gender, race, inhaled corticosteroid use, baseline FEV1, creatinine clearance, and smoking status) had clinically relevant effects on UMEC or VI systemic exposure to warrant dose adjustment based on these covariates.

Renal impairment

For both UMEC and VI the primary route of elimination following inhaled dosing is via the hepatic route, primarily through biliary secretion and metabolism for UMEC and through metabolism, primarily by CYP450 3A4 for VI. However, even for compounds that are eliminated mainly by the hepatic route, there remains a possibility that systemic exposure may be altered in subjects with impaired renal function and so the applicant has evaluated the changes in systemic exposure of UMEC and/or VI in subjects with impaired renal function in Study DB2114636 (UMEC and UMEC/VI) and study HZA113970 (VI).

Study DB2114636 was a single-blind, non-randomized, 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.

Umeclidinium bromide

Summary statistics for plasma UMEC PK parameters are presented below.

Parameter	Group	N	n	n*	Geometric Mean	95% CI	CVb(%)
UMEC 125 mcg							
AUC(0–2) (h*pg/mL)	Healthy	9	9	1	56.5	(34.8, 91.6)	69.7
	Severe renal impairment	9	9	0	59.1	(40.5, 86.3)	52.3
Cmax (pg/mL)	Healthy	9	9	0	127.6	(84.8, 191.9)	57.1
	Severe renal impairment	9	9	0	113.2	(75.2, 170.4)	57.3
tlast (h)*	Healthy	9	9	0	2.00	(0.25, 4.00)	NA
	Severe renal impairment	9	9	0	2.00	(0.50, 4.00)	NA
tmax (h)*	Healthy	9	9	0	0.08	(0.08, 0.12)	NA
	Severe renal impairment	9	9	0	0.08	(0.08, 0.12)	NA
UMEC/VI 125/25 mcg							
AUC(0–2) (h*pg/mL)	Healthy	9	9	0	60.4	(44.6, 81.9)	41.1
	Severe renal impairment	9	9	0	66.3	(48.8, 90.1)	41.5
Cmax (pg/mL)	Healthy	9	9	0	152.4	(101.1, 229.7)	57.4
	Severe renal impairment	9	9	0	149.2	(104.2, 213.5)	49.3
tlast (h)*	Healthy	9	9	0	2.00	(0.50, 4.02)	NA
	Severe renal impairment	9	9	0	2.00	(0.50, 4.00)	NA
tmax (h)*	Healthy	9	9	0	0.08	(0.08, 0.12)	NA
	Severe renal impairment	9	9	0	0.08	(0.08, 0.12)	NA

*Presented as median and range.
NA=not applicable; n*=number imputed.

Following administration of UMEC/VI 125/25 mcg, there was no evidence of a clinically relevant increase in UMEC plasma exposure (AUC(0-2) or Cmax) for subjects with severe renal impairment compared with healthy controls.

On average Ae(0-24) was 89% (90% CI: 81%, 93%) lower in subjects with severe renal impairment compared with healthy subjects for UMEC/VI 125/25 mcg. There was no effect of renal impairment on urine t1/2 (healthy subjects: 11.34 hours (95% CI 7.58, 16.97); subjects with severe renal impairment: 9.22 hours (95% CI: 6.54, 12.99).

Vilanterol

Summary statistics of plasm VI pharmacokinetic parameters are presented below.

Parameter	Group	N	n	Geometric Mean	95% CI	CVb(%)
AUC(0–1) (h*pg/mL)	Healthy	9	9	28.7	(20.6, 40.0)	45.3
	Severe renal impairment	9	9	34.8	(25.9, 46.6)	39.6
Cmax (pg/mL)	Healthy	9	9	74.8	(53.1, 105.4)	46.9
	Severe renal impairment	9	9	77.1	(56.9, 104.7)	41.3
tlast (h)*	Healthy	9	9	1.00	(0.50, 2.00)	NA
	Severe renal impairment	9	9	1.00	(1.00, 4.00)	NA
tmax (h)*	Healthy	9	9	0.08	(0.08, 0.12)	NA
	Severe renal impairment	9	9	0.12	(0.08, 0.25)	NA

*Presented as median and range.

Following dosing with UMEC/VI 125/25 mcg, there was no evidence of a clinically relevant increase in VI plasma exposure for subjects with severe renal impairment compared with healthy subjects.

Neither UMEC 125 mcg nor UMEC/VI 125/25 mcg administered to subjects with severe renal impairment resulted in clinically significant increases in either UMEC or VI systemic exposure. Therefore, no dose adjustment is recommended in patients with impaired renal function.

Hepatic impairment

The hepatic route has been determined as the major route of elimination of UMEC. Following intravenous administration of (14C)-UMEC, 58% of total radioactivity was recovered in the feces, suggesting biliary secretion. In addition, results from in vitro studies indicated that UMEC is a metabolic substrate for the CYP2D6 isozyme, which may contribute to its clearance. VI is rapidly cleared by extensive first pass metabolism mediated by the P450 isozyme CYP3A4. Hence there is a distinct possibility that PK of UMEC and/or VI may be changed in patients with impaired liver function. Two studies, study DB2114637 (UMEC and UMEC/VI) and study HZA111789 (VI) have been conducted in subjects with hepatic impairment to address this issue.

Study DB2114637 was an open-label, non-randomized 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. Hepatically impaired subjects were classified using the Child-Pugh classification -moderate: Child-Pugh B (7 to 9 points). Nine subjects with moderate hepatic impairment were enrolled along with 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.

Umeclidinium bromide

The summary statistics for UMEC PK parameters on Day 1 and 7 are presented below.

UMEC Parameter Day 1	Group	N	n	Geometric Mean	95% CI	CVb(%)
UMEC 125 mcg						
$AUC_{(0-2)}$ (h*pg/mL)	Healthy	9	9	87	(68, 112)	32.9
	Moderate Hepatic Impairment	9	9	74	(55, 100)	41.1
C_{max} (pg/mL)	Healthy	9	9	220	(151, 320)	51.9
	Moderate Hepatic Impairment	9	9	165	(108, 253)	60.0
t_{last} (h)*	Healthy	9	9	2.00	(2.00, 8.08)	NA
	Moderate Hepatic Impairment	9	9	2.00	(1.00, 4.00)	NA
t_{max} (h)*	Healthy	9	9	0.08	(0.08, 0.12)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA
UMEC/VI 125/25 mcg						
$AUC_{(0-2)}$ (h*pg/mL)	Healthy	9	9	72	(48, 107)	55.4
	Moderate Hepatic Impairment	9	9	66	(52, 83)	30.5
C_{max} (pg/mL)	Healthy	9	9	190	(117, 309)	70.3
	Moderate Hepatic Impairment	9	9	160	(124, 207)	34.2
t_{last} (h)*	Healthy	9	9	2.00	(1.00, 4.03)	NA
	Moderate Hepatic Impairment	9	9	2.00	(1.00, 4.00)	NA
t_{max} (h)*	Healthy	9	9	0.08	(0.08, 0.10)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA

*=presented as median and range
CI=confidence interval; NA=not applicable

UMEC Parameter Day 7	Group	N	n	Geometric Mean	95% CI	CVb(%)
UMEC 125 mcg						
$AUC_{(0-2)}$ (h*pg/mL)	Healthy	9	9	122	(101, 147)	24.9
	Moderate Hepatic Impairment	9	9	105	(76, 146)	44.9
$AUC_{(0-\tau)}$ (h*pg/mL)	Healthy	9	9	482	(383, 607)	30.6
	Moderate Hepatic Impairment	9	9	438	(359, 536)	26.5
C_{max} (pg/mL)	Healthy	9	9	283	(220, 363)	33.3
	Moderate Hepatic Impairment	9	9	214	(126, 362)	77.5
t_{last} (h)*	Healthy	9	9	23.72	(8.00, 36.00)	NA
	Moderate Hepatic Impairment	9	9	36.00	(12.00, 36.00)	NA
t_{max} (h)*	Healthy	9	9	0.08	(0.08, 0.12)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA

*=presented as median and range
CI=confidence interval; NA=not applicable
As the dosing interval for UMEC is once-daily, $AUC_{(0-24)}$ corresponds to $AUC_{(0-\tau)}$.

Following single-dose administration of UMEC/VI 125/25 mcg, plasma UMEC exposures were on average lower in subjects with moderate hepatic impairment.

Following single-dose administration of UMEC/VI 125/25 mcg, urinary excretion of UMEC was, on average, lower in subjects with moderate hepatic impairment compared with healthy subjects.

Vilanterol

Summary statistics for VI Pk parameters are presented below.

VI Parameter	Group	N	n	Geometric Mean	95% CI	CVb(%)
$AUC_{(0-1)}$ (h*pg/mL)	Healthy	9	9	46	(32, 66)	48.9
	Moderate Hepatic Impairment	9	9	36	(27, 46)	35.4
C_{max} (pg/mL)	Healthy	9	9	124	(87, 176)	48.6
	Moderate Hepatic Impairment	9	9	96	(70, 132)	42.7
t_{last} (h)*	Healthy	9	9	1.00	(0.50, 4.00)	NA
	Moderate Hepatic Impairment	9	9	1.00	(0.53, 2.00)	NA
t_{max} (h)*	Healthy	9	9	0.08	(0.08, 0.25)	NA
	Moderate Hepatic Impairment	9	9	0.08	(0.08, 0.12)	NA

*=presented as median and range
CI=confidence interval; NA=not applicable

Following single-dose administration of UMEC/VI 125/25 mcg, VI systemic exposures were on average lower in subjects with moderate hepatic impairment compared with healthy subjects.

Both UMEC 125 mcg and UMEC/VI 125/25 mcg administered to subjects with moderate hepatic impairment led to UMEC and VI systemic exposures that were on average lower in the subjects with moderate hepatic impairment compared to healthy subjects and no dose adjustment is recommended in patients with moderate hepatic impairment. UMEC/VI has not been studied in subjects with severe hepatic impairment.

Gender

Population PK analyses showed that gender is not a significant covariate in the PK of UMEC or VI and hence dose adjustments are not warranted based on gender. A specific PK study has not been conducted to evaluate a difference in PK due to gender and such a study is not required. The available PK data and the population PK analyses are reassuring that gender is not a significant factor in the PK of UMEC or VI.

Race

No specific studies were conducted to evaluate the effect of race on PK or PD parameters. Several studies were conducted solely in Japanese healthy subjects and the PK data from studies in Japanese subjects are discussed below.

Population PK datasets for both UMEC (n=1635) and VI (n=1637) were evaluated for an effect of race on the PK of UMEC and VI.

This population PK analysis did not show any racial differences in apparent clearance or volume of distribution for UMEC or VI.

Weight

In the population PK analyses, weight was found to be a significant covariate of apparent inhaled clearance of both UMEC & VI, and weight was also a significant covariate of apparent volume of distribution of UMEC. 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.

Though changes in weight affect the PK of UMEC and VI, it is accepted that the changes are not clinically significant to recommend any changes in dose based on weight.

Elderly population

In the population PK analyses, age was found to be a significant covariate of apparent inhaled clearance of both UMEC and VI. 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.

It is accepted that despite the observation the change in age may affect the PK of UMEC and VI, dosage adjustment based on age are not required.

Pharmacokinetic interaction studies

In vitro

Umeclidinium bromide

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 normal and CYP2D6 poor metabolizer subjects there was no clinically significant difference in the systemic exposure to UMEC following 7 days repeat dosing with 4- to 8-fold higher supra-therapeutic IH doses. No dose adjustment for use of CYP2D6 and UMEC/VI appears to be warranted.

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. There was no evidence of biologically significant UMEC induction of CYP P450 enzymes in a 1 month rat study that used inhaled doses of UMEC up to 2000 mcg/kg/day (approximately 120 mg for a 60 kg human).

Vilanterol

In-vitro studies suggest that VI is metaboised primarily by CYP3A4. Co-administration with strong inhibitors of CYP3A4 may lead to increased exposure to VI (and other LABAs) and strong inhibitors have been contra-indicated in clinical studies. Clinical studies with moderate (verapamil) and strong (ketoconazole) CYP3A4 inhibitors were conducted with the strong inhibitor showing higher VI systemic exposure and the moderate inhibitor showing no effect on systemic exposure.

Vilanterol is an in vitro inhibitor of CYP3A4 and CYP2D6 (IC50 values between 3.5 and 12 microM). At clinical doses, the highest anticipated Cmax in humans (<0.2 ng/mL or 0.5 nM) is at least 1000-fold lower than the lowest IC50 value (3.5 microM) (equivalent to 1.6 mcg/mL) as a worst case for all CYPs and transporters investigated. There was no evidence of biologically significant VI induction of CYP P450 enzymes in a 14-day rat study that used IH doses up to 32,900 mcg/kg/day (approximately 1974 mg for a 60 kg human).

Therefore the inhibition potential and induction potential of UMEC and/or VI on CYP P450 enzymes at low clinical IH doses is considered to be negligible.

In vivo

Umeclidinium bromide/vilanterol

Three studies (DB2114365, DB2113208 and DB2113950) provide information on this aspect.

Study DB2114635

Study DB2114635 was a thorough QT study which also included PK evaluation. Summary statistics of UMEC 500 mcg and UMEC/VI 500/50 mcg are provided in the below table.

Table 14. Summary Statistics of Day 10 UMEC PK Parameters (DB2114635)

Parameter	Treatment	N	n	Geometric Mean	95% CI	%CVb
C_{max} (pg/mL)	UMEC 500 mcg	75	73	1541	1412, 1682	38.8
	UMEC/VI 500/100 mcg	73	70	1400	1285, 1526	37.1
$AUC_{(0-\tau)}$ (h•pg/mL)	UMEC 500 mcg	75	73	2444	2278, 2624	31.0
	UMEC/VI 500/100 mcg	73	70	2146	1978, 2328	35.2

Source Data: Study DB2114635, Table 11.2
N=number of subjects who received a specific treatment; n=the number of subjects with non-missing values (including not calculable where applicable).

UMEC systemic exposure following UMEC 500 mcg was similar or slightly higher than UMEC systemic exposure following UMEC/VI 500/100 mcg in terms of Cmax and AUC.

The above results indicate that the systemic exposure of UMEC was comparable or slightly higher when UMEC was administered alone as compared to when it is administered as UMEC/VI.

Study DB2113950

This was a randomized, open label study in healthy subjects to evaluate the PK of UMEC/VI and UMEC alone when administered concomitantly with verapamil (240mg). Verapamil, a moderate CYP3A4 inhibitor and potent P-gp inhibitor is one of the drugs frequently used by subjects with COPD as a result of co-morbidities such as hypertension and other cardiovascular conditions.

The study consisted of 2 treatment sequences:

	Period 1 (Day 1 to 8)	Period 2 (Day 9 to 13)
Cohort 1	UMEC (500 mcg) once-daily for 8 days	UMEC (500 mcg) once-daily and 240 mg verapamil once-daily for 5 days
Cohort 2	UMEC/VI (500/25 mcg) once-daily for 8 days	UMEC/VI (500/25 mcg) for 5 days and 240 mg verapamil once-daily

The primary objective was to assess the effect of verapamil 240 mg qd on the steady state PK of inhaled UMEC and UMEC/VI. In the period one of two cohorts, when verapamil was not administered concomitantly, the results can be used to compare the effect of combination of VI on the PK of UMEC.

UMEC pharmacokinetics

Summary statistics of Day 8 UMEC plasma PK parameters following UMEC monotherapy and following UMEC/VI are presented in the below table.

Table 15. Summary Statistics of Day 8 UMEC Plasma PK Parameters (DB2113950)

Parameter	Treatment	N	n	Geometric Mean	95% CI	%CVb
$AUC_{(0-\tau)}$ (h•pg/mL)	UMEC 500 mcg	16	15	1847	1518, 2247	36.6
	UMEC/VI 500/25 mcg	16	15	1755	1348, 2284	50.4
C_{max} (pg/mL)	UMEC 500 mcg	16	15	1183	926, 1511	46.5
	UMEC/VI 500/25 mcg	16	15	1233	818, 1859	85.7

Data Source: Study DB2113950, Table 12.3
N=number of subjects who received a specific treatment; n=the number of subjects with non-missing values (including not calculable where applicable).

On average, steady state plasma systemic exposure of UMEC was comparable when administered as UMEC alone compared with UMEC/VI, with overlapping 95% CIs. This suggests a lack of PK interaction between UMEC and VI.

The above results indicate that the systemic exposure of UMEC was comparable when UMEC was administered alone as compared to when it is administered as UMEC/VI. Taking the overall results from this study and study DB2114635, it can be concluded that the exposure of UMEC is not affected by combining it with VI.

UMEC exposure in terms of AUC was approximately 40% higher in the presence of verapamil, however this was not considered clinically relevant. There was no effect of verapamil on the Cmax of UMEC.

UMEC exposure in terms of AUC was approximately 40% higher in the presence of verapamil, however this was not considered clinically relevant. There was no effect of verapamil on the Cmax of UMEC.

VI pharmacokinetics

A summary of derived plasma PK parameters to assess differences in exposure in VI is presented in the below table.

Table 16. Statistical Analysis of Derived Plasma Parameters to Assess Difference in Exposure to VI (DB2113950)

Parameter	Treatment Comparison	Adjusted Geometric Means	Ratio of Adjusted Geometric Means	90% CI of Ratio
$AUC_{(0-2)}$ (h•pg/mL)	UMEC/VI + V vs. UMEC/VI	116 / 102	1.14	0.94, 1.37
C_{max} (pg/mL)	UMEC/VI + V vs. UMEC/VI	242 / 230	1.05	0.90, 1.22

Data Source: Study DB2113950, Table 12.4
Abbreviations: V=verapamil

The results showed no evidence of effect of verapamil on the PK of VI. However more than 70% of samples showed NQ concentrations for VI at a LLQ of 30 pg/ml.

Study DB2113208

This study evaluated the potential changes to PK of UMEC and VI when they are administered in combination to healthy Japanese volunteers.

UMEC Pharmaockinetics

The summary statistics of UMEC PK parameters as assessed from this study is given in the below table.

Table 17. Summary Statistics of GSK573719 PK Parameters

Parameter	Treatment	N	n	n*	Geometric Mean	95% CI	CVb(%)
AUC(0-0.25) (h*pg/mL)	GSK573719 500 µg	15	15	2	126.519	(82.969, 192.928)	88.7
	GSK573719 500 µg /GW642444 50 µg	15	15	0	179.603	(140.326, 229.873)	46.9
AUC(0-2) (h*pg/mL)	GSK573719 500 µg	15	15	2	312.130	(194.090, 501.959)	104.3
	GSK573719 500 µg /GW642444 50 µg	15	15	0	413.471	(315.589, 541.712)	51.8
AUC(0-4) (h*pg/mL)	GSK573719 500 µg	15	15	2	377.787	(226.444, 630.280)	116.2
	GSK573719 500 µg /GW642444 50 µg	15	15	0	513.611	(380.274, 693.702)	58.5
AUC(0-t) (h*pg/mL)	GSK573719 500 µg	15	15	2	374.225	(213.422, 656.186)	134.0
	GSK573719 500 µg /GW642444 50 µg	15	15	0	537.640	(380.159, 760.359)	69.2
AUC(0-∞) (h*pg/mL)	GSK573719 500 µg	15	15	3	368.704	(196.798, 690.770)	161.7
	GSK573719 500 µg /GW642444 50 µg	15	15	0	617.322	(434.415, 877.242)	70.4
Cmax (pg/mL)	GSK573719 500 µg	15	15	2	578.301	(224.078, 1492.478)	421.3
	GSK573719 500 µg /GW642444 50 µg	15	15	0	1289.384	(991.659, 1676.496)	50.2
t½ (h)	GSK573719 500 µg	15	12	3	1.563	(1.288, 1.897)	31.2
	GSK573719 500 µg /GW642444 50 µg	15	15	0	1.776	(1.166, 2.703)	88.2
tmax (h)[1]	GSK573719 500 µg	15	13	2	0.080	(0.08, 0.13)	NA
	GSK573719 500 µg /GW642444 50 µg	15	15	0	0.080	(0.08, 0.08)	NA
tlast (h)[1]	GSK573719 500 µg	15	13	2	4.000	(1.00, 8.00)	NA
	GSK573719 500 µg /GW642444 50 µg	15	15	0	5.000	(1.00, 16.00)	NA

1. Presented as Median and range;
n*: No of subjects for whom parameter cannot be derived because of NQ concentrations, n=No of subjects with non missing observations including NC values. Cmax was imputed with 1/2 LLQ (LLQ=10 pg/mL) AUC(0-0.25), AUC(0-2), AUC(0-4),AUC(0-t) and AUC(0-inf) were imputed with ½ the lowest observed value for that parameter by analyte. Lowest observed AUC(0-0.25) was 54.08 hr*pg/mL,AUC(0-2) was 93.45hr*pg/mL,AUC(0-4) was 95.36 hr*pg/mL,AUC(0-t) was 83.92 hr*pg/mL and ,AUC(0-inf) was 95.62 hr*pg/mL
NA : not applicable; AUC (0-t) = area under concentration-time curve from time 0 to time of last quantifiable concentration; Cmax = maximum observed plasma concentration; tmax = time of maximum observed plasma concentration; tlast= last time point where the concentration is above the limit of quantification, CI = confidence interval.

Following a single dose administration of either GSK573719 alone or combination of GSK573719 and GW642444, GSK573719 was rapidly absorbed with all of the Cmax values occurring at 5 min following which plasma concentrations declined rapidly.

VI Pharmacokinetics

The summary of the plasma PK parameter estimates of VI from this study is presented below.

Table 18. Summary Statistcis of GW642444 PK Parameters

Parameter	Treatment	N	n	n*	Geometric Mean	95% CI	CV(%)
AUC(0-1) (h•pg/mL)	GW642444 50 µg	16	16	0	207.995	(171.502, 252.254)	37.4
	GSK573719 500 µg/ GW642444 50 µg	15	15	1	225.337	(177.127, 286.669)	45.6
AUC(0-t) (h•pg/mL)	GW642444 50 µg	16	16	0	234.342	(183.621, 299.074)	48.3
	GSK573719 500 µg/ GW642444 50 µg	15	15	1	271.343	(204.657, 359.759)	54.4
AUC(0-∞) (h•pg/mL)	GW642444 50 µg	16	16	1	233.768	(176.956, 308.819)	56.0
	GSK573719 500 µg/ GW642444 50 µg	15	15	1	315.562	(237.212, 419.791)	55.2
Cmax (pg/mL)	GW642444 50 µg	16	16	0	495.929	(396.693, 619.989)	43.8
	GSK573719 500 µg/ GW642444 50 µg	15	15	0	499.298	(330.787, 753.651)	85.9
t½ (h)	GW642444 50 µg	16	15	1	0.422	(0.361, 0.493)	28.9
	GSK573719 500 µg/ GW642444 50 µg	15	14	1	0.707	(0.515, 0.971)	59.3
tmax (h)[1]	GW642444 50 µg	16	16	0	0.080	(0.08, 0.10)	NA
	GSK573719 500 µg/ GW642444 50 µg	15	15	0	0.080	(0.08, 0.08)	NA
tlast (h)[1]	GW642444 50 µg	16	16	0	1.500	(1.00, 4.00)	NA
	GSK573719 500 µg/ GW642444 50 µg	15	15	0	2.000	(0.08, 5.00)	NA

1. Presented as Median and range;
n*: No of subjects for whom parameter cannot be derived because of NQ concentrations. n=No of subjects with non missing observations including NC values. Cmax was imputed with 1/2 LLQ (LLQ=30 pg/mL) AUC(0-1), AUC(0-t) and AUC(0-inf) were imputed with ½ the lowest observed value for that parameter by analyte Lowest observed AUC(0-1) was 114.38 hr*pg/mL,AUC(0-t) was 114.38 hr*pg/mL,AUC(0-inf) was 132.01 hr*pg/mL.

Following a single dose administration of either GW642444 alone or combination of GSK573719 and GW642444, GW642444 was rapidly absorbed with most of the Cmax values occurring at 5 min following which plasma concentrations declined rapidly.

For GSK573719, Cmax indicated that the combination treatment arm gave higher systemic exposure than GSK573719 alone. On the other hand, the treatment ratio for AUC parameters provided no evidence of a difference. For GW642444, there was no evidence of a difference in GW642444 systemic exposure when delivered as GSK573719 500 µg and GW642444 50 µg combination compared with GW642444 alone for Cmax. However AUC parameters indicated that the combination treatment arm gave higher systemic exposure than GW642444 alone.

In addition to the above studies, two other studies (study HZA105548 and study B2C112205) evaluated the effects of ketoconazle, a strong CYP3A4 inhibitor and a potent P-gp inhibitor on the PK of VI.

Ketoconazole co-administration increased VI AUC(0-t') and Cmax on average by 65% and 22%, respectively.

Following co-administration of repeat qd (400 mg) ketoconazole and single-dose VI 25 mcg there was, on average, a 90% increase in VI systemic exposure as measured by AUC(0–t), and an 11% decrease in the VI Cmax.

2.4.3. Pharmacodynamics

Mechanism of action

Laventair is a combination of two different medicines: umeclidinium bromide (UMEC) and vilanterol trifenatate (VI).

Umeclidinium bromide (GSK573719)

Umeclidinium is a long acting muscarinic receptor antagonist (also referred to as an anticholinergic). It is a quinuclidine derivative with activity across multiple muscarinic receptor subtypes. Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle. It demonstrates slow reversibility at the human M3 muscarinic receptor subtype *in vitro* and a long duration of action *in vivo* when administered directly to the lungs in pre-clinical models.

Vilanterol (GW64244)

Vilanterol trifenatate is a selective long-acting, $beta_2$ adrenergic agonist (LABA). The pharmacologic effects of $beta_2$ adrenoceptor agonist drugs, including vilanterol trifenatate, are at least in part attributable to stimulation of intracellular adenylate cyclase, the enzyme that catalyzes the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels cause relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

Primary and Secondary pharmacology

Primary pharmacology

Minimal primary pharmacology data was collected as bronchodilatory effect of treatments are best assessed in patients with impaired lung function (asthma or COPD). In healthy volunteers, specific airway conductance (sGaw) was selected as a sensitive measure for the PD effect. Most of these studies were with monocomponents and are not discussed here. Only one study, study DB2113208 was conducted with the combination of UMEC/VI and this study used FEV1 as the PD endpoint. This study is discussed below under secondary pharmacology.

Umeclidinium bromide (GSK573719)

Study AC4113073 evaluated doses of 62.5, 125, 250, 500, and 1000 mcg once-daily and 62.5, 125, and 250 mcg twice-daily for 14 days using an incomplete block crossover design. Study AC4115321 was of similar design to study AC4113073 with 15.6, 31.25, 62.5, and 125 mcg once-daily as well as 15.6 mcg and 31.25 mcg twice-daily given for 7 days. 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.

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. Further the results indicate no advantage of a twice-daily dosing interval over a once-daily dosing of UMEC

Vilanterol (GW64244)

A population dose-response relationship between once-daily doses of VI (3, 6.25, 12.5, 25, and 50 mcg) and mean change from Baseline trough (pre-bronchodilator and predose) FEV1 was established in subjects with COPD (study B2C111045).

A physiological Emax model supports VI as a potent bronchodilator (ED50 = 12.8 mcg [95% CI: 7.4, 18.2] with a predicted Emax for trough FEV1 of 167 mL [95% CI: 106, 228]). This translates into VI 12.5 mcg providing 49% of the maximum trough FEV1 effect, compared with 66% for VI 25 mcg and 80% for VI 50 mcg.

Study DB2113208

This was a randomized, placebo-controlled, four way cross over study to assess the safety, tolerability, pharmacodynamics and pharmacokinetics of single inhaled doses of UMEC and VI as mono-therapies and concurrently in healthy Japanese subjects. The pharmacodynamic results of this study are given below.

For minimum blood potassium (0-4 h), the comparison of UMEC 500 µg and VI 50 µg versus UMEC 500 µg showed the greatest mean decrease of -0.17 mmol/L (95% CI:-0.27, -0.07). This large decrease may have been influenced by the average increases that were observed for UMEC only. The comparison of UMEC 500 µg versus placebo showed an increase. For other comparisons 95% CI embraced zero.

For maximum HR (0-4 h), average increases were observed for all comparisons relative to placebo. Similar effects were observed when the GSK573719 500 µg and GW642444 50 µg combination was compared with each monotherapy, indicating that co administration does not alter the effect of either compound on heart rate parameters.

FEV1 values were higher for all treatment groups compared with placebo. The combination group showed the largest difference relative to placebo with FEV1 peaking up at 6 h with difference in adjusted mean [95% CI of 287 mL (14 mL, 560 mL)].

QTc(B) and QTc(F) (0-4 h) showed a small differences for the comparisons of GSK573719 versus placebo and combination versus GW642444). Increases in QTc parameters were observed for GW642444 relative to placebo. The average effect of the combination relative to placebo was larger than the effect of GW642444 alone. However this effect was not seen in the weighted mean analysis, where the effect of combination therapy lay between those of GSK573719 alone and GW642444 alone.

For blood potassium, an average decreases were observed for GW642444 and combination (treatment groups containing GW642444) versus placebo. Average increase was observed for GSK573719 versus placebo. A larger decrease was seen for the combination relative to GSK573719 500 µg alone than was seen for the combination relative to placebo. This was driven by the increase observed for GSK573719.

There were no obvious trends observed between individual change in maximum HR and GSK573719 or GW642444 Cmax when administered as GSK573719 500 μg/GW642444 50 µg concurrently or as GSK573719 or GW642444 administered alone.

Study DB2113950

This was a drug-drug interaction study with verapamil and this study also evaluated the pharmacodynamic effects of the combination UMEC/VI.

There were no clinically significant vital signs, 12-lead ECG or Holter findings. No subject had a heart rate increase >40 bpm from baseline or a resting heart rate >130 bpm. No subject had a QTc >500 msec or an absolute change from baseline >60 msec.

Statistical analyses of vital signs and ECG parameters are summarised below.

Endpoint	Derived parameter	Treatment difference (90% CI)	
		719 vs. 719+V	719/444 vs. 719/444+V
Heart rate (bpm)	Maximum (0–4 h)	5.74 (-3.25, 14.73)	0.40 (-3.04, 3.84)
	Weighted mean (0–4 h)	2.85 (-2.59, 8.29)	0.61 (-2.22, 3.44)
QTcB (msec)	Maximum (0–4 h)	6.71 (1.06, 12.36)	8.07 (1.51, 14.62)
	Weighted mean (0–4 h)	7.43 (2.07, 12.79)	10.93 (6.56, 15.31)
QTcF (msec)	Maximum (0–4 h)	8.96 (4.75, 13.16)	7.67 (3.74, 11.59)
	Weighted mean (0–4 h)	9.40 (5.06, 13.74)	9.19 (5.57, 12.80)
Holter heart rate (bpm)	Maximum (0–24 h)	-14.5 (-19.3, -9.73)	-11.1 (-17.0, -5.27)
	Mean (0–24 h)	-5.98 (-8.28, -3.68)	-3.80 (-6.13, -1.47)

719 = GSK573719 500 µg; 444 = GW642444 25 µg; V = verapamil 240 mg.

For maximum heart rate (0-4 h), average changes were small for all comparisons with and without verapamil. The clinical relevance of such potential effects is to be determined in the light of the expected verapamil effects.

Values of QTcB and QTcF (0-4 h) showed increases for comparisons that probably highlight the effect of verapamil on the ECG. The clinical relevance of such potential effects is to be determined in the light of the expected verapamil effects.

For blood potassium, a small decrease was observed with the addition of verapamil in both cohorts. The clinical relevance of such potential effects is to be determined in the light of the expected verapamil effects.

Blood potassium and blood glucose

Two studies (B2C108784 in healthy subjects and B2C110165 in COPD patients) evaluated the effect of VI on blood potassium and blood glucose. These studies also showed there were no obvious treatment differences on repeated dosing of VI 100mcg once daily for 14 days. The only positive treatment difference from placebo was observed following the administration of VI 100mcg which was 0.06mmol/L in healthy subjects and 0.32 mmol/L in COPD patients for the 0-4 hours weighted mean glucose. The effect of UMEC alone and the effect of UMEC/VI were assessed in studies DB2113208 and DB2113950 and these studies also showed no significant effect on poatassium or glucose.

Thorough QTc study (DB2114635)

A thorough QTc study was conducted to evaluate the effect of UMEC/VI on QT prolongation. This was a randomized, placebo-controlled, 10-day repeat dose, 4-period, incomplete block study in healthy subjects. The treatments tested were Placebo, Moxifloxacin 400mg dose, UMEC 500mcg (supratherapeutic dose), UMEC/VI 125/25 therapeutic dose and UMEC/VI 500/100 (supratherapeutic dose).

A summary of point estimates and 90% CIs for the adjusted mean difference from placebo in change from baseline QTcF for the comparison of interest is given in the table below.

Table 19. 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.

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 study was negative for UMEC and UMEC/VI at therapeutic doses 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 timepoint.

Heart-rate

Repeat-dose UMEC/VI 125/25 mcg and 500/100 mcg for 10 days resulted in a maximum increase in time-matched heart rate (mean change from baseline) compared with placebo of 8.4 bpm (90% CI: 7.0, 9.8) and 20.3 bpm (90% CI: 18.9, 21.7), respectively; both were at 10 minutes after dosing. Heart rates rapidly declined after these maximum differences.

Blood pressure

The effects of UMEC and VI on BP were evaluated in monocomponent studies. In these studies, at therapeutic doses there was no significant effect of UMEC or VI on blood pressure. However UMEC at

1000mcg and VI at 100 mcg showed an increase in systolic and diastolic BP of around 3 mm Hg, which were not clinically significant.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

The absolute bioavailability for umeclidinium bromide and vilanterol when administered by inhlation was on average 12.8 % and 27.3 % respectively. The oral bioavailability of both umeclidinium bromide and vilanterol was low, on average < 1% and < 2 % respectively. Given this low oral bioavailability, systemic exposure for umeclidinium bromide and vilanterol following inhaled administration is primarily due to absorption of the inhaled portion of the dose delivered to the lung.

Following intravenous dosing, both umeclidinium bromide and vilanterol are extensively distributed with average volumes of distribution at steady state of 86.2 L and 165 L, respectively. Both umeclidinium and vilanterol have a low association with red blood cells. In vitro plasma protein binding in human plasma of umeclidinium bromide and vilanterol was moderate and high, respectively. Umeclidinium bromide and vilanterol are both substrate for P-glycoprotein (P-gp), however concomitant administration of umeclidinium bromide/vilanterol with P-gp inhibitors is considered unlikely to alter umeclidinium bromide or vilanterol systemic exposure.

Based on in vitro data, the major routes of metabolism of umeclidinium bromide and vilanterol in human are mediated primarily by CYP2D6 and CYP34A, respectively. Umeclidinium bromide is primarily metabolised through oxidation (hydroxylation, O-dealkylation) and conjugation to a range of metabolites with either reduced pharmacological activity or for which the pharmacological activity has not been established. Vilanterol is primarily metabolised by O dealkylation to a range of metabolites with significantly reduced β1- and β2-agonist activity.

Following oral administration, umeclidinium bromide was eliminated in human mainly by metabolism and excreted in the faeces, with < 1 % of the recovered radioactivity dose eliminated in the urine. Following oral administration, vilanterol was eliminated mainly by metabolism followed by excretion of metabolites in urine and faeces approximately 70% and 30% of the radioactive dose respectively in a human radiolabel study conducted by the oral route.

The effects of age on the pharmacokinetics of umeclidinium and vilanterol were determined in population PK analyses. The analyses however demonstated that the effect of age on PK is marginal and that no dose adjustement is warranted for elderly patients.

A clinical pharmacology study of umeclidinium bromide/vilanterol showed that severe renal impairment did not result in significantly greater exposure to umeclidinium bromide or vilanterol compared with healthy subjects. No dose adjustment is therefore required for patients with renal impairment.

Following repeat dosing of umeclidinium bromide/vilanterol for 7 days, there was a slight decrease in umeclidinium bromide and vilanterol exposure in subject with hepatic impairment (Child-Pugh B) compared with healthy subjects. Therefore no dose adjustement is recommended for patients with moderate hepatic impairment. Umeclidinium bromide/vilanterol FDC has not been studies in patients with severe hepatic impairment and should be used with caution as described in the product information.

There was no evidence for age, race, gender, weight or BMI (body mass index) to influence the pharmacokinetics of umeclidinium bromide and vilanterol based on population PK analyses. Therefore no dose adjustement is recommended based on race, gender, weight or BMI.

Three studies were conducted which allowed for the evaluation of a potential PK interaction between UMEC and VI (study DB2114635, study DB2113208, and study DB2113950), as well as results from the Population PK analysis. These studies and the Population PK analysis showed no difference in PK parameters when UMEC or VI was administered as monotherapy compared with when administered in combination, thereby indicating a lack of a PK interaction between UMEC and VI.

In vitro studies conducted using human recombinant CYP enzymes showed that UMEC was metabolized principally by CYP2D6. In a clinical study conducted in healthy normal metabolizer subjects and healthy CYP2D6 poor metabolizer subjects, there was no clinically significant difference in the systemic exposure to UMEC following 7 days of repeat dosing with IH doses up to 1000 mcg. No dose adjustment is recommended in patients using concomitant CYP2D6 inhibitors or subjects with genetic polymorphisms of CYP2D6 metabolism.

Based on in vitro data, the major routes of metabolism of VI in humans are mediated primarily by CYP3A4. Concomitant administration of strong CYP3A4 inhibitors may inhibit the metabolism of, and increase the systemic exposure to, vilanterol. Co-administration with ketoconazole (400 mg) in healthy volunteers increased mean vilanterol $AUC_{(0-t)}$ and $C_{max,}$ 65% and 22% respectively. The increase in vilanterol exposure was not associated with an increase in beta-adrenergic agonist related systemic effects on heart rate, blood potassium or QT interval (corrected using the Fridericia method). Caution is advised when co-administering umeclidinium/vilanterol with ketoconazole and other known strong CYP3A4 inhibitors as there is potential for an increased systemic exposure to vilanterol. Verapamil, a moderate CYP3A4 inhibitor, did not significantly affect the pharmacokinetics of vilanterol.

Both UMEC and VI are substrates of P-gp. In a clinical study conducted in healthy subjects where IH UMEC and VI were co-administered with verapamil, a potent inhibitor of P-gp and moderate inhibitor of CYP3A4, there was no effect of verapamil on UMEC Cmax, VI Cmax, or VI AUC and only a moderate increase (1.4-fold) in AUC for UMEC.

The applicant conducted interaction studies to identify the clinically significant interactions between UMEC and VI when used as fixed dose combination product. In general the CHMP agreed that there are no major concerns on the pharmacokinetics. However there are some aspects of the metabolism of UMEC and VI that are not yet completely understood and additional in-vitro studies may provide some useful answers. The applicant will, as requested by the CHMP, conduct the following in-vitro studies:

- binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations
- provide data for VI as a substrate of OATP1B1 and 1B3
- provide data for UMEC as a substrate for BCRP and BSEP
- provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers.
- provide data for UMEC as a substrate of OATP1B1 and 1B3.

as additional Pharmacovigilance activities as described in the Risk Management Plan (RMP).

Pharmacodynamics

Laventair is a combination of two active ingredients, umeclidinium bromide, a LAMA and vilanterol trifenatate, a LABA. Both compounds act locally on airways to produce bronchodilation by separate mechanisms. Umeclidinium exerts its bronchodilatory activity by competitively inhibiting the binding of acetylcholine with muscarinic receptors on airway smooth muscle. The activity of vilanterol is mediated through increased cyclic AMP levels, which cause relaxation of bronchial smooth muscle (bronchodilatory effect) and inhibition of release of mediators of immediate hypersensitivity from cells, especially from mast cells.

The primary and secondary pharmacology parameters studied in the clinical development of UMEC/VI included all the well characterised and reported PD effects of LAMAs and LABAs. The three studies discussed under pharmacokinetics (study DB2114635 – thorough QTc study, Study DB2113950 – verapamil interaction study and Study DB2113208 – PK study in Japanese subjects) also evaluated the pharmacodynamics of the combination. In addition there were other studies which evaluated the PD of the individual components which are considered supportive of the PD actions of UMEC/VI.

All the relevant clinical data generated have been used in modelling to predict concentration dependent effects and to plot dose-response curves. For the primary pharmacology effect of bronchodilation, the effects of UMEC and VI on trough FEV1 have been modelled and relevant parameters like Emax, ED50 and %age maximal response at a proposed dose have been calculated. However while the dose-response effects of the individual components have been well characterised, the dose-response effect of the fixed dose combination of UMEC/VI have not been characterised.

The effects of UMEC and VI on the generally anticipated pharmacodynamic effects have been studied. Clinically significant secondary pharmacology effects like heart rate, blood potassium, blood glucose and ECG effects (particularly effect on QTc) were generally not seen at the therapeutic concentrations.

The effect of umeclidinium/vilanterol on the QT interval was evaluated in a placebo and active (moxifloxacin) controlled QT study involving once daily administration of umeclidinium/vilanterol 113/22 micrograms or 500/100 micrograms (pre-dispensed dose with umeclidinium at eight times the recommended dose and vilanterol at four times the recommended dose) for 10 days in 103 healthy volunteers. The maximum mean difference in prolongations of QT interval from placebo after baseline-correction was 4.3 (90% CI=2.2 to 6.4) milliseconds seen 10 minutes after administration with umeclidinium/vilanterol 113/22 micrograms and 8.2 (90% CI=6.2 to 10.2) milliseconds seen 30 minutes after administration with umeclidinium/vilanterol 500/100 micrograms. Therefore, no clinically relevant pro-arrhythmic potential related to QT-interval prolongations was observed with umeclidinium/vilanterol 113/22 micrograms.

A dose-dependent increase in heart rate was also observed. The maximum mean difference in heart rate from placebo after baseline-correction was 8.4 (90% CI=7.0 to 9.8) beats/minute and 20.3 (90% CI=18.9 to 21.7) beats/minute seen 10 minutes after administration of umeclidinium/vilanterol 113/22 micrograms and 500/100 micrograms respectively.

In addition, no clinically significant effects on cardiac rhythm were observed on 24-hour Holter monitoring in 53 patients with COPD who were treated with umeclidinium/vilanterol 55/22 micrograms once daily in one 6-month study, or in a further 55 patients who received umeclidinium/vilanterol 113/22 micrograms once daily in another 6-month study and 226 patients who received 113/22 micrograms once daily in the 12-month study.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of the umeclidinium bromide/vilanterol FDC has been well documented. UMEC/VI has a pharmacokinetic profile with low potential for interactions due to the low plasma concentration achieved after inhaled dosing. Exposure differences based on gender, age, weight, race, renal impairment and mild hepatic impairment were estimated and were not considered clinically relevant. UMEC/VI FDC has not been studied in patients with severe hepatic impairment and should be used with caution as described in the product information. As some aspects of the metabolism of UMEC and VI that are not yet completely characterised, the applicant will conduct a number of in-vitro studies as additional Pharmacovigilance activities as described in the RMP.

The pharmacodynamics of UMEC/VI indicates that this combination is potentially effective in the treatment of COPD. The pharmacodynamics of UMEC/VI is considered to be adequately characterised

by the studies performed in phase I and II. The results of these studies are appropriately reflected in the SmPC.

2.5. Clinical efficacy

2.5.1. Dose response studies

There are 3 main dose-finding studies for UMEC and one main dose-finding study for VI in COPD patients. There are 2 other dose-finding (and dose-frequency) studies of VI in asthma which is the basis for the selection of dose of VI in COPD. No dose-finding studies with the umeclidinium bromide/vilanterol FDC were submitted.

The key studies supporting choice of dose and dose interval and comparing morning and evening dosing are shown in the table below.

Table 20. Studies to Support Doses and Dose Regimen of UMEC and VI Used in UMEC/VI Phase III Studies

Study Number	Study Objective(s)	Study Design	Duration	Relevant Treatment Arms (mcg) (once-daily unless otherwise specified)	Population
UMEC Dose Selection					
AC4113589, m 5.3.5.1	Dose-ranging	R, DB, PG, PC	28 days	UMEC 125 UMEC 250 UMEC 500 PLA	COPD
AC4113073, m5.3.5.1	Dose-ranging, dosing-interval, and PK	R, DB, XO, PC Incomplete block	3 periods per subject, 14 days per period	Once-daily: UMEC 62.5 UMEC 125 UMEC 250 UMEC 500 UMEC 1000 TIO 18 OL PLA Twice-daily: UMEC 62.5 UMEC 125 UMEC 250 PLA	COPD
AC4115321, m5.3.5.1	Dose-ranging and dosing-interval	R, DB, XO, PC Incomplete block	3 periods per subject, 7 days per period	Once-daily: UMEC 15.6 UMEC 31.25 UMEC 62.5 UMEC 125 TIO 18 OL PLA Twice-daily: UMEC 15.6 UMEC 31.25 PLA	COPD
AC4115408, m5.3.5.1	Efficacy and safety	R, DB, PG, PC	12 weeks	UMEC 125 UMEC 62.5 PLA	COPD
VI Dose Selection					
B2C111045, m5.3.5.1	Dose-ranging	R, DB, PG, PC Stratified a	28 days	VI 3 VI 6.25 VI 12.5 VI 25 VI 50 PLA	COPD

Study Number	Study Objective(s)	Study Design	Duration	Relevant Treatment Arms (mcg) (once-daily unless otherwise specified)	Population
HZA113310, m5.3.5.1	Dose-ranging and dosing-interval	R, DB, XO, PC	5 periods per subject, 7 days per period	Once-daily: VI 6.25 VI 12.5 VI 25 Twice-daily: VI 6.25 PLA	Asthma
B2C109575, m 5.3.5.1	Dose-ranging	R, DB, PG, PC Stratified b	28 days	VI 3 VI 6.25 VI 12.5 VI 25 VI 50 PLA	Asthma

Abbreviations: COPD=chronic obstructive pulmonary disease; DB=double-blind; OL=open-label; PC=placebo-controlled; PG=parallel-group, PLA=placebo; R=randomized, TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol; XO=cross-over

a. Subjects' reversibility to salbutamol was used to stratify the randomization.
b. Subjects' baseline FEV_1 (≥40% to ≤65% and > 65% to ≤90% of predicted normal) was used to stratify the randomization.

Umeclidinium bromide

Three studies, all in COPD patients, evaluated UMEC doses ranging from 15.6 mcg once daily to 1000 mcg once daily. One study (study AC113589) was a placebo controlled 28-day study evaluating doses 125 mcg, 250 mcg and 500 mcg of UMEC. The second and third studies were dose-ranging and dose-interval finding studies, both placebo-controlled. One study (study AC4113073), of 14 days duration evaluated doses of UMEC 62.5, 125, 250, 500 and 1000 mcg in comparison to Tiotropium 18 mcg given once daily and UMEC doses 62.5, 125 and 250 mcg given twice daily as well. The other study (study AC4115321), of 7 days duration, evaluated the UMEC doses of 15.6, 31.25, 62.5, and 125 mcg in comparison to Tiotropium given once daily and UMEC doses of 15.6 and 31.25 given twice daily.

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, with safety profiles that were comparable to placebo. At doses of 250 mcg and above, AEs were more common. 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 dose response model incorporating data from the two crossover studies suggests 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.

In addition study AC4115408 a 12 week 'efficacy and safety' phase III study in COPD patients, which evaluated both 125 mcg and 62.5 mcg doses in comparison to placebo, provides supporting evidence for the doses of UMEC selected. This study demonstrated both 62.5 and 125 mcg doses were effective over 12 weeks and showed a separation in efficacy between these doses as observed in Phase IIb.

A summary of trough FEV1 (primary endpoint) findings from the Phase IIb studies and AC4115408 is shown in the table below. These studies also support that the steady state pharmacodynamic effect of UMEC is observed after 7 days of treatment.

Table 21. Summary of the Difference from Placebo for LS Mean Change from Baseline in Trough FEV1(L) (95% CI) (Individual Study Results for AC4113589 and AC4115408ITT Populations 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)	
AC4115408 at Day 85			0.127 (0.052, 0.202)	0.152 (0.076, 0.229)			

Data Source: CSR AC4115321, Table 7.02; CSR AC4113073, Table 6.02; CSR AC4113589, Table 6.02; CSR AC4115408, Table 6.05

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. All doses are once-daily.

The evaluations of once- and twice-daily dosing in the Phase IIb studies AC4115321 and AC4113073 provide substantial evidence to support a once-daily dosing interval for UMEC. 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.

Table 22. Statistical Analysis: Trough FEV1(L) on Day 8 (AC4115321 mITT Population)

		UMEC Once-daily			
Trough FEV_1 (L)	**Placebo N=60**	**15.6 N=60**	**31.25 N=57**	**62.5 N=59**	**125 N=60**
n	59	58	56	59	59
LS mean (SE)	1.342 (0.022)	1.455 (0.022)	1.443 (0.023)	1.466 (0.022)	1.525 (0.022)
LS mean change (SE)	-0.074 (0.022)	0.038 (0.022)	0.027 (0.023)	0.049 (0.022)	0.109 (0.022)
Difference from placebo	-	0.113	0.101	0.124	0.183
95% CI	-	(0.058,0.168)	(0.045,0.158)	(0.068,0.179)	(0.127,0.239)
p-value	-	<0.001	<0.001	<0.001	<0.001

	UMEC Twice-daily		TIO
Trough FEV_1 (L)	**15.6 N=56**	**31.25 N=58**	**Once-daily N=56**
n	55	57	56
LS mean (SE)	1.467 (0.023)	1.481 (0.023)	1.443 (0.023)
LS mean change (SE)	0.051 (0.023)	0.065 (0.023)	0.027 (0.023)
Difference from placebo	0.125	0.139	0.101
95% CI	(0.069,0.182)	(0.083,0.196)	(0.045,0.157)
p-value	<0.001	<0.001	<0.001

Data Source: AC4115321 CSR, Table 7.02

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; mITT=modified intent-to-treat; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide

Note: Analysis performed using a mixed model with covariates of mean baseline, period baseline, treatment and period as fixed effects and subject as a random effect.

Note: For each treatment period, baseline was defined as the mean of the values obtained 5 and 30 minutes predose on Day 1 and trough was defined as the FEV_1 value obtained 23 and 24 hours after the morning dose administered on Day 7.

The above table provides the results of trough FEV1 on day 8 and gives a within study comparison of the 15.6 mcg BID vs 31.25 mcg OD and 31.25 mcg BID vs 62.5mcg OD from study AC4115321.

The below table provides the results of trough FEV1 on day 15 and gives a within study comparison of the 62.5BID vs 125 OD, 125 BID vs 250 OD and 250 BID vs 500 OD.

Table 23. Statistical Analysis: Trough FEV1(L) at Day 15 (AC4113073 mITT Population)

	PLA N=158	UMEC 62.5 QD N=35	UMEC 125 QD N=34	UMEC 250 QD N=36	UMEC 500 QD (N=38
n	150	34	33	35	37
LS mean	1.395	1.524	1.542	1.490	1.535
Standard error	0.017	0.033	0.034	0.033	0.032
LS mean change	-0.047	0.081	0.099	0.048	0.092
Standard error	0.017	0.033	0.034	0.033	0.032
Difference to placebo	-	0.128	0.147	0.095	0.140
95% CI	-	0.060, 0.196	0.077, 0.216	0.027, 0.162	0.074, 0.205
p-value	-	<0.001	<0.001	0.006	<0.001

	UMEC 1000 QD N=32	UMEC 62.5 BD N=34	UMEC 125 BD N=37	UMEC 250 BD N=33	TIO N=35
n	29	31	33	32	34
LS mean	1.581	1.475	1.529	1.567	1.500
Standard error	0.036	0.035	0.034	0.034	0.033
LS mean change	0.138	0.032	0.087	0.124	0.058
Standard error	0.036	0.035	0.034	0.034	0.033
Difference to placebo	0.186	0.079	0.134	0.172	0.105
95% CI	0.113, 0.259	0.008, 0.151	0.064, 0.204	0.101, 0.242	0.037, 0.173
p-value	<0.001	0.030	<0.001	<0.001	0.003

Data source: CSR AC4113073, Table 6.02

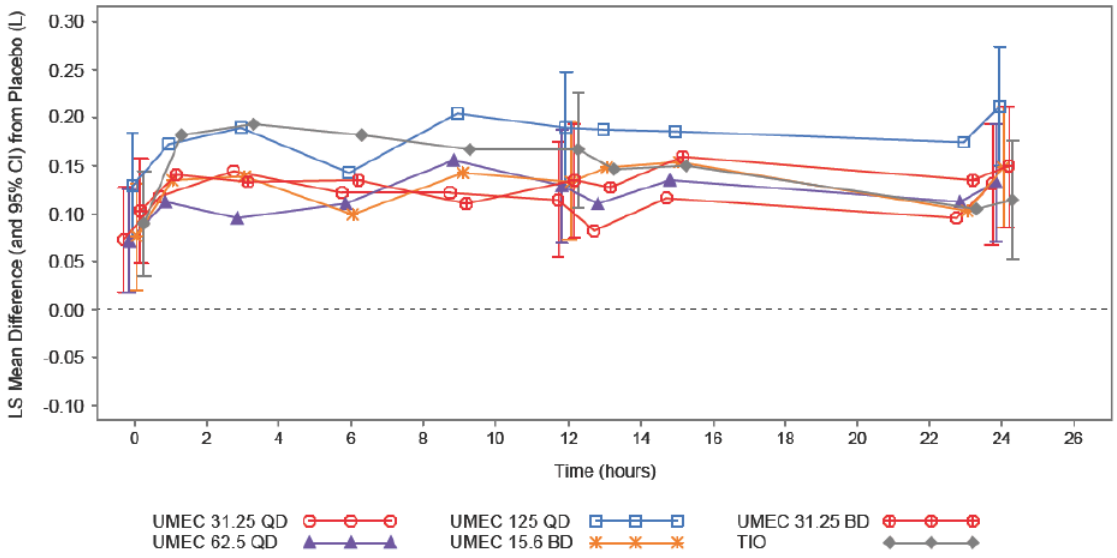
Abbreviations: BD=twice-daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; mITT=modified intent-to-treat; PLA=Placebo; QD=once-daily; TIO=tiotropium; UMEC=umeclidinium bromide

Note: Analysis performed using a mixed model with covariates of mean baseline, period baseline, treatment and period as fixed effects and subject as a random effect.

Note: Trough FEV_1 is defined as the FEV_1 value obtained 24 hours after the morning dose administered at Day 14.

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 later 12 hours of the dosing interval. Notably, administration of a second dose of UMEC at 12 hours following the morning dose did not result in an appreciable change in FEV1 in the subsequent 12 hours. Furthermore, the improvements in FEV1 from placebo observed at time points over the first 12 hours were maintained at time points over the second 12 hours with UMEC once-daily (see figure below). This is reflected in the ratios for the difference from placebo in 0 to 12 hour FEV1 weighted mean values obtained after PM dosing over those obtained after AM dosing which showed comparable results for both dosing regimens thereby supporting the effectiveness of once daily administration for UMEC.

Figure 1. Difference (95% CI) from Placebo in LS Mean Change from Baseline in FEV1 Over Time at Day 7: UMEC Once-Daily (31.25, 62.5 and 125 mcg) and Twice-Daily (15.6 abd 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; VI=vilanterol
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.

Vilanterol

Two 28 days studies, one in asthma (study B2C109575) and the other in COPD (study B2C111045) evaluated the dose-related increase in FEV1 over the dose-range of 3, 6.25, 12.5, 25 and 50 mcg. An additional study in asthma (study HZA113310) supports these findings over a 7 day treatment period. Since an asthma population is highly responsive to beta-agonist bronchodilation, the dose response (study B2C109575) and dosing interval findings (study HZA113310) conducted in subjects with asthma provide supportive information for VI in COPD.

Study B2C111045 clearly demonstrated that the 25 and 50 mcg doses of VI are more efficacious than doses of 3, 6.25, and 12.5 mcg. Compared with placebo, clinically meaningful differences of ≥0.1 L in trough FEV1 were observed on Day 29 with the 12.5, 25, and 50 mcg doses, while differences of ≥0.13 L were observed only with the 25 mcg and 50 mcg doses. A Bayesian analysis of the change from baseline in trough FEV1 demonstrated that the probabilities of having a true treatment difference of >0.1 L over placebo were more than 90% with both the 25 mcg and 50 mcg doses, but much lower (<64%) for the 3, 6.25, and 12.5 mcg doses. VI 25 and 50 mcg once daily were also associated with greater improvements in secondary and other efficacy parameters including 0 to 24 hour weighted mean FEV1, individual serial FEV1 time points, and the percentage of symptom-free periods. All VI doses were well tolerated throughout the study period. Therefore, based on the efficacy findings as well as the safety profile, the 25 mcg dose was chosen as the lowest effective dose for evaluation in Phase III.

Trough FEV1 (primary endpoint) findings from the VI Phase IIb studies are shown in the below table.

Table 24. Summary of the Difference from Placebo in LS Mean Change from Baseline in Trough FEv1 (L) (95% CI) (Individual Study Results for B2C111045, B2C109575 and HZA113310 ITT Populations)

	Difference from Placebo for LS Mean Change from Baseline in Trough FEV_1 (L) (95% CI) by once daily VI dose (mcg) [a]				
Study	**3**	**6.25**	**12.5**	**25**	**50**
COPD					
B2C111045 at Day 29	0.092 (0.039,0.144)	0.098 (0.046, 0.150)	0.110 (0.057,0.162)	0.137 (0.085, 0.190)	0.165 (0.112,0.217)
Asthma					
B2C109575 at Day 28	0.064 (-0.036, 0.164)	0.069 (-0.029, 0.168)	0.130 (0.030, 0.230)	0.121 (0.023, 0.220)	0.162 (0.062, 0.261)
HZA113310 at Day 7		0.094 (0.049, 0.140)	0.102 (0.057, 0.147)	0.125 (0.080, 0.170)	

Data Source: CSR B2C111045, Table 7.02; CSR B2C109575, Table 7.4; CSR HZA113310, Table 6.2
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT= intent-to-treat; VI=vilanterol
Note: Number of subjects included in analysis is provided in data source tables.
a. Trough FEV_1 values are from last scheduled on treatment visit for each study. All doses are once-daily.

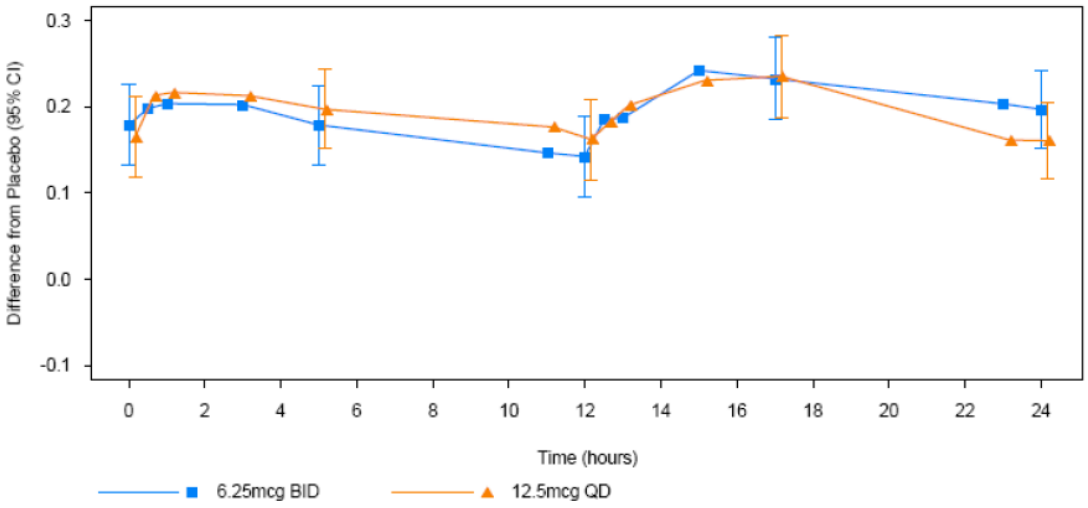
A once-daily dosing interval for VI was supported by demonstration of similar efficacy when the same total daily dose was given once-daily or twice-daily. In study HZA113310, performed in asthmatics, there was minimal difference in 0 to 24 hour weighted mean FEV1 between VI 12.5 mcg once-daily (LS mean difference from placebo of 0.168 L) and 6.25 mcg twice-daily (LS mean difference from placebo of 0.166 L), demonstrating no advantage for twice-daily dosing over once-daily dosing for the same total daily dose. The 24 hour serial FEV1 curves supported the once daily dosing profile of VI.

Table 25. Statistical Analysis of Weighted Mean 24-hour Clinical FEV1 (L) on Day 7 (HZA113310 ITT Population)

		VI			
	Placebo N=74	**6.25 QD N=73**	**6.25 BD N=74**	**12.5 QD N=73**	**25 QD N=73**
n	74	73	74	73	73
LS Mean (SE)	2.467 (0.0617)	2.621 (0.0617)	2.633 (0.0617)	2.636 (0.0617)	2.652 (0.0617)
LS Mean Change (SE)	0.028 (0.0195)	0.181 (0.0195)	0.194 (0.0195)	0.196 (0.0195)	0.213 (0.0195)
Column vs. Placebo					
LS Mean Difference		0.153	0.166	0.168	0.185
95% CI		(0.115, 0.192)	(0.128, 0.204)	(0.130, 0.206)	(0.146, 0.223)
p-value		<0.001	<0.001	<0.001	<0.001

Data Source: CSR HZA113310, Table 6.7
Abbreviations: ANCOVA=analysis of covariance; BD=twice-daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; QD=once-daily; SE=standard error; VI=vilanterol
Note: Analysis performed using mixed model ANCOVA with fixed effects of treatment, period, sex, and age. Subject is fitted as a random effect and the period baseline FEV_1 measurement is included as part of a bivariate response. The model for the period baseline value is not affected by treatment group.

Figure 2. Repeated Measures Difference from Placebo in LS Mean Change from Period Baseline FEV1 (L) Over Time on Day 7 for VI 6.25 mcg Twice-daily and 12.5 mcg Once-daily (HZA113310 ITT Population)



Data Source: CSR HZA113310, Figure 6.106
Abbreviations: BID=twice-daily; CI=confidence interval; FEV_1=forced expiratory volume in 1 second; LS=least squares; QD=once-daily; TIO=tiotropium; UMEC=umeclidinium bromide
Note: Serial FEV_1 measurements taken at the following time points; predose, 30 and 60 minutes, 3, 5, 11, 12, 12.5, 13, 15, 17, 23 and 24 hours postdose.
Note: Analysis adjusted for the mean of the period baselines, period, period baseline, treatment, sex, age, time (nominal), time by mean of the period baselines interaction, time by period baseline interaction and time by treatment interaction.

However, the statistical analysis of trough FEV1 on day 7 which is given in the table below and was the primary objective suggests that the BD regimen might be better than the OD regimen.

Table 26. Statistical Analysis of Trough FEV1 (L) on Day 7 (ITT)

	Placebo (N=74)	6.25mcg QD (N=73)	6.25mcg BD (N=74)	12.5mcg QD (N=73)	25mcg QD (N=73)
n	74	73	74	73	73
LS Mean (SE)	2.498 (0.0625)	2.593 (0.0626)	2.638 (0.0625)	2.601 (0.0625)	2.624 (0.0625)
LS Mean Change (SE)	0.059 (0.0221)	0.153 (0.0222)	0.198 (0.0221)	0.161 (0.0221)	0.184 (0.0221)
Column vs Placebo					
LS Mean Difference		0.094	0.140	0.102	0.125
95% C.I.		(0.049, 0.140)	(0.095, 0.185)	(0.057, 0.147)	(0.080, 0.170)
p-value		<0.001	<0.001	<0.001	<0.001

Source: Table 6.2
Notes: Analysis performed using mixed model ANCOVA with fixed effects of treatment, period, sex and age. Subject was fitted as a random effect and the period baseline measurement was included as part of a bivariate response. The model for the period baseline value was not affected by treatment group.

2.5.2. Main studies

In total there are 7 main studies (DB2113361, DB2113373, DB2113360, DB2113374, DB2114417, DB2114418 and DB2113359) supporting of this application.

These 7 main clinical studies include 3 pairs of replicate studies and one long term study for 52 weeks (study DB2113359). The 3 pairs of replicate studies include:

- Two placebo controlled studies (studies DB2113361 and DB2113373) of 24 weeks treatment duration
- Two active controlled (tiotropium) (studies DB2113360 and DB2113374) studies of 24 weeks treatment duration
- Two exercise endurance studies (studies DB2114417 and DB2114418) of 12 weeks treatment duration.

Table 27. Phase III Efficacy Studies

Study	Study Design and Objective	Duration	Endpoints [a]
Primary Efficacy Studies			
DB2113361 DB2113373 DB2113360 DB2113374	R, DB, PG, PC (DB2113361, DB2113373) R, DB, DD, PG, AC (DB2113360, DB2113374) Safety and efficacy (all) Population PK (DB2113361, DB2113373)	24 weeks	Primary: • Trough FEV_1 (Day 169) Secondary: • TDI focal score (Week 24; DB2113361/DB2113371 only)[a] • 0-6hr WM FEV_1 (Week 24) Other: • TDI focal score (Week 24; DB2113360/DB2113374 only) • FEV_1 measures and TDI at other visits • Serial FEV_1 • Peak FEV_1 • Trough FEV_1 responder analyses • Time to onset • FVC (trough and serial) • Rescue albuterol use • Mean SOBDA score • TDI responder analysis • SOBDA responder analysis • Time to first exacerbation • EQ-5D, CAT, morning PEF, patient device preference (DB2113360/DB2113374 only) HRQoL: • SGRQ • SGRQ responder analysis
Supportive Efficacy Studies			
DB2114417 DB2114418	R, DB, PC, XO Incomplete block Exercise endurance and lung function	12 weeks per period, 2 periods per subject	Co-primary: • EET post dose (Week 12) and Trough FEV_1 (Week 12) Secondary: • Inspiratory Capacity • Forced Residual Capacity • Residual Volume • 3-hour post-dose FEV_1 Other: • Rescue salbutamol use
DB2113359	R, DB, PG, PC Long-term safety	52 weeks	Incidence of Adverse Events Incidence of COPD exacerbations Time to First COPD exacerbation Supplemental use of Salbutamol and/or ipratropium bromide Percentage of rescue free days Trough FEV_1 Trough FVC

Abbreviations: AC=active-controlled; CAT=COPD assessment test; COPD=chronic obstructive pulmonary disease; DB=double-blind; DD=double-dummy; EET=exercise endurance time; EQ-5D=EuroQol-5D; FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; HRQoL=health-related quality of life; PC=placebo-controlled; PEF=peak expiratory flow; PG=parallel group; PK=pharmacokinetic; R=randomized; SGRQ=St. George's Respiratory Questionnaire; SOBDA=shortness of breath with daily activities; TDI=transition dyspnea index; WM=weighted mean; XO=cross-over

a. Following CHMP Scientific Advice, TDI is the key secondary endpoint for the placebo controlled studies for assessment in EU. Weighted mean FEV_1 (0-6hrs) is a secondary endpoint for assessment in all submissions. For TIO controlled studies, the key secondary endpoint is weighted mean FEV_1 (0-6hrs) and TDI is an "other" endpoint.

Studies DB2113361 and DB2113373

Methods

Studies DB2113361 and DB2113373 were two phase IIIa, 24-Week, randomized, double-blind, placebo-controlled studies 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 (COPD).

Study Participants

Inclusion criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

1. **Type of subject:** Outpatient.
2. **Informed Consent:** A signed and dated written informed consent prior to study participation.
3. **Age:** 40 years of age or older at Visit 1.
4. **Gender:** Male and female subjects were eligible to participate in the study.
5. **Diagnosis:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society (ATS)/European Respiratory Society [Celli, 2004] as follows:

   Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
6. **Smoking History:** Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years [number of pack-years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years both equal 10 pack-years)]. Former smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1.
7. **Severity of Disease:** A post-salbutamol FEV1/FVC ratio of <0.70 and a post-salbutamol FEV1 of ≤70% of predicted normal values calculated using the National Health and Nutrition Examination Survey (NHANES) III reference equations at Visit 1 [Hankinson, 1999; Hankinson, 2010].
8. **Dyspnea:** A score of ≥2 on the Modified Medical Research Council (mMRC) Dyspnea Scale at Visit 1.

Exclusion criteria

Subjects who met any of the following criteria must not have been enrolled in the study:

1. **Pregnancy:** Women who were pregnant or lactating or were planning on becoming pregnant during the study.
2. **Asthma:** A current diagnosis of asthma.
3. **Other Respiratory Disorders:** Known respiratory disorders other than COPD including, but not limited to, α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease. Allergic rhinitis was not exclusionary.
4. **Other Diseases/Abnormalities:** Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or hematological abnormalities that were uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that had been resected for cure is not exclusionary). Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.
5. **Chest X-Ray:** A chest X-ray or computed tomography (CT) scan that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must have been taken at Visit 1 if a chest X-ray or CT scan was not available within 6 months prior to Visit 1. For subjects in Germany, if a chest X-ray (or CT scan) was not available in the 6 months prior to Visit 1, the subject was not eligible for the study.
6. **Contraindications:** A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate, or a medical condition such as of narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction that, in the opinion of the investigator, contraindicated study participation or use of an inhaled anticholinergic.
7. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1.
8. **Lung Resection:** Lung volume reduction surgery within the 12 months prior to Visit 1.
9. **12-lead ECG:** An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead ECG which caused the underlying rhythm and ECG to be obscured. Investigators were provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. Specific ECG findings that precluded subject eligibility are listed in Appendix 3 of the protocol. The study investigator determined the medical significance of any ECG abnormalities not listed in Appendix 3 of the protocol.
10. **Holter Monitoring:** An abnormal and significant finding from 24-hour Holter monitoring at Visit 1. This exclusion only applied to the subset of subjects performing 24-hour Holter monitoring. Investigators were provided with Holter reviews conducted by an independent cardiologist to assist in evaluation of subject eligibility. Specific findings that precluded subject study eligibility are listed in Appendix 5 of the protocol. The study investigator determined the medical significance of any Holter abnormalities not listed in Appendix 5 of the protocol.
11. **Screening Labs:** Significantly abnormal finding from clinical chemistry or hematology tests at Visit 1.

12. **Medication Prior to Spirometry:** Unable to withhold salbutamol for the 4-hour period required prior to spirometry testing at each study visit.
13. **Oxygen**: Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for >12 hours a day. As-needed oxygen use (i.e., ≤12 hours per day) was not exclusionary.
14. **Nebulized Therapy**: Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., salbutamol via nebulized therapy).
15. **Pulmonary Rehabilitation Program**: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.
16. **Drug or Alcohol Abuse**: A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.

Treatments

The Applicant provided the study drug for use in this study. All blinded study drug was delivered via an NDPI. The NDPI provided a total of 30 doses. Each NDPI was comprised of one or two double-foil, laminate, blister strips.

The NDPIs containing study drug were identical in appearance. Subjects were instructed to take one inhalation each morning from their NDPI.

All subjects received supplemental salbutamol (MDI and/or nebules) to be used on an as-needed basis (rescue medication) throughout the study. Salbutamol was sourced from local commercial stock. If not available locally, the Applicant sourced it centrally.

Ipratropium bromide MDI for additional responsiveness testing at Visit 1 was sourced from local commercial stock. If not available locally, then the Applicant sourced it centrally.

Objectives

The primary objective of the study was to evaluate the efficacy and safety of UMEC/VI Inhalation Powder, UMEC Inhalation Powder, and VI Inhalation Powder when administered once-daily via a Novel Dry Powder Inhaler (NDPI) over 24 weeks in subjects with COPD.

A secondary objective of the study was to characterize the PK of UMEC and VI administered in combination and individually using population PK methodology, explore effects of covariates on PK parameters, to evaluate PK-pharmacodynamic (PD) relationships, if any, between UMEC or VI systemic exposure and systemic PD endpoints following administration of the UMEC/VI combination and the individual treatments to subjects with COPD.

Outcomes / endpoints

The primary efficacy endpoint was the trough FEV_1 on Day 169. Trough FEV_1 on Day 169 was defined as the mean of the FEV_1 values obtained 23 and 24 hours after dosing on Day 168 (i.e., at the Week 24 Visit).

The secondary efficacy endpoints were:

- Mean TDI focal score at Week 24. (TDI focal score was considered a key secondary endpoint for relevant regulatory authority submissions, including to the EMA and other relevant

regulatory authorities, and was considered an 'other endpoint' for regulatory submission to the US FDA and other relevant regulatory authorities.)

- Weighted mean FEV_1 over 0 to 6 hours postdose at Week 24.

Sample size

The sample size was calculated in order to provide sufficient power for the comparison of the primary and secondary endpoints, including TDI.

The sample size calculations used a two-sided 5% significance level and an estimate of residual standard deviation (SD) for TDI of 3.24 units. The estimate of SD is based on Mixed Model Repeated Measures (MMRM) analyses of a previous study in COPD subjects with the FP/salmeterol combination.

In order to provide additional safety data for the active treatments, subjects were randomized to active treatment arms or placebo in a 3:2 ratio. A study with 273 evaluable subjects in each active arm and 182 evaluable subjects in the placebo arm would have 90% power to detect a 1-unit difference between treatments in TDI. This treatment difference has been selected as the generally accepted minimally important difference for this endpoint [Witek and Mahler, 2003].

With this number of evaluable subjects per active arm, the study would have >99% power to detect a 100 mL difference between UMEC/VI and either UMEC or VI, or between an active treatment and placebo, at the two-sided 5% significance level. It would have 90% power to detect a difference of 58 mL between UMEC/VI and either UMEC or VI, or 68 mL between an active treatment and placebo. These calculations used an estimate of residual SD for trough FEV_1 of 210 mL. The estimate of SD was based on MMRM analyses of previous studies in COPD subjects with UMEC, VI, and the FP/salmeterol combination.

For the EMA and other relevant submissions, statistical inference for TDI was conditional on having achieved statistical significance on the primary endpoint, trough FEV_1. Powering trough FEV_1 at >99% would maintain 90% power (conditional on trough FEV_1 analysis) for the analysis of TDI for this submission.

It was estimated that approximately 30% of subjects would withdraw without providing a Day 168 (Week 24) assessment. Although, in MMRM, all available post-baseline assessments up to endpoint for subjects in the ITT population are utilized in the analysis, data for subjects who withdrew prematurely from the study were not explicitly imputed.

Hence, to account for a 30% withdrawal rate, 399 subjects were to be randomized to each active treatment arm and 266 subjects were to be randomized to placebo.

Randomisation

Subjects were assigned to study treatment in accordance with a randomization schedule. The randomization code was generated by the Applicant using a validated computerized system RandAll version 2.5. Subjects were randomized using RAMOS, an Interactive Voice Response System (IVRS). This is a telephone based system used by the investigator or designee.

Following the completion of the Run-in Period, eligible subjects were to be randomized in a 3:3:3:2 (3 active:2 placebo) ratio (n=399 to active treatment and n=266 to placebo) to one of the following 4 possible treatments:

- UMEC/VI 125/25 mcg once-daily
- UMEC 125 mcg once-daily

- VI 25 mcg once-daily
- Placebo once-daily.

Blinding (masking)

Study drugs taken during the 24-week Treatment Period were administered in a double-blind fashion. Neither the subject nor the study physician knew which study drug the subject was receiving.

Statistical methods

The following treatment comparisons were performed on trough FEV1 on Day 169:

- UMEC/VI vs. placebo
- UMEC vs. placebo
- VI vs. placebo
- UMEC/VI vs. VI
- UMEC/VI vs. UMEC.

In order to account for multiplicity across treatment comparisons and endpoints, 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. The hierarchy consisted of the five treatment comparisons described above, performed in that order, on the primary and secondary endpoints.

All programming was performed in a Harmonization for Analysis and Reporting (HARP) environment using SAS Version 9 and S-Plus Version 7 or a later release.

The primary endpoint of trough FEV1 on Day 169 was analyzed for the ITT population using a MMRM analysis [Siddiqui, 2009], including covariates of baseline FEV1, smoking status, 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, 28, 56, 84, 112, 168, and 169. 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 169.

Missing data were not explicitly imputed in the primary MMRM analysis, although there was an underlying assumption that data were missing at random. All available scheduled post-baseline assessments up to endpoint were utilized and, via modeling of the within-subject correlation structure, the derived treatment differences at Day 169 were adjusted to take into account missing data.

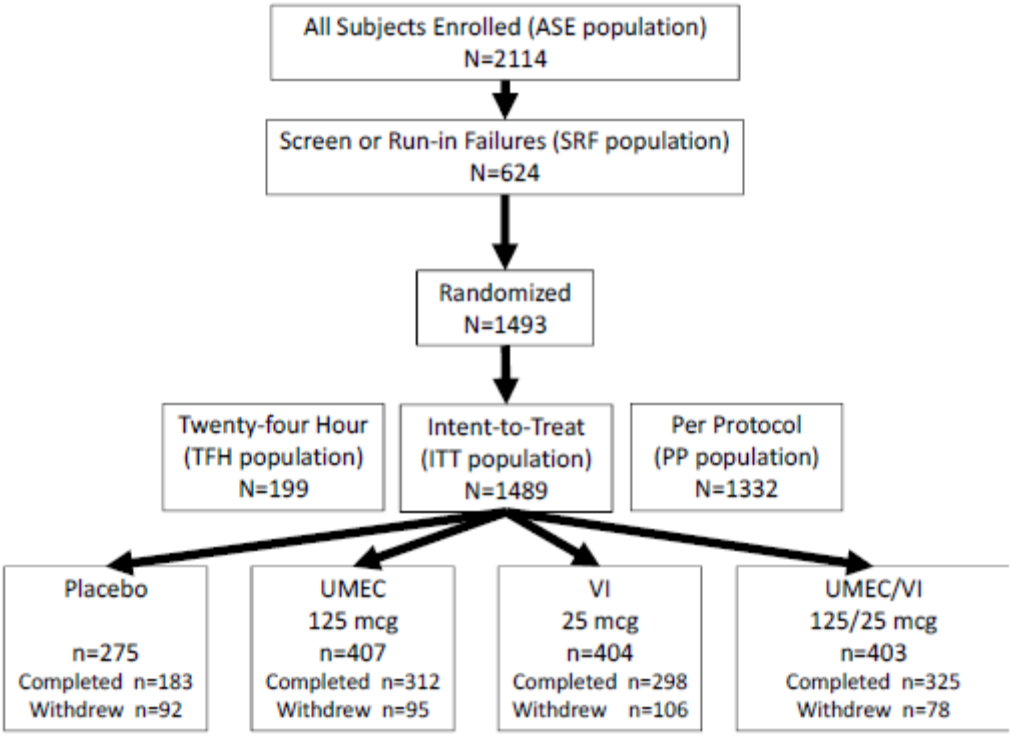
Results

Participant flow

Study DB2113361

An overview of subject disposition is shown in the figure below.

Figure 3. Subject Disposition (Study DB2113361)

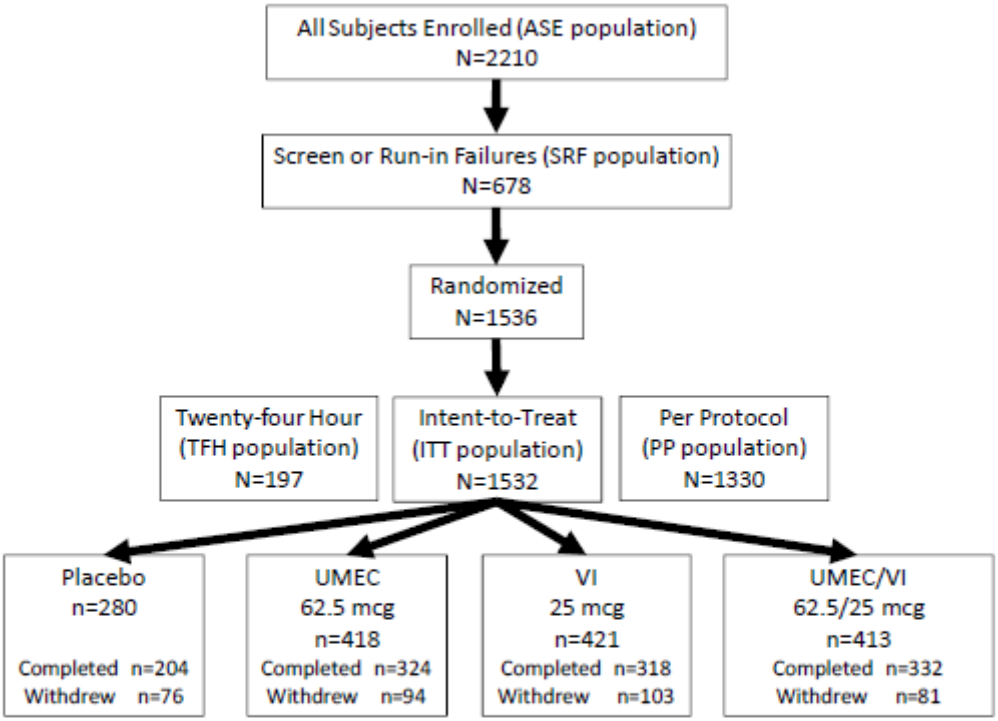


Data Source: Table 5.01 and Table 5.03
Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol
Note: Randomized includes all subjects who were randomized and given a randomization number.
Note: Two subjects were included in the Randomized total as well as the Screen and Run-in Failures total. Two additional subjects were randomized and did not receive any dose of study drug.
Note: Subjects were considered to have completed if they completed the last clinic visit excluding follow-up (Visit 9) and did not withdraw at that visit.

Study DB2113373

An overview of subject disposition is shown in the figure below.

Figure 4. Subject Disposition (Study DB2113373)



Data Source: Table 5.01, Table 5.03
Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol
Note: Randomized includes all subjects who were randomized and given a randomization number.
Note: Four subjects were randomized in error but did not receive study drug and were therefore not included in the ITT population. These subjects are included in the Randomized total as well as the Screen and Run-in Failures total.
Note: Subjects were considered to have completed if they completed the last clinic visit excluding follow-up (Visit 9) and did not withdraw at that visit.

Conduct of the study

There were two amendments to the original clinical trial protocol for both studies DB2113361 and DB2113373. These amendments were considered not influencing the studies results.

Baseline data

Study DB2113361

Demographics

Demographic characteristics in the ITT population were generally similar between treatment groups (see table below).

Table 28. Summary of Demographic Characteristics (DB2113361 ITT Population)

Demographic Characteristic	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403	Total N=1489
Age (years), n	275	407	404	403	1489
Mean	62.2	63.1	62.8	63.4	62.9
SD	8.53	8.48	8.80	8.08	8.47
Min, Max	42, 86	40, 86	40, 84	40, 83	40, 86
Sex, n	275	407	404	403	1489
Female, n (%)	100 (36)	137 (34)	139 (34)	139 (34)	515 (35)
Male, n (%)	175 (64)	270 (66)	265 (66)	264 (66)	974 (65)
Ethnicity, n	275	407	404	403	1489
Hispanic/Latino, n (%)	1 (<1)	0	0	2 (<1)	3 (<1)
Not Hispanic/Latino, n (%)	274 (>99)	407 (100)	404 (100)	401 (>99)	1486 (>99)
Race, n	275	407	404	403	1489
White, n (%)	238 (87)	363 (89)	354 (88)	359 (89)	1314 (88)
African American/African heritage, n (%)	9 (3)	4 (<1)	7 (2)	4 (<1)	24 (2)
American Indian or Alaska native, n (%)	0	0	1 (<1)	1 (<1)	2 (<1)
Asian, n (%)	27 (10)	40 (10)	42 (10)	39 (10)	148 (10)
Central/South Asian heritage	0	0	1 (<1)	0	1 (<1)
Japanese/East Asian heritage/Southeast Asian heritage	27 (10)	40 (10)	41 (10)	39 (10)	147 (10)
Native Hawaiian or other Pacific Islander, n (%)	0	0	0	0	0
African American/African heritage & White	1 (<1)	0	0	0	1 (<1)
Height (cm), n	275	407	404	403	1489
Mean	169.3	169.9	169.5	169.9	169.7
SD	8.95	8.70	8.71	9.44	8.95
Min, Max	145, 189	147, 198	148, 196	138, 200	138, 200
Weight (kg), n	275	407	404	402	1488
Mean	76.36	76.57	78.33	76.80	77.07
SD	19.821	19.004	19.341	17.824	18.938
Min, Max	34.0, 152.7	33.8, 160.1	37.0, 146.1	36.0, 142.4	33.8, 160.1
Body Mass Index (kg/m²), n	275	407	404	402	1488
Mean	26.49	26.41	27.16	26.45	26.64
SD	6.110	5.828	5.982	5.147	5.753
Min, Max	14.9, 50.7	14.4, 56.7	13.3, 45.7	13.9, 47.6	13.3, 56.7

Data Source: Table 5.11 and Table 5.14
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Full detailed racial combination data were presented in Table 5.15.

Demographics were generally similar between the ITT population and the PP population.

Smoking History

Overall, subjects at screening had extensive smoking histories, with a mean of 38.9 years smoked and 44.0 pack-years (see table below). At screening, 52% of subjects were classified as current smokers (subjects who stopped smoking within 6 months prior to screening).

Few subjects (<1%) reported changes in smoking status during the study.

Table 29. Summary of Smoking History and Status (DB2113361 ITT Population)

	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403	Total N=1489
Years smoked, n	275	407	404	403	1489
Mean	38.4	39.6	38.4	39.2	38.9
SD	10.19	10.06	9.85	10.14	10.05
Median	40.0	40.0	40.0	40.0	40.0
Min, Max	10, 65	11, 65	10, 65	10, 65	10, 65
Smoking pack years [a], n	275	407	404	403	1489
Mean	43.6	44.0	42.8	45.4	44.0
SD	23.06	23.32	23.22	25.51	23.85
Median	40.0	40.0	39.0	40.0	40.0
Min, Max	10, 175	10, 153	10, 175	3, 225	3, 225
Smoking status at Screening, n	275	407	404	403	1489
Current smoker	143 (52)	216 (53)	210 (52)	200 (50)	769 (52)
Former smoker	132 (48)	191 (47)	194 (48)	203 (50)	720 (48)

Data Source: Table 5.22 and Table 5.23
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack years = (number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 30. Summary of COPD History (DB2113361 ITT Population)

	Number (%) of Subjects				
	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403	Total N=1489
Duration of COPD					
<1 year	16 (6)	39 (10)	32 (8)	29 (7)	116 (8)
≥1 to <5 years	94 (34)	146 (36)	167 (41)	135 (33)	542 (36)
≥5 to <10 years	101 (37)	117 (29)	116 (29)	131 (33)	465 (31)
≥10 to <15 years	48 (17)	58 (14)	70 (17)	73 (18)	249 (17)
≥15 to <20 years	9 (3)	25 (6)	13 (3)	11 (3)	58 (4)
≥20 to <25 years	3 (1)	10 (2)	3 (<1)	18 (4)	34 (2)
≥25 years	4 (1)	12 (3)	3 (<1)	6 (1)	25 (2)
COPD Type [a]					
Chronic bronchitis	199 (73)	266 (66)	273 (68)	283 (70)	1021 (69)
Emphysema	160 (59)	241 (59)	230 (57)	227 (56)	858 (58)

Data Source: Table 5.20
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to Screening, the majority of subjects across treatment groups reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (72% to 78%) and no COPD exacerbations requiring hospitalization (90% to 92%; Table 5.21).

Screening and Baseline Lung Function

Subjects had moderate to very severe airflow obstruction at screening and lung function parameters were similar across treatment groups (see table below).

Table 31. Summary of Screening Lung Function Test Results (DB2113361 ITT Population)

Parameter	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403	Total N=1489
Pre-bronchodilator FEV_1 (L), n	275	407	401	402	1485
Mean	1.271	1.299	1.292	1.267	1.283
SD	0.4697	0.4879	0.4934	0.4806	0.4838
Median	1.200	1.220	1.230	1.215	1.220
Min, Max	0.43, 2.63	0.35, 3.09	0.39, 2.85	0.24, 2.57	0.24, 3.09
Post-salbutamol FEV_1 (L), n	274	406	402	401	1483
Mean	1.402	1.457	1.436	1.414	1.430
SD	0.4693	0.5034	0.5071	0.4836	0.4929
Median	1.340	1.400	1.370	1.380	1.370
Min, Max	0.51, 2.66	0.34, 3.23	0.36, 3.24	0.37, 2.82	0.34, 3.24
Post-ipratropium FEV_1 (L) [a], n	273	403	402	400	1478
Mean	1.500	1.555	1.521	1.502	1.521
SD	0.4930	0.5297	0.5333	0.5045	0.5173
Median	1.430	1.510	1.470	1.465	1.470
Min, Max	0.53, 2.81	0.39, 3.46	0.37, 3.38	0.48, 2.94	0.37, 3.46
Post-salbutamol FEV_1/FVC	274	406	402	401	1483
Mean	46.430	46.972	47.084	45.905	46.614
SD	11.3018	10.5943	11.1940	11.0383	11.0105
Median	45.900	46.600	47.350	46.100	46.500
Min, Max	21.90, 69.30	22.50, 69.80	19.10, 69.50	13.10, 69.90	13.10, 69.90
Post-salbutamol Percent Predicted FEV_1 (%), n	274	406	402	401	1483
Mean	47.6	48.8	48.5	47.7	48.2
SD	12.47	12.32	12.74	12.53	12.52
Median	48.2	49.1	50.4	47.9	48.7
Min, Max	17, 70	16, 76	17, 70	13, 76	13, 76
Percent Reversibility to Salbutamol (%), n	274	406	400	401	1481
Mean	12.0	13.9	13.2	13.8	13.3
SD	13.47	14.12	13.61	13.98	13.83
Median	9.1	11.2	10.9	11.5	10.8
Min, Max	-14, 71	-34, 83	-35, 66	-33, 65	-35, 83
Reversibility to Salbutamol (mL), n	274	406	400	401	1481
Mean	128.2	156.3	146.6	145.9	145.7
SD	143.13	157.67	168.54	149.47	156.10
Median	113.5	137.5	125.0	139.0	127.0
Min, Max	-273, 661	-628, 913	-909, 795	-470, 837	-909, 913
Percent Reversibility to Salbutamol and Ipratropium (%), n	273	403	399	400	1475
Mean	20.6	22.1	20.6	21.4	21.2
SD	17.43	17.28	17.90	17.32	17.48
Median	18.4	20.2	17.9	19.4	19.0
Min, Max	-19, 107	-14, 103	-37, 97	-49, 100	-49, 107

Parameter	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403	Total N=1489
Reversibility to Salbutamol and Ipratropium (mL), n	273	403	399	400	1475
Mean	228.8	255.6	232.5	232.6	238.1
SD	173.72	191.12	209.81	179.36	190.37
Median	220.0	230.0	210.0	220.0	220.0
Min, Max	-290, 820	-180, 1090	-740, 960	-690, 980	-740, 1090

Data Source: Table 5.24
Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
a. Post-ipratropium spirometry was conducted following completion of post-salbutamol spirometry.

Other Screening and baseline lung function parameters are provided in Table 5.24. A descriptive summary of Screening lung function test results by country is provided in Table 5.25.

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status at Screening is summarized in the table below. Overall, the majority of subjects were GOLD Stage II and III (92%). A higher percentage of subjects showed reversibility after administration of salbutamol followed by ipratropium (54%) compared with reversibility to salbutamol alone (31%). The proportion of subjects who reported the use of ICS was similar across treatment groups.

Table 32. Summary of Gold Stage and Reversibility (DB2113361 ITT Population)

	Number (%) of Subjects				
	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403	Total N=1489
GOLD Stage (percent predicted FEV_1), n	274	406	402	401	1483
Stage I (≥80%)	0	0	0	0	0
Stage II (≥50% to <80%)	121 (44)	194 (48)	207 (51)	177 (44)	699 (47)
Stage III (≥30% to <50%)	132 (48)	180 (44)	159 (40)	189 (47)	660 (45)
Stage IV (<30%)	21 (8)	32 (8)	36 (9)	35 (9)	124 (8)
Reversible to Salbutamol, n [a]	274	406	400	401	1481
Reversible	77 (28)	132 (33)	119 (30)	133 (33)	461 (31)
Non-reversible	197 (72)	274 (67)	281 (70)	268 (67)	1020 (69)
Reversibility to Salbutamol and Ipratropium, n [b]	273	403	399	400	1475
Reversible	146 (53)	228 (57)	203 (51)	213 (53)	790 (54)
Non-reversible	127 (47)	175 (43)	196 (49)	187 (47)	685 (46)
ICS use, n [c]	275	407	404	403	1489
ICS users	138 (50)	193 (47)	191 (47)	176 (44)	698 (47)
ICS non-users	137 (50)	214 (53)	213 (53)	227 (56)	791 (53)

Data Source: Table 5.26
Abbreviations: FEV1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol
a. Reversible was an increase in FEV1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV1.
b. Reversible was an increase in FEV1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV1.
c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

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Demographics

Demographic characteristics in the ITT population were generally similar between treatment groups (see table below).

Table 33. Summary of Demographic Characteristics (DB2113373 ITT Population)

Demographic Characteristic	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413	Total N=1532
Age (years), n	280	418	421	413	1532
Mean	62.2	64.0	62.7	63.1	63.1
SD	9.04	9.16	8.52	8.71	8.86
Min, Max	40, 83	40, 93	40, 88	40, 86	40, 93
Sex, n	280	418	421	413	1532
Female, n (%)	85 (30)	120 (29)	136 (32)	108 (26)	449 (29)
Male, n (%)	195 (70)	298 (71)	285 (68)	305 (74)	1083 (71)
Ethnicity, n	280	418	421	413	1532
Hispanic/Latino, n (%)	25 (9)	37 (9)	36 (9)	35 (8)	133 (9)
Not Hispanic/Latino, n (%)	255 (91)	381 (91)	385 (91)	378 (92)	1399 (91)
Race, n	280	418	421	413	1532
White, n (%)	237 (85)	354 (85)	364 (86)	348 (84)	1303 (85)
African American/African heritage, n (%)	9 (3)	14 (3)	9 (2)	15 (4)	47 (3)
American Indian or Alaska native, n (%)	1 (<1)	3 (<1)	5 (1)	0	9 (<1)
Asian, n (%)	22 (8)	35 (8)	34 (8)	35 (8)	126 (8)
Central/South Asian heritage	0	0	1 (<1)	1 (<1)	2 (<1)
Japanese/East Asian heritage/Southeast Asian heritage	22 (8)	35 (8)	33 (8)	34 (8)	124 (8)
Native Hawaiian or other Pacific Islander, n (%)	0	0	0	1 (<1)	1 (<1)
African American/African heritage & American Indian or Alaska native & White	0	1 (<1)	0	0	1 (<1)
African American/African heritage & White	1 (<1)	1 (<1)	1 (<1)	0	3 (<1)
American Indian or Alaska native & White	10 (4)	10 (2)	8 (2)	14 (3)	42 (3)
Height (cm), n	280	418	421	413	1532
Mean	167.8	168.7	168.1	169.1	168.4
SD	9.22	9.34	9.39	9.43	9.36
Min, Max	139, 190	138, 200	142, 193	145, 198	138, 200
Weight (kg), n	280	418	420	413	1531
Mean	76.03	75.62	75.54	78.28	76.39
SD	18.983	18.643	18.755	19.866	19.089
Min, Max	35.5, 170.0	36.2, 153.1	40.0, 139.0	34.3, 160.9	34.3, 170.0
Body Mass Index (kg/m²), n	280	418	420	413	1531
Mean	26.90	26.46	26.64	27.26	26.81
SD	5.899	5.595	5.930	6.016	5.861
Min, Max	12.3, 48.1	14.5, 47.1	15.6, 48.3	14.8, 48.5	12.3, 48.5

Data Source: Table 5.11 and Table 5.14
Abbreviations: ITT=intent to treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Full detailed race and racial combination data were presented in Table 5.15.

Demographics were generally similar between the ITT population and the PP population.

Smoking History

Overall, subjects at screening had extensive smoking histories, with a mean of 38.4 years smoked and 46.2 pack-years for all subjects (see table below). At screening, 50% of subjects were classified as

current smokers (subjects who stopped smoking within 6 months prior to screening). Few subjects (<1%) reported changes in smoking status during the study.

Table 34. Summary of Smoking History and Status (DB2113373 ITT Population)

	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413	Total N=1532
Years smoked, n	280	418	421	413	1532
Mean	38.6	39.1	37.8	38.2	38.4
SD	10.12	10.95	11.41	11.27	11.02
Median	39.5	40.0	40.0	39.0	40.0
Min, Max	8, 67	6, 75	10, 68	8, 63	6, 75
Smoking pack years [a], n	280	418	421	413	1532
Mean	47.2	46.8	44.7	46.5	46.2
SD	27.21	27.03	23.16	25.80	25.71
Median	40.0	41.0	40.0	42.0	40.0
Min, Max	10, 185	10, 225	10, 159	10, 180	10, 225
Smoking status at Screening, n	280	418	421	413	1532
Current smoker	150 (54)	207 (50)	199 (47)	203 (49)	759 (50)
Former smoker	130 (46)	211 (50)	222 (53)	210 (51)	773 (50)

Data Source: Table 5.22, Table 5.23
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack years = (number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 35. Summary of COPD History at Screening (DB2113373 ITT Population)

	Number (%) of Subjects				
	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413	Total N=1532
Duration of COPD					
<1 year	20 (7)	36 (9)	36 (9)	36 (9)	128 (8)
≥1 to <5 years	107 (38)	151 (36)	157 (37)	160 (39)	575 (38)
≥5 to <10 years	82 (29)	127 (30)	115 (27)	123 (30)	447 (29)
≥10 to <15 years	51 (18)	70 (17)	73 (17)	63 (15)	257 (17)
≥15 to <20 years	9 (3)	15 (4)	19 (5)	16 (4)	59 (4)
≥20 to <25 years	6 (2)	10 (2)	12 (3)	9 (2)	37 (2)
≥25 years	5 (2)	9 (2)	9 (2)	6 (1)	29 (2)
COPD Type [a]					
Chronic bronchitis	182 (65)	274 (66)	260 (62)	283 (69)	999 (65)
Emphysema	173 (62)	271 (65)	273 (65)	236 (57)	953 (62)

Data Source: Table 5.20
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to screening, the majority of subjects across treatment groups reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (70% to 76%) and no COPD exacerbations requiring hospitalization (87% to 91%).

Screening and Baseline Lung Function

Subjects had moderate to very severe airflow obstruction at screening and lung function parameters were similar across treatment groups (see table below).

Table 36. Summary of Screening Lung Function Test Results (DB2113373 ITT Population)

Parameter	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413	Total N=1532
Pre-bronchodilator FEV_1 (L), n	279	417	421	413	1530
Mean	1.198	1.211	1.237	1.276	1.233
SD	0.4470	0.4764	0.4861	0.5246	0.4878
Median	1.130	1.140	1.190	1.180	1.160
Min, Max	0.38, 2.81	0.31, 2.80	0.34, 3.17	0.30, 3.07	0.30, 3.17
Post-salbutamol FEV_1 (L), n	280	417	420	412	1529
Mean	1.355	1.347	1.402	1.425	1.385
SD	0.4629	0.4730	0.5011	0.5426	0.4992
Median	1.310	1.290	1.340	1.350	1.320
Min, Max	0.47, 2.83	0.42, 2.71	0.49, 3.20	0.35, 2.98	0.35, 3.20

Parameter	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413	Total N=1532
Post-ipratropium FEV_1 (L), n [a]	271	412	412	406	1501
Mean	1.445	1.446	1.491	1.519	1.478
SD	0.5015	0.5133	0.5346	0.5726	0.5341
Median	1.430	1.390	1.435	1.440	1.430
Min, Max	0.51, 3.14	0.43, 3.25	0.51, 3.21	0.37, 3.10	0.37, 3.25
Post-salbutamol FEV_1/FVC, n	280	417	420	412	1529
Mean	47.082	46.775	47.372	48.011	47.328
SD	11.4695	11.0696	11.4928	11.4189	11.3531
Median	47.000	47.100	47.300	47.900	47.400
Min, Max	22.30, 73.70	19.70, 69.50	20.30, 69.60	21.40, 69.90	19.70, 73.70
Post-salbutamol Percent Predicted FEV_1 (%), n	280	417	420	412	1529
Mean	46.7	46.8	48.2	47.8	47.4
SD	12.71	13.39	13.27	13.19	13.18
Median	46.4	48.3	48.6	49.6	48.2
Min, Max	21, 70	13,70	15, 74	16, 70	13, 74
Percent Reversibility to Salbutamol (%), n	279	415	420	412	1526
Mean	15.3	13.9	15.7	13.9	14.6
SD	15.54	14.92	15.57	15.06	15.26
Median	12.7	11.4	12.3	11.8	12.1
Min, Max	-30, 79	-15, 109	-21, 79	-35, 101	-35, 109
Reversibility to Salbutamol (mL), n	279	415	420	412	1526
Mean	158.5	137.3	164.4	151.2	152.4
SD	166.43	147.36	165.61	168.81	162.08
Median	138.0	125.0	136.5	132.5	133.0
Min, Max	-323, 823	-322, 654	-364, 1034	-363, 981	-364, 1034
Percent Reversibility to Salbutamol and Ipratropium (%), n	270	411	412	406	1499
Mean	22.7	22.3	23.6	22.2	22.7
SD	19.61	18.51	19.42	18.82	19.04
Median	20.9	19.8	20.1	20.1	20.2
Min, Max	-30, 110	-28, 153	-26, 121	-14, 137	-30, 153
Reversibility to Salbutamol and Ipratropium (mL), n	270	411	412	406	1499
Mean	244.5	235.7	255.6	247.5	246.0
SD	209.06	179.41	197.21	208.46	197.82
Median	225.0	220.0	230.0	230.0	230.0
Min, Max	-320, 900	-210, 900	-260, 1600	-250, 1140	-320, 1600

Data Source: Table 5.24
Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
a. Post-ipratropium spirometry was conducted following completion of post-salbutamol spirometry.

Other Screening and baseline lung function parameters are provided in Table 5.24. A descriptive summary of Screening lung function test results by country is provided in Table 5.25.

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status at screening is summarized in the table below. Overall, the majority of subjects were GOLD Stage II or III. A higher percentage of subjects showed reversibility after administration of salbutamol followed by ipratropium (55%) compared with reversibility to salbutamol alone (33%).

The proportion of subjects who reported the use of ICS was similar across treatment groups.

Table 37. Summary of GOLD Stage and Reversibility (DB2113373 ITT Population)

	Number (%) of Subjects				
	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413	Total N=1532
GOLD Stage (percent predicted FEV_1), n	280	417	420	412	1529
Stage I (≥80%)	0	0	0	0	0
Stage II (≥50% to <80%)	119 (43)	191 (46)	197 (47)	201 (49)	708 (46)
Stage III (≥30% to <50%)	133 (48)	172 (41)	179 (43)	166 (40)	650 (43)
Stage IV (<30%)	28 (10)	54 (13)	44 (10)	45 (11)	171 (11)
Reversible to Salbutamol, n [a]	279	415	420	412	1526
Reversible	91 (33)	121 (29)	155 (37)	129 (31)	496 (33)
Non-reversible	188 (67)	294 (71)	265 (63)	283 (69)	1030 (67)
Reversible to Salbutamol and Ipratropium, n [b]	270	411	412	406	1499
Reversible	146 (54)	223 (54)	230 (56)	227 (56)	826 (55)
Non-reversible	124 (46)	188 (46)	182 (44)	179 (44)	673 (45)
ICS Use, n [c]	280	418	421	413	1532
ICS Users	137 (49)	219 (52)	212 (50)	212 (51)	780 (51)
ICS Non-users	143 (51)	199 (48)	209 (50)	201 (49)	752 (49)

Data Source: Table 5.26

Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroids; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

a. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

b. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Numbers analysed

Study DB2113361

A summary of subject populations is presented in the table below.

Table 38. Summary of Subject Populations (DB2113361 ASE Population)

	Number (%) of Subjects				
Population	Placebo	UMEC 125 mcg	VI 25 mcg	UMEC/VI 125/25 mcg	Total
All Subjects Enrolled (ASE)					2114
Screen or Run-in Failures [a]					624 (30)
Randomized	277	409	404	403	1493
Intent-to-treat (ITT)	275	407	404	403	1489
Per Protocol (PP) [b]	251 (91)	373 (92)	353 (87)	355 (88)	1332 (89)
Twenty-four Hour (TFH) [b]	36 (13)	53 (13)	55 (14)	55 (14)	199 (13)

Data Source: Table 5.01

Abbreviations: ASE=all subjects enrolled; ITT=intent-to-treat; PP=per protocol; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol

Notes: Randomized includes all subjects who were randomized and given a randomization number. Two subjects were included in the Randomized row as well as the Screen and Run-in Failures row. Two subjects were randomized and did not receive any dose of study drug.

ASE: All subjects who were screened and for whom a record exists on the study database.

ITT: All randomized subjects who received at least a single dose of study drug.

PP: All subjects in the ITT population who were not identified as full protocol deviators.

TFH: Subjects in the ITT population for whom 24-hour spirometry and Holter monitoring data were collected.

a. Percentages are based on the ASE population.

b. Percentages are based on the ITT population.

Study DB2113373

A summary of analysis populations is presented in the table below.

Table 39. Summary of Subject Populations (DB2113373 ASE Population)

Population	Number (%) of Subjects				
	Placebo	UMEC 62.5 mcg	VI 25 mcg	UMEC/VI 62.5/25 mcg	Total
All Subjects Enrolled (ASE)					2210
Screen or Run-in Failures,[a]					678 (31)
Randomized	280	421	421	414	1536
Intent-to-treat (ITT)	280	418	421	413	1532
Per Protocol (PP)[b]	233 (83)	362 (87)	372 (88)	363 (88)	1330 (87)
Twenty-four Hour (TFH)[b]	37 (13)	54 (13)	53 (13)	53 (13)	197 (13)

Data Source: Table 5.01

Abbreviations: ASE=all subjects enrolled; PP=per protocol; TFH=twenty-four hour; UMEC=umeclidinium bromide; VI=vilanterol

Notes: Randomized includes all subjects who were randomized and given a randomization number. Four subjects were included in the Randomized row as well as the Screen and Run-in Failures row.

ASE: All subjects who were screened and for whom a record exists in the study database.

ITT: All randomized subjects who received at least a single dose of study drug.

PP: All subjects in the ITT population who were not identified as full protocol deviators.

TFH: Subjects in the ITT population for whom 24-hour spirometry and Holter monitoring data were collected.

a. Percentages are based on the ASE population.

b. Percentages are based on the ITT population.

Outcomes and estimation

Study DB2113361

Trough FEV1 at Day 169: Primary Endpoint

The primary efficacy endpoint was trough FEV1 at Day 169. Trough FEV1 at Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168 (i.e., at the Week 24 Visit).

The UMEC/VI 125/25 mcg, UMEC 125 mcg, and VI 25 mcg treatment groups demonstrated statistically significant greater LS mean changes from baseline in trough FEV1 at Day 169 compared with placebo (see table below). The UMEC/VI 125/25 mcg treatment group also demonstrated statistically significant greater LS mean change from baseline in trough FEV1 at Day 169 compared with both the VI 25 mcg and UMEC 125 mcg treatment groups.

Table 40. Primary Efficacy Analysis: Trough FEV1 (L) at Day 169 (DB2113361 ITT Population)

Day 169	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403
n [a]	269	404	402	401
n [b]	182	312	299	323
LS mean (SE)	1.245 (0.0153)	1.405 (0.0119)	1.370 (0.0121)	1.484 (0.0119)
LS mean change (SE)	-0.031 (0.0153)	0.129 (0.0119)	0.093 (0.0121)	0.207 (0.0119)
Column vs. Placebo Difference		0.160	0.124	0.238
95% CI		(0.122,0.198)	(0.086,0.162)	(0.200,0.276)
p-value		<0.001	<0.001	<0.001
UMEC/VI 125/25 vs. Column Difference		0.079	0.114	
95% CI		(0.046,0.112)	(0.081,0.148)	
p-value		<0.001	<0.001	

Data Source: Table 6.05

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

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the 2 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 current time point.

Transition Dyspnea Index Focal Score at Day 168, Day 28, and Day 84

In accordance with the CHMP guidance, the TDI score was designated as a key secondary efficacy endpoint for evaluation by the EMA and any other relevant regulatory authorities.

Clinically meaningful mean improvements in TDI scores from baseline (i.e., >1; demonstrating an improvement in dyspnea) were observed in the UMEC/VI 125/25 mcg, UMEC 125mcg, and VI 25 mcg treatment groups at Day 168. A statistically significant greater LS mean TDI focal score was demonstrated for the UMEC/VI 125/25 mcg group compared with placebo at Day 168 (see table below).

The UMEC 125 mcg treatment group did not demonstrate statistically significant differences in LS mean TDI focal score compared with placebo at Day 168. Based on application of the testing hierarchy, the results of all further statistical analyses should be interpreted only descriptively in instances where the TDI score at Day 168 was designated as the key secondary efficacy endpoint.

Table 41. Statistical Analysis: TDI Focal Score (DB2113361 ITT Population)

	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403
Day 28				
n [a]	234	376	362	371
n [b]	234	375	361	368
LS mean (SE)	0.0 (0.16)	1.2 (0.12)	1.0 (0.13)	1.6 (0.13)
Column vs. Placebo Difference		1.1	1.0	1.6
95% CI		(0.7,1.5)	(0.6,1.4)	(1.2,2.0)
p-value		<0.001	<0.001	<0.001
UMEC/VI 125/25 vs. Column Difference		0.5	0.6	
95% CI		(0.1,0.8)	(0.2,0.9)	
p-value		0.010	0.001	
Day 84				
n [a]	234	376	362	371
n [b]	211	346	332	350
LS mean (SE)	0.7 (0.17)	1.4 (0.14)	1.2 (0.14)	1.9 (0.14)
Column vs. Placebo Difference		0.7	0.5	1.2
95% CI		(0.2,1.1)	(0.1,0.9)	(0.7,1.6)
p-value		0.002	0.024	<0.001
UMEC/VI 125/25 vs. Column Difference		0.5	0.7	
95% CI		(0.1,0.9)	(0.3,1.0)	
p-value		0.012	<0.001	

	Placebo N=275	UMEC 125 mcg N=407	VI 25 mcg N=404	UMEC/VI 125/25 mcg N=403
Day 168				
n [a]	234	376	362	371
n [b]	186	313	294	324
LS mean (SE)	0.8 (0.20)	1.2 (0.16)	1.3 (0.16)	1.8 (0.15)
Column vs. Placebo Difference		0.4	0.5	1.0
95% CI		(-0.1,0.9)	(0.0,1.0)	(0.5,1.5)
p-value		0.108	0.054	<0.001
UMEC/VI 125/25 vs. Column Difference		0.6	0.5	
95% CI		(0.2,1.0)	(0.1,1.0)	
p-value		0.006	0.019	

Data Source: Table 6.62
Abbreviations: BDI=Baseline Dyspnea Index; CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; TDI=Transition Dyspnea Index; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis performed using a repeated measures model with covariates of treatment, BDI focal score, smoking status, center group, Day, Day by BDI focal score, 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 current time point.

Study DB2113373

Trough FEV1 at Day 169: Primary Endpoint

The primary efficacy endpoint was trough FEV1 on Treatment Day 169. Trough FEV1 on Treatment Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Treatment Day 168 (i.e., at the Week 24 Visit).

The UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, and VI 25 mcg treatment groups demonstrated statistically significant greater LS mean changes from baseline in trough FEV1 at Day 169 compared with placebo (see table below). The UMEC/VI 62.5/25 mcg treatment group also demonstrated statistically significant greater LS mean changes from baseline in trough FEV1 at Day 169 compared with both the VI 25 mcg and UMEC 62.5 mcg treatment groups.

Table 42. Primary Efficacy Analysis: Trough FEV1 (L) at Day 169 (DB2113373 ITT Poulation)

Day 169	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413
n [a]	278	416	419	411
n [b]	201	322	317	330
LS mean (SE)	1.239 (0.0158)	1.354 (0.0126)	1.311 (0.0127)	1.406 (0.0126)
LS mean change (SE)	0.004 (0.0158)	0.119 (0.0126)	0.076 (0.0127)	0.171 (0.0126)
Column vs. Placebo Difference		0.115	0.072	0.167
95% CI		(0.076,0.155)	(0.032,0.112)	(0.128,0.207)
p-value		<0.001	<0.001	<0.001
UMEC/VI 62.5/25 mcg vs. Column Difference		0.052	0.095	
95% CI		(0.017,0.087)	(0.060,0.130)	
p-value		0.004	<0.001	

Data Source: Table 6.05

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in one second; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the 2 assessments made 30 and 5 minutes predose at Day 1), smoking status, center group, Day, Day by baseline, and Day by treatment interactions.

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

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

Transition Dyspnea Index Focal Score at Day 168, Day 28, and Day 84

In accordance with the CHMP guidance, the TDI score was designated as a key secondary efficacy endpoint for evaluation by the EMA and any other relevant regulatory authorities.

Clinically meaningful mean improvements in TDI scores from baseline (i.e., >1; demonstrating an improvement in dyspnea) were observed in the UMEC/VI 62.5/25mcg, UMEC 62.5 mcg, and VI 25 mcg treatment groups at Day 168. Statistically significant greater LS mean TDI focal scores were demonstrated for the UMEC/VI 62.5/25 mcg, UMEC 62.5 mcg, and VI 25 mcg treatment groups compared with placebo at Day 168 (see table below).

The UMEC/VI 62.5/25 mcg treatment group did not demonstrate statistically significant differences in LS mean TDI focal score compared with either the VI 25 mcg or UMEC 62.5 mcg treatment groups. Based on application of the testing hierarchy, the results of all further statistical analyses should be interpreted only descriptively in instances where the TDI score at Day 168 was designated as a secondary efficacy endpoint.

Table 43. Statistical Analysis: TDI Focal Score (DB2113373 ITT Population)

	Placebo N=280	UMEC 62.5 mcg N=418	VI 25 mcg N=421	UMEC/VI 62.5/25 mcg N=413
Day 28				
n [a]	260	394	389	389
n [b]	260	392	387	389
LS mean (SE)	0.4 (0.17)	1.6 (0.14)	1.5 (0.14)	2.0 (0.14)
Column vs. Placebo Difference		1.2	1.1	1.6
95% CI		(0.8,1.7)	(0.7,1.6)	(1.1,2.0)
p-value		<0.001	<0.001	<0.001
UMEC/VI 62.5/25 mcg vs. Column Difference		0.3	0.4	
95% CI		(-0.1,0.7)	(0.0,0.8)	
p-value		0.090	0.038	
Day 84				
n [a]	260	394	389	389
n [b]	234	358	365	371
LS mean (SE)	1.0 (0.18)	1.9 (0.14)	1.9 (0.14)	2.3 (0.14)
Column vs. Placebo Difference		0.9	0.9	1.3
95% CI		(0.5,1.4)	(0.4,1.3)	(0.8,1.7)
p-value		<0.001	<0.001	<0.001
UMEC/VI 62.5/25 mcg vs. Column Difference		0.3	0.4	
95% CI		(-0.1,0.7)	(0.0,0.8)	
p-value		0.108	0.052	
Day 168				
n [a]	260	394	389	389
n [b]	204	326	317	336
LS mean (SE)	1.2 (0.20)	2.2 (0.16)	2.1 (0.16)	2.4 (0.16)
Column vs. Placebo Difference		1.0	0.9	1.2
95% CI		(0.5,1.5)	(0.4,1.4)	(0.7,1.7)
p-value		<0.001	<0.001	<0.001
UMEC/VI 62.5/25 mcg vs. Column Difference		0.3	0.4	
95% CI		(-0.2,0.7)	(-0.1,0.8)	
p-value		0.244	0.117	

Data Source: Table 6.62

Abbreviations: BDI=Baseline Dyspnea Index; CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; TDI=Transition Dyspnea Index; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, BDI focal score, smoking status, center group, Day, Day by BDI focal score, and Day by treatment interactions.

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

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

Studies DB2113360 and DB2113374

Studies DB2113360 and DB2113374 are two phase IIIa, multicenter, randomized, double-blind, double-dummy, parallel-group study to evaluate the efficacy and safety of two doses of UMEC/VI (125/25 mcg and 62.5/25 mcg once-daily) when administered via a novel dry powder inhaler (NDPI) compared with UMEC 125 mcg administered once-daily via a NDPI and compared with TIO once-daily when administered via HandiHaler over a treatment period of 24 weeks in subjects with COPD.

Methods

Study participants

Inclusion criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

1. **Type of subject:** Outpatient.
2. **Informed Consent:** A signed and dated written informed consent prior to study participation.
3. **Age**: Subjects 40 years of age or older at Visit 1.
4. **Gender**: Male or female subjects.
5. **Diagnosis**: An established clinical history of COPD in accordance with the definition by the American Thoracic Society (ATS)/European Respiratory Society [Celli, 2004] as follows:

   Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
6. **Smoking History**: Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years [number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1.
7. **Severity of Disease**: A post-salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 and a post-salbutamol FEV1 of ≤70% of predicted normal values calculated using National Health and Nutritional Examination survey (NHANES) III reference equations at Visit 1 [Hankinson, 1999; Hankinson, 2010]
8. **Dyspnea**: A score of ≥2 on the modified Medical Research Council (mMRC) Dyspnea Scale at Visit 1.

Exclusion criteria

Subjects meeting any of the following criteria must not have been enrolled in the study:

1. **Pregnancy**: Women who were pregnant or lactating or were planning on becoming pregnant during the study
2. **Asthma**: A current diagnosis of asthma
3. **Other Respiratory Disorders**: Known respiratory disorders other than COPD including but not limited to α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease. Allergic rhinitis was not exclusionary.
4. **Other Diseases/Abnormalities**: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or hematological abnormalities that were uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that has been resected for cure is not exclusionary). Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through disease/condition exacerbated during the study.
5. **Chest X-Ray**: A chest X-ray or computed tomography (CT) scan that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must have been taken at Visit 1 if a chest X-ray or CT scan was not available within 6

months prior to Visit 1. For subjects in Germany, if a chest X-ray (or CT scan) was not available in the 6 months prior to Visit 1, the subject was not eligible for the study.

6. **Contraindications**: A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate, or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction that, in the opinion of the study physician, contraindicated study participation or use of an inhaled anticholinergic.
7. **Hospitalization**: Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
8. **Lung Resection**: Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1)
9. **12-lead ECG**: An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead ECG which caused the underlying rhythm and ECG to be obscured. Investigators were provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. Specific ECG findings that precluded subject eligibility are listed in Appendix 5 of the protocol. The study investigator determined the medical significance of any ECG abnormalities not listed in Appendix 5 of the protocol.
10. **Screening Labs**: Significantly abnormal finding from clinical chemistry or hematology tests at Visit 1
11. **Medication Prior to Spirometry**: Unable to withhold salbutamol for the 4-hour period required prior to spirometry testing at each study visit
12. **Oxygen**: Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e., ≤12 hours per day) was not exclusionary.
13. **Nebulized Therapy**: Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., salbutamol) via nebulized therapy.
14. **Pulmonary Rehabilitation Program**: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.
15. **Drug or Alcohol Abuse**: A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.

Treatments

The Applicant provided the study drug for use in this study. The following double-blind study drugs were used in this study:

- UMEC/VI 125/25 mcg once-daily via NDPI + placebo once-daily via HandiHaler
- UMEC/VI 62.5/25 mcg once-daily via NDPI + placebo once-daily via HandiHaler
- VI 25 mcg once-daily via NDPI + placebo once-daily via HandiHaler
- TIO 18 mcg once-daily via HandiHaler + placebo once-daily via NDPI

Subjects were instructed to take one dose each morning from both the NDPI and the HandiHaler.

On the morning of each clinic study visit, subjects refrained from taking their morning dose of study drug until instructed to do so by clinic personnel. Study drug was given at the clinic at approximately the same time of day as Day 1 (Visit 2). On the other days during the Treatment Period (i.e., "non-clinic days"), subjects were instructed to take their study drug each morning at approximately the same time of day as the dose time on Day 1 (Visit 2).

Double-blind UMEC/VI, VI, and matching placebo (identical in appearance to the inhaler containing active study drug) were administered via an NDPI for oral inhalation. The NDPI for UMEC/VI and placebo contained two, double-foil, laminate, blister strips within the NDPI. The NDPI provided a total of 30 doses (60 blisters) and delivered, when actuated, the contents of a single blister simultaneously from each of the 2 blister strips. The NDPI for VI alone contained a single, double-foil, laminate blister strip, with a total of 30 doses in the NDPI.

Objectives

Primary Objective

The primary objective of this study was to compare the efficacy of two doses of UMEC/VI (125/25 mcg and 62.5/25 mcg once-daily) with VI (25 mcg once-daily) and with TIO (18 mcg once-daily) over 24 weeks for the treatment of subjects with COPD.

Secondary Objectives

Secondary objectives of this study were to compare effects of two doses of UMEC/VI (125/25 mcg and 62.5/25 mcg once-daily) with VI (25 mcg once-daily) and with TIO (18 mcg once-daily) on safety and quality of life assessments over 24 weeks in subjects with COPD.

Outcomes/endpoints

The primary efficacy endpoint was the clinic visit trough (pre-bronchodilator and predose) FEV_1 on Day 169.

Trough FEV_1 on Treatment Day 169 was defined as the mean of the FEV_1 values obtained at 23 and 24 hours after dosing on Treatment Day 168 (i.e., at the Week 24 visit).

The secondary efficacy endpoint was the weighted mean 0 to 6 hour FEV_1 obtained postdose at Week 24.

Sample size

The sample size for the individual studies was calculated in order to provide sufficient power for the comparisons of trough FEV_1, and also for the comparisons of TDI for UMEC/VI and TIO in the meta-analysis. This meta-analysis of TDI will include data from both this study and Study DB2113374, and will be provided as a separate report.

The sample size calculations used a 2-sided 5% significance level and an estimate of residual standard deviation (SD) for trough FEV_1 of 210 mL. The estimate of SD was based on Mixed Model Repeated Measures (MMRM) analyses of previous studies in COPD subjects with UMEC, VI, and the FP/salmeterol combination. A study with 94 evaluable subjects per arm has 90% power to detect a 100 mL difference (which is recognized as a minimal important difference) between treatments in trough FEV_1.

For the meta-analysis of TDI, the sample size calculations used a two-sided 5% significance level and an estimate of residual SD for TDI of 3.24 units. The estimate of SD was based on MMRM analysis of a previous study in COPD subjects with the FP/salmeterol combination. An analysis including 221

evaluable subjects per arm has 90% power to detect a 1-unit difference between treatments in TDI. This treatment difference was selected as the generally accepted minimally important difference (MID) for this endpoint [Witek, 2003; Mahler, 1984]. In order to achieve this, a sample size of 111 evaluable subjects per arm per study was required.

In order to meet ICH guidelines on exposure to new medicinal products (E1A) for UMEC/VI, the planned number of evaluable subjects in each arm was increased to 146.

A study with 146 evaluable subjects per treatment arm would provide 98% power to detect a 100 mL difference in trough FEV1 between treatment groups and 96% power to detect a difference of 1 unit in TDI in the meta-analysis using the assumptions above. As statistical inference for a particular UMEC/VI dose vs. TIO on TDI in the meta-analysis was conditional on having achieved statistical significance for that comparison on the primary efficacy endpoint, trough FEV1, in each individual study, powering trough FEV1 in each study and TDI in the meta-analysis each at >90% provides 92% power (conditional on trough FEV1 analysis) for the combined analysis of TDI.

It was estimated that approximately 30% of subjects could withdraw without providing a Week 24 assessment. Although, in MMRM, all available post-baseline assessments up to the endpoint for subjects in the ITT population are utilized in the analysis, data for subjects who withdrew prematurely from the study were not explicitly imputed. Hence, to allow for a 30% withdrawal rate, 208 subjects were to be randomized to each treatment arm.

Randomisation

Subjects were assigned to study treatment in accordance with the randomization schedule. The randomization code was generated by the Applicant using a validated computerized system RandAll version 2.5. Subjects were randomized 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.

Subjects who met the eligibility criteria were randomly assigned to one of the blinded study treatment regimens in equal proportion.

Blinding (masking)

Study drug taken during the 24-week treatment period was administered in a double-blind fashion. Neither the subject nor the study physician knew which study drug the subject was receiving. Measures were taken to ensure integrity of the blind. As there were differences in the appearance in active TIO and placebo capsules, both the active marketed product and placebo blister packages were covered with opaque over-labels, the HandiHalers were covered with labels to mask any identifying marks on the inhaler, and medications were administered by a third party at the study site not involved in efficacy or safety endpoints that could be influenced by knowledge of study treatment assignment.

Statistical methods

The following treatment comparisons were performed for trough FEV1 on Day 169:

- UMEC/VI 125/25 mcg vs. TIO
- UMEC/VI 125/25 mcg vs. VI 25 mcg

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 consisted of the treatment comparisons above, performed for the primary and secondary efficacy endpoints, followed by the same treatment comparisons on the same endpoints for the lower UMEC/VI dose.

All programming was performed in a Harmonization for Analysis and Reporting (HARP) environment using SAS Version 9 and S-Plus Version 7 or a later release.

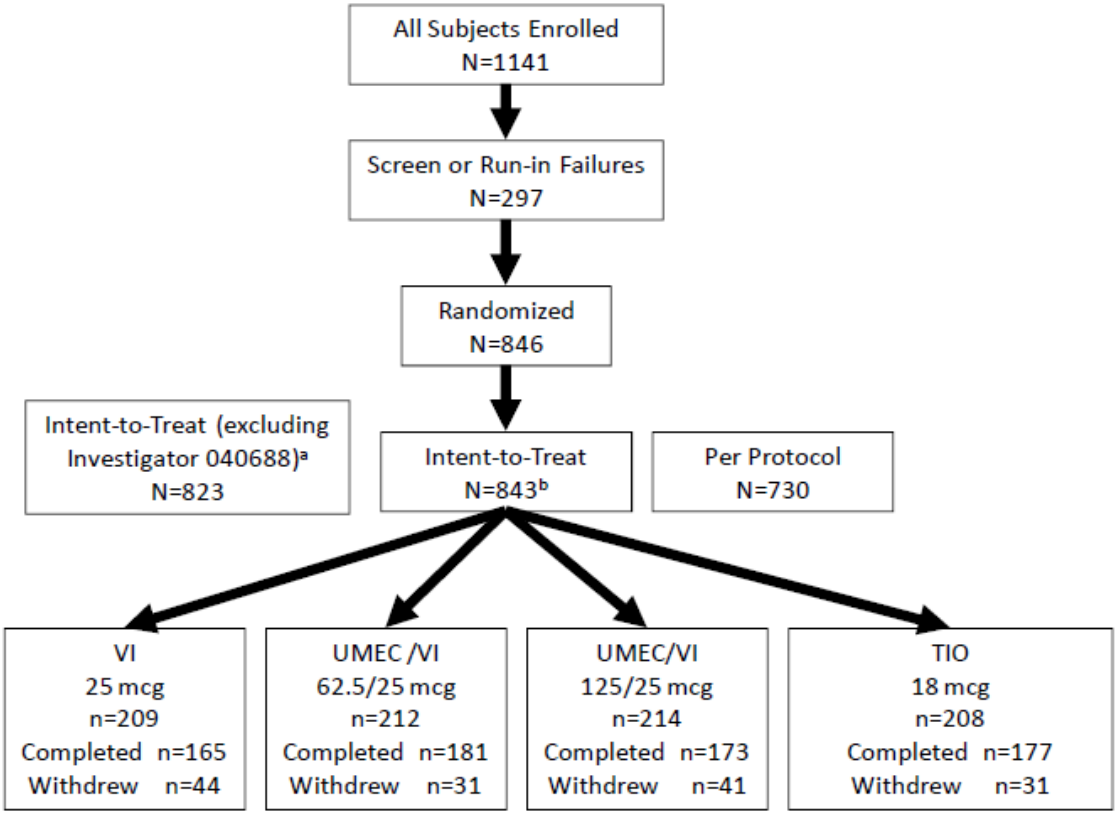
Results

Participant flow

Study DB22113360

An overview of subject disposition is shown in the figure below.

Figure 5. Subject Disposition (Study DB2113360)

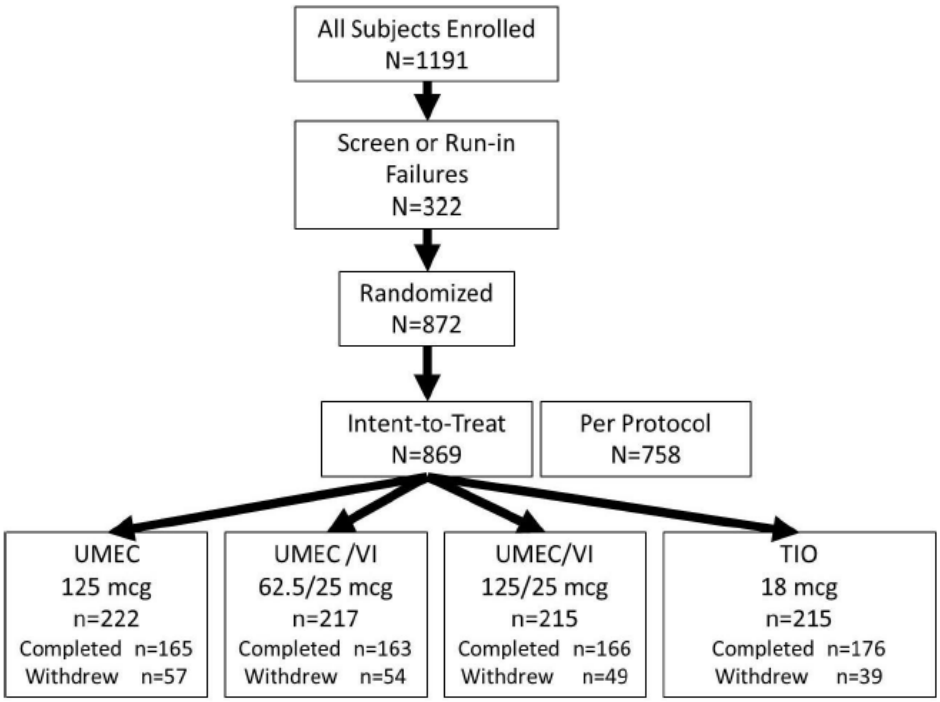


Data Source: Table 5.01 and Table 5.03
Abbreviations: ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Of the 3 subjects who were randomized but not in the ITT population, 2 subjects are included in the Randomized total as well as the Screen and Run-in Failures total (indicating that they were randomized in error) and 1 subject who was randomized but discontinued before receiving any dose of study drug.
Note: Subjects were considered to have completed if they completed the last clinic visit (Visit 9) excluding follow-up.
Note: Randomized subjects included all subjects who were randomized and given a randomization number.
a. This ITT population was used as the primary population for all efficacy and health outcomes analyses. Additional information is provided in Section 5.2 and Section 5.3.
b. This ITT population was used as the primary population for all study population and safety analyses.

Study DB2113374

An overview of subject disposition is shown in the figure below.

Figure 6. Subject Disposition (Study DB2113374)



Data Source: Table 5.01 and Table 5.03
Abbreviations: TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Subjects were considered to have completed if they completed the last clinic visit (Visit 9) excluding follow-up.
Note: Randomized included all subjects who were randomized and given a randomized number.
Note: Three subjects were included in the Randomized population as well as the Screen and Run-in Failures population.

Conduct of the study

There was one amendment to the original clinical trial protocol for both studies DB2113360 and DB2113374. This amendment was considered not influencing the study results.

Baseline data

Study DB2113360

Demographics

Demographic characteristics in the ITT population were similar between treatment groups (see table below).

Table 44. Summary of Demographic Characteristics (DB2113360 ITT Population)

Demographic Characteristic	VI 25 mcg N=209	UMEC/VI 62.5/25 mcg N=212	UMEC/VI 125/25 mcg N=214	TIO N=208	Total N=843
Age (years), n	209	212	214	208	843
Mean	63.2	63.0	62.9	62.6	62.9
SD	9.10	8.67	8.87	9.39	9.00
Min, Max	40, 84	42, 85	43, 82	41, 88	40, 88
Sex, n	209	212	214	208	843
Female, n (%)	66 (32)	64 (30)	63 (29)	68 (33)	261 (31)
Male, n (%)	143 (68)	148 (70)	151 (71)	140 (67)	582 (69)
Ethnicity, n	209	212	214	208	843
Hispanic/Latino, n (%)	21 (10)	24 (11)	25 (12)	23 (11)	93 (11)
Not Hispanic/Latino, n (%)	188 (90)	188 (89)	189 (88)	185 (89)	750 (89)
Race, n	209	212	214	208	843
African American/African Heritage, n (%)	3 (1)	7 (3)	9 (4)	6 (3)	25 (3)
American Indian or Alaska Native, n (%)	19 (9)	16 (8)	21 (10)	20 (10)	76 (9)
Asian, n (%)	0	3 (1)	1 (<1)	2 (<1)	6 (<1)
Central/South Asian Heritage	0	0	1 (<1)	0	1 (<1)
Japanese/East Asian Heritage/South East Asian Heritage	0	3 (1)	0	2 (<1)	5 (<1)
White, n (%)	184 (88)	182 (86)	180 (84)	177 (85)	723 (86)
African American/African Heritage & White, n (%)	1 (<1)	0	0	1 (<1)	2 (<1)
American Indian or Alaska Native & Asian, n (%)	1 (<1)	0	0	0	1 (<1)
American Indian or Alaska Native & White, n (%)	1 (<1)	4 (2)	3 (1)	2 (<1)	10 (1)
Height (cm), n	209	212	214	208	843
Mean	170.7	170.2	170.9	168.8	170.1
SD	8.13	9.30	8.51	9.41	8.87
Min, Max	150, 190	149, 198	145, 195	146, 192	145, 198
Weight (kg), n	209	212	214	208	843
Mean	79.81	79.47	77.61	78.77	78.91
SD	18.071	18.701	17.186	17.813	17.937
Min, Max	42.0, 140.0	38.0, 157.9	46.7, 129.1	41.0, 140.0	38.0, 157.9
Body mass index (kg/m²), n	209	212	214	208	843
Mean	27.35	27.39	26.51	27.56	27.20
SD	5.741	6.112	5.141	5.471	5.632
Min, Max	15.2, 47.1	16.6, 55.9	16.7, 43.4	15.4, 59.6	15.2, 55.9

Data Source: Table 5.11 and Table 5.14
Abbreviations: ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Full detailed race and racial combination data are provided in Table 5.15.

Demographics were similar between the ITT and PP.

Smoking History

At screening, 51% of subjects overall were classified as current smokers (including subjects who stopped smoking within 6 months prior to screening; see table below). During the course of the study, there were no subjects who changed their smoking status from the previous visit.

Mean smoking pack-years at Screening was similar between treatment groups (see table below).

The percentage of current smokers in the UMEC/VI 125/25 mcg treatment group was higher compared with the other 3 treatment groups.

Table 45. Summary of Smoking History and Status (DB2113360 ITT Population)

Smoking History/Status	VI 25 mcg N=209	UMEC/VI 62.5/25 mcg N=212	UMEC/VI 125/25 mcg N=214	TIO N=208	Total N=843
Years smoked, n	209	212	214	208	843
Mean	36.2	37.0	37.0	36.4	36.7
SD	11.51	10.82	11.47	11.16	11.23
Min, Max	10, 60	10, 65	7, 68	10, 65	7, 68
Smoking pack-years [a], n	209	212	214	208	843
Mean	41.6	44.8	43.5	41.9	43.0
SD	25.36	27.65	24.98	24.44	25.63
Min, Max	10, 174	10, 250	10, 180	10, 150	10, 250
Smoking status at Screening, n	209	212	214	208	843
Current smoker	106 (51)	98 (46)	124 (58)	99 (48)	427 (51)
Former smoker	103 (49)	114 (54)	90 (42)	109 (52)	416 (49)

Data Source: Table 5.22 and Table 5.23
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack-years=(number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 46. Summary of COPD History (DB2113360 ITT Population)

	Number (%) of Subjects				
	VI 25 mcg N=209	UMEC/VI 62.5/25 mcg N=212	UMEC/VI 125/25 mcg N=214	TIO N=208	Total N=843
Duration of COPD					
<1 year	13 (6)	20 (9)	19 (9)	20 (10)	72 (9)
≥1 to <5 years	73 (35)	75 (35)	74 (35)	79 (38)	301 (36)
≥5 to <10 years	62 (30)	63 (30)	60 (28)	54 (26)	239 (28)
≥10 to <15 years	40 (19)	30 (14)	38 (18)	34 (16)	142 (17)
≥15 to <20 years	13 (6)	11 (5)	11 (5)	14 (7)	49 (6)
≥20 to <25 years	7 (3)	8 (4)	10 (5)	6 (3)	31 (4)
≥25 years	1 (<1)	5 (2)	2 (<1)	1 (<1)	9 (1)
COPD type [a], n					
Chronic bronchitis	147 (70)	147 (69)	144 (67)	149 (72)	587 (70)
Emphysema	116 (56)	123 (58)	129 (60)	125 (60)	493 (58)

Data Source: Table 5.20
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to screening, the majority of subjects across treatment groups (range: 66% to 72%) reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics. In addition, the percentage of subjects who did not have a COPD exacerbation resulting in hospitalization in the 12 months prior to screening was similar across treatment groups (range: 81% to 89%).

Screening and Baseline Lung Function

Overall, subjects had moderate to very severe airflow obstruction at screening, and lung function parameters were similar across treatment groups (see table below).

Table 47. Summary of Screening Lung Function Test Results (DB2113360 ITT Population)

Parameter	VI 25 mcg N=209	UMEC/VI 62.5/25 mcg N=212	UMEC/VI 125/25 mcg N=214	TIO N=208	Total N=843
Pre-bronchodilator FEV_1 (L), n	207	212	213	204	836
Mean	1.327	1.314	1.300	1.298	1.310
SD	0.4967	0.4869	0.4611	0.5021	0.4860
Median	1.250	1.225	1.290	1.245	1.250
Min, Max	0.41, 3.07	0.41, 2.67	0.42, 2.64	0.36, 2.79	0.36, 3.07
Post-salbutamol FEV_1 (L), n	206	211	212	206	835
Mean	1.449	1.441	1.433	1.415	1.435
SD	0.4795	0.4745	0.4621	0.5025	0.4790
Median	1.430	1.390	1.405	1.395	1.400
Min, Max	0.44, 2.84	0.45, 3.07	0.51, 2.75	0.45, 2.70	0.44, 3.07
Post-ipratropium FEV_1 (L), n [a]	207	210	212	204	833
Mean	1.557	1.546	1.540	1.519	1.541
SD	0.5399	0.5049	0.4950	0.5360	0.5183
Median	1.490	1.500	1.470	1.475	1.480
Min, Max	0.44, 3.22	0.47, 3.18	0.59, 2.93	0.54, 2.91	0.44, 3.22
Post-salbutamol FEV_1/FVC, n	206	211	212	206	835
Mean	48.173	47.673	47.917	48.342	48.023
SD	10.9416	11.0588	11.4955	11.8678	11.3287
Median	47.700	48.700	47.250	49.350	48.000
Min, Max	18.90, 77.70	18.50, 69.70	15.60, 69.50	22.30, 69.70	15.60, 77.70
Post-salbutamol percent predicted FEV_1 (%), n	206	211	212	206	835
Mean	47.7	48.0	47.2	47.8	47.7
SD	12.65	12.94	12.79	13.36	12.92
Median	48.4	49.9	48.9	49.2	49.1
Min, Max	19, 70	16, 70	16, 70	16, 72	16,72
Percent reversibility to salbutamol (%), n	205	211	212	203	831
Mean	11.3	12.4	12.2	10.8	11.7
SD	13.74	14.97	14.18	13.62	14.13
Median	9.0	10.4	9.6	9.1	9.7
Min, Max	-41, 65	-45, 60	-22, 63	-16, 61	-45, 65
Reversibility to salbutamol (mL), n	205	211	212	203	831
Mean	119.6	128.6	132.7	115.9	124.3
SD	177.72	185.93	152.54	158.90	169.16
Median	116.0	121.0	118.0	104.0	116.0
Min, Max	-1076, 555	-1200, 723	-266, 703	-363, 652	-1200, 723

Parameter	VI 25 mcg N=209	UMEC/VI 62.5/25 mcg N=212	UMEC/VI 125/25 mcg N=214	TIO N=208	Total N=843
Percent reversibility to salbutamol and ipratropium (%), n	206	210	212	202	830
Mean	19.2	21.1	21.2	19.5	20.3
SD	17.98	19.41	20.70	18.82	19.25
Median	16.3	18.1	16.6	15.8	16.7
Min, Max	-16, 114	-36, 106	-17, 116	-17, 94	-36, 116
Reversibility to salbutamol and ipratropium (mL), n	206	210	212	202	830
Mean	227.5	233.7	239.4	217.2	229.6
SD	206.59	218.22	226.40	201.39	213.32
Median	200.0	220.0	210.0	200.0	210.0
Min, Max	-430, 1240	-950, 1350	-290, 1510	-210, 820	-950, 1510

Data Source: Table 5.24
Abbreviations: FEV_1= forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Post-ipratropium spirometry was conducted following post-salbutamol spirometry.

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status for post-bronchodilator tests performed at screening are summarized in the table below.

Table 48. Summary of GOLD Stage, Reversibility, and ICS Use (DB2113360 ITT Population)

	Number (%) of Subjects				
	VI 25 mcg N=209	UMEC/VI 62.5/25 mcg N=212	UMEC/VI 125/25 mcg N=214	TIO N=208	Total N=843
GOLD Stage (percent predicted FEV_1), n	206	211	212	206	835
Stage I (≥80%)	0	0	0	0	0
Stage II (≥50% to <80%)	94 (46)	104 (49)	99 (47)	96 (47)	393 (47)
Stage III (≥30% to <50%)	91 (44)	85 (40)	87 (41)	87 (42)	350 (42)
Stage IV (<30%)	21 (10)	22 (10)	26 (12)	23 (11)	92 (11)
Reversible to salbutamol, n [a]	205	211	212	203	831
Reversible	52 (25)	57 (27)	61 (29)	47 (23)	217 (26)
Non-reversible	153 (75)	154 (73)	151 (71)	156 (77)	614 (74)
Reversible to salbutamol and ipratropium, n [b]	206	210	212	202	830
Reversible	98 (48)	113 (54)	106 (50)	99 (49)	416 (50)
Non-reversible	108 (52)	97 (46)	105 (50)	103 (51)	414 (50)
ICS use, n [c]	209	212	214	208	843
ICS users	84 (40)	93 (44)	103 (48)	93 (45)	373 (44)
ICS non-users	125 (60)	119 (56)	111 (52)	115 (55)	470 (56)

Data Source: Table 5.26

Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.
b. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.
c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Study DB2113374

Demographics

Demographic characteristics in the ITT population were similar between treatment groups (see table below).

Table 49. Summary of Demographic Characteristics (DB2113374 ITT Population)

Demographic Characteristic	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
Age (years), n	222	217	215	215	869
Mean	64.5	65.0	63.8	65.2	64.6
SD	8.33	8.62	8.51	8.30	8.44
Min, Max	40, 84	40, 85	42, 84	41, 83	40, 85
Sex, n	222	217	215	215	869
Female, n (%)	74 (33)	77 (35)	67 (31)	62 (29)	280 (32)
Male, n (%)	148 (67)	140 (65)	148 (69)	153 (71)	589 (68)
Ethnicity, n	222	217	215	215	869
Hispanic/Latino, n (%)	42 (19)	38 (18)	35 (16)	38 (18)	153 (18)
Not Hispanic/Latino, n (%)	180 (81)	179 (82)	180 (84)	177 (82)	716 (82)
Race, n	222	217	215	215	869
African American/African Heritage	6 (3)	8 (4)	9 (4)	8 (4)	31 (4)
American Indian or Alaska Native	0	0	0	0	0
Asian	37 (17)	35 (16)	37 (17)	36 (17)	145 (17)
Central/South Asian Heritage	0	0	0	0	0
Japanese/East Asian Heritage/South East Asian Heritage	37 (17)	35 (16)	37 (17)	36 (17)	145 (17)
Native Hawaiian or other Pacific Islander	0	1 (<1)	0	0	1 (<1)
White	170 (77)	164 (76)	160 (74)	163 (76)	657 (76)
African American/African Heritage & White	0	0	1 (<1)	0	1 (<1)
American Indian or Alaska Native & White	8 (4)	9 (4)	8 (4)	8 (4)	33 (4)
Asian & White	1 (<1)	0	0	0	1 (<1)
Height (cm), n	222	217	215	215	869
Mean	167.7	167.9	167.5	168.6	167.9
SD	8.86	10.56	8.93	8.60	9.26
Min, Max	142, 193	144, 198	145, 193	148, 190	142, 198

Demographic Characteristic	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
Weight (kg), n	222	217	215	215	869
Mean	74.70	75.50	74.84	75.68	75.18
SD	18.269	19.141	18.671	20.653	19.168
Min, Max	36.3, 122.5	38.0, 143.4	36.5, 170.0	40.7, 157.3	36.3, 170.0
BMI (kg/m²), n	222	217	215	215	869
Mean	26.45	26.72	26.55	26.43	26.54
SD	5.736	6.118	5.771	6.095	5.922
Min, Max	14.6, 52.4	14.5, 47.9	15.8, 52.5	15.1, 53.2	14.5, 53.2

Data Source: Table 5.11 and Table 5.14
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Full detailed race and racial combination data were provided in Table 5.14 and Table 5.15.

Demographics were similar between the ITT and PP populations.

Smoking History

At screening, 45% of subjects overall were classified as current smokers (including subjects who stopped smoking within 6 months prior to screening; see table below). During the course of the study, only 3 subjects changed their smoking status from the previous visit.

At the Day 84 visit, 1 subject in the UMEC 125 mcg treatment group and 1 subject in the UMEC/VI 125/25 mcg treatment group had stopped smoking, and 1 subject in the UMEC/VI 62.5/25 mcg group had started smoking.

Mean smoking pack-years and smoking status at screening were similar between treatment groups (see table below).

Table 50. Summary of Smoking History and Status (DB2113374 ITT Population)

Smoking History/Status	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
Years smoked, n	222	217	215	215	869
Mean	39.8	40.4	38.3	39.9	39.6
SD	11.48	10.41	10.87	9.69	10.65
Min, Max	8, 66	10, 67	10, 69	5, 64	5, 69
Smoking pack years [a], n	222	217	215	215	869
Mean	47.6	47.8	46.9	54.0	49.1
SD	27.58	26.13	24.90	31.59	27.76
Min, Max	10, 190	10, 150	10, 132	10, 265	10, 265
Smoking status at Screening, n	222	217	215	215	869
Current smoker	98 (44)	92 (42)	96 (45)	102 (47)	388 (45)
Former smoker	124 (56)	125 (58)	119 (55)	113 (53)	481 (55)

Data Source: Table 5.22 and Table 5.23
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack years = (number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 51. Summary of COPD History (DB2113374 ITT Population)

	Number (%) of Subjects				
	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
Duration of COPD					
<1 year	16 (7)	28 (13)	31 (14)	16 (7)	91 (10)
≥1 to <5 years	96 (43)	80 (37)	74 (34)	83 (39)	333 (38)
≥5 to <10 years	65 (29)	53 (24)	71 (33)	65 (30)	254 (29)
≥10 to <15 years	22 (10)	37 (17)	21 (10)	34 (16)	114 (13)
≥15 to <20 years	12 (5)	10 (5)	12 (6)	12 (6)	46 (5)
≥20 to <25 years	7 (3)	3 (1)	3 (1)	3 (1)	16 (2)
≥25 years	4 (2)	6 (3)	3 (1)	2 (<1)	15 (2)
COPD Type [a], n	219	216	215	214	864
Chronic bronchitis	120 (55)	134 (62)	125 (58)	120 (56)	499 (58)
Emphysema	152 (69)	132 (61)	136 (63)	136 (64)	556 (64)

Data Source: Table 5.20
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to screening, the majority of subjects across treatment groups (65% to 72%) reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics. In addition, the percentage of subjects who did not have a COPD exacerbation resulting in hospitalization in the 12 months prior to Screening was similar across treatment groups (93% to 96%).

Screening and Baseline Lung Function

Overall, subjects had moderate to very severe airflow obstruction at Screening and lung function parameters were similar across treatment groups (see table below).

Table 52. Summary of Screening Lung Function Test Results (DB2113374 ITT Population)

Parameter	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
Pre-bronchodilator FEV_1 (L), n	219	217	215	214	865
Mean	1.140	1.170	1.159	1.175	1.161
SD	0.4479	0.4655	0.4384	0.4287	0.4449
Median	1.060	1.090	1.090	1.105	1.090
Min, Max	0.42, 3.07	0.35, 2.76	0.36, 3.00	0.42, 2.72	0.35, 3.07
Post-salbutamol FEV_1 (L), n	221	216	214	214	865
Mean	1.294	1.322	1.313	1.328	1.314
SD	0.4679	0.4899	0.4235	0.4310	0.4535
Median	1.240	1.240	1.260	1.265	1.250
Min, Max	0.46, 3.02	0.44, 3.07	0.41, 2.84	0.51, 2.57	0.41, 3.07
Post-ipratropium FEV_1 (L), n [a]	217	216	213	214	860
Mean	1.399	1.421	1.398	1.405	1.406
SD	0.5092	0.5304	0.4685	0.4507	0.4901
Median	1.330	1.320	1.350	1.340	1.340
Min, Max	0.46, 3.25	0.47, 3.69	0.44, 3.29	0.56, 2.67	0.44, 3.69
Post-salbutamol FEV_1/FVC	221	216	214	214	865
Mean	45.290	46.232	45.938	45.804	45.813
SD	11.3722	11.8586	10.3947	11.6544	11.3210
Median	44.600	47.050	45.000	44.850	45.400
Min, Max	20.80, 69.20	23.30, 69.90	20.10, 68.90	19.80, 69.80	19.80, 69.90
Post-salbutamol Percent Predicted FEV_1 (%), n	221	216	214	214	865
Mean	46.2	47.7	47.1	47.4	47.1
SD	13.03	13.55	12.88	13.10	13.13
Median	45.5	49.6	46.6	47.7	47.5
Min, Max	18, 70	17, 70	14, 70	16, 70	14, 70
Percent Reversibility to Salbutamol (%), n	219	216	214	214	863
Mean	16.1	14.9	15.8	15.5	15.6
SD	15.25	14.95	15.17	15.55	15.21
Median	13.2	13.6	15.6	12.6	13.4
Min, Max	-36, 91	-33, 89	-27, 82	-14, 93	-36, 93
Reversibility to Salbutamol (mL), n	219	216	214	214	863
Mean	159.5	149.9	152.3	152.7	153.6
SD	156.00	161.39	171.77	149.74	159.67
Median	149.0	141.0	146.5	142.5	145.0
Min, Max	-581, 581	-513, 930	-801, 995	-252, 755	-801, 995
Percent Reversibility to Salbutamol and Ipratropium (%), n	215	216	213	213	857
Mean	25.7	24.0	23.6	23.1	24.1
SD	18.85	19.09	18.27	20.08	19.07
Median	22.8	21.3	20.9	19.4	20.9
Min, Max	-28, 111	-20, 116	-17, 100	-14, 122	-28, 122

Parameter	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
Reversibility to Salbutamol and Ipratropium (mL), n	215	216	213	213	857
Mean	262.6	249.5	244.4	230.1	246.7
SD	189.30	217.73	183.88	185.28	194.62
Median	250.0	220.0	230.0	210.0	230.0
Min, Max	-460, 990	-330, 1620	-180, 1210	-210, 920	-460, 1620

Data Source: Table 5.24
Abbreviations: FEV_1= forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Post-ipratropium spirometry was conducted following completion of post-salbutamol spirometry.

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status for post-bronchodilator tests performed at Screening are summarized in the table below.

Table 53. Summary of Gold Stage, Reversibility, and ICS Use (DB2113374 ITT Population)

	Number (%) of Subjects				
	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215	Total N=869
GOLD Stage (percent predicted FEV_1), n	221	216	214	214	865
Stage I (≥80%)	0	0	0	0	0
Stage II (≥50% to <80%)	86 (39)	106 (49)	89 (42)	103 (48)	384 (44)
Stage III (≥30% to <50%)	106 (48)	83 (38)	102 (48)	83 (39)	374 (43)
Stage IV (<30%)	29 (13)	27 (13)	23 (11)	28 (13)	107 (12)
Reversible to Salbutamol, n [a]	219	216	214	214	863
Reversible	75 (34)	64 (30)	79 (37)	60 (28)	278 (32)
Non-reversible	144 (66)	152 (70)	135 (63)	154 (72)	585 (68)
Reversible to Salbutamol and Ipratropium, n [b]	215	216	213	213	857
Reversible	130 (60)	115 (53)	125 (59)	110 (52)	480 (56)
Non-reversible	85 (40)	101 (47)	88 (41)	103 (48)	377 (44)
ICS use, n [c]	222	217	215	215	869
ICS users	124 (56)	103 (47)	113 (53)	115 (53)	455 (52)
ICS non-users	98 (44)	114 (53)	102 (47)	100 (47)	414 (48)

Data Source: Table 5.26
Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.
b. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.
c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Numbers analysed

Study DB2113360

A summary of subject populations is presented in the table below. The ITT population excluding Investigator 040688 was used as the primary population for efficacy and health outcomes analyses; the entire ITT population was used for study population and safety analyses. Sensitivity analyses using the entire ITT population were performed for primary and secondary efficacy analyses.

Table 54. Summary of Subject Populations (DB2113360 ASE Population)

	Number (%) of Subjects				
Population	VI 25 mcg	UMEC/VI 62.5/25 mcg	UMEC/VI 125/25 mcg	TIO	Total
All Subjects Enrolled (ASE)					1141
Screen or Run-in Failures [a]					297 (26)
Randomized	209	212	216	209	846
Intent-to-Treat (ITT)	209	212	214	208	843
ITT (excluding Investigator 040688) [b]	205 (98)	207 (98)	208 (97)	203 (98)	823 (98)
Per Protocol (PP) [c]	182 (89)	179 (86)	185 (89)	184 (91)	730 (89)

Data Source: Table 5.01

Abbreviations: ASE=all subjects enrolled; ITT=intent-to-treat; PP=per protocol; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Two subjects were included in the Randomized row as well as the Screen and Run-in Failures row (indicating that they were randomized in error).

ASE: All subjects who were screened and for whom a record exists in the study database.

ITT: All randomized subjects who received at least a single dose of study drug.

PP: All subjects in the ITT population who were not identified as full protocol deviators.

a. Percentage is based on the ASE population.

b. This ITT population excludes all subjects from Investigator 040668; additional details are presented in Section 5.2. Percentages are based on the ITT population.

c. Percentages are based on the ITT population (excluding Investigator 040688).

Study DB2113374

A summary of subject populations is presented in the table below.

Table 55. Summary of Subject Populations (DB2113374 ASE Population)

	Number (%) of Subjects				
Population	UMEC 125 mcg	UMEC/VI 62.5/25 mcg	UMEC/VI 125/25 mcg	TIO	Total
All Subjects Enrolled (ASE)					1191
Screen or Run-in Failures [a]					322 (27)
Randomized	222	218	217	215	872
Intent-to-treat (ITT)	222	217	215	215	869
Per Protocol (PP) [b]	193 (87)	187 (86)	184 (86)	194 (90)	758 (87)

Data Source: Table 5.01

Abbreviations: ASE=all subjects enrolled; ITT=Intent-to-treat; PP=per protocol; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Randomized includes all subjects who were randomized and given a randomized number.

Notes: Three subjects were included in the Randomized row as well as the Screen and Run-in Failures row.

ASE: All subjects who were screened and for whom a record exists on the study database.

ITT: All randomized subjects who received at least a single dose of study drug.

PP: All subjects in the ITT population who were not identified as full protocol deviators.

a. Percentages are based on the ASE population.

b. Percentages are based on the ITT population.

Outcomes and estimation

Study DB2113360

Trough FEV1 at Day 169: Primary Endpoint

The primary efficacy endpoint was trough FEV1 on Day 169. Trough FEV1 on Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168 (i.e., at the Week 24 [Day 168] Visit).

Statistically significant improvements in least squares (LS) mean change from baseline trough FEV1 were demonstrated for both the UMEC/VI 62.5/25 mcg and the UMEC/VI 125/25 mcg treatment groups compared with both the VI 25 mcg and TIO treatment groups at Day 169 (see table below).

Table 56. Primary Efficacy Analysis: Trough FEV_1 (L) at Day 169 (DB2113360 ITT Population Excluding Investigator 040688)

Day 169	VI 25 mcg N=205	UMEC/VI 62.5/25 mcg N=207	UMEC/VI 125/25 mcg N=208	TIO N=203
n [a]	203	207	204	201
n [b]	162	177	167	173
LS mean (SE)	1.431 (0.0189)	1.521 (0.0183)	1.519 (0.0187)	1.431 (0.0186)
LS mean change (SE)	0.121 (0.0189)	0.211 (0.0183)	0.209 (0.0187)	0.121 (0.0186)
UMEC/VI 62.5/25 vs. Column				
Difference	0.090			0.090
95% CI	(0.039,0.142)			(0.039,0.141)
p-value	<0.001			<0.001
UMEC/VI 125/25 vs. Column				
Difference	0.088			0.088
95% CI	(0.036,0.140)			(0.036,0.140)
p-value	<0.001			<0.001

Data Source: Table 6.05

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

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 one or more visits.

b. Number of subjects with analyzable data at the current visit.

Weighted Mean FEV1 Over 0 to 6 Hours Postdose at Day 168 (Secondary Endpoint), Day 1, and Day 84

The secondary efficacy endpoint was the 0 to 6 hour postdose weighted mean FEV1 on Day 168.

Statistically significant improvements in LS mean change from baseline in 0 to 6 hour weighted mean FEV1 were demonstrated for both the UMEC/VI 62.5/25 mcg and UMEC/VI 125/25 mcg treatment groups compared with both the VI 25 mcg and TIO treatment groups at Day 168, as well as at Days 1 and 84 (see table below).

Table 57. Statistical Analysis: 0 to 6 hour Weighted Mean FEV_1 (L) (DB2113360 ITT Population Excluding Investigator 040688)

Day	VI 25 mcg N=205	UMEC/VI 62.5/25 mcg N=207	UMEC/VI 125/25 mcg N=208	TIO N=203
Day 1				
n [a]	204	207	206	202
n [b]	201	204	204	196
LS mean (SE)	1.470 (0.0103)	1.537 (0.0102)	1.543 (0.0103)	1.456 (0.0104)
LS mean change (SE)	0.157 (0.0103)	0.224 (0.0102)	0.230 (0.0103)	0.143 (0.0104)
UMEC/VI 62.5/25 vs. Column				
Difference	0.067			0.080
95% CI	(0.039,0.095)			(0.052,0.109)
p-value	<0.001			<0.001
UMEC/VI 125/25 vs. Column				
Difference	0.074			0.087
95% CI	(0.045,0.102)			(0.058,0.116)
p-value	<0.001			<0.001
Day 84				
n [a]	204	207	206	202
n [b]	179	191	182	175
LS mean (SE)	1.484 (0.0182)	1.563 (0.0177)	1.572 (0.0180)	1.494 (0.0183)
LS mean change (SE)	0.171 (0.0182)	0.250 (0.0177)	0.259 (0.0180)	0.181 (0.0183)
UMEC/VI 62.5/25 vs. Column				
Difference	0.079			0.070
95% CI	(0.029,0.129)			(0.020,0.120)
p-value	0.002			0.006
UMEC/VI 125/25 vs. Column				
Difference	0.088			0.079
95% CI	(0.038,0.138)			(0.028,0.129)
p-value	<0.001			0.002
Day 168: Secondary endpoint				
n [a]	204	207	206	202
n [b]	161	173	166	168
LS mean (SE)	1.491 (0.0189)	1.567 (0.0183)	1.576 (0.0187)	1.494 (0.0187)
LS mean change (SE)	0.178 (0.0189)	0.254 (0.0183)	0.263 (0.0187)	0.181 (0.0187)
UMEC/VI 62.5/25 vs. Column				
Difference	0.077			0.074
95% CI	(0.025,0.128)			(0.022,0.125)
p-value	0.004			0.005
UMEC/VI 125/25 vs. Column				
Difference	0.086			0.083
95% CI	(0.033,0.138)			(0.031,0.134)
p-value	0.001			0.002

Data Source: Table 6.17

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

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 one or more visits.

b. Number of subjects with analyzable data at the current visit.

Transition Dyspnea Index Focal Score at Days 28, 84, and 168

The results of the statistical analysis of the TDI focal score at Days 28, 84, and 168 are presented in the table below.

Table 58. TDI Focal Score (DB2113360 ITT Population Excluding Investigator 040688)

Day	VI 25 mcg N=205	UMEC/VI 62.5/25 mcg N=207	UMEC/VI 125/25 mcg N=208	TIO N=203
Day 28				
n [a]	193	199	192	188
n [b]	189	198	191	187
LS mean (SE)	1.3 (0.19)	1.6 (0.19)	1.9 (0.19)	1.3 (0.20)
UMEC/VI 62.5/25 vs. Column Difference	0.3			0.3
95% CI	(-0.2,0.9)			(-0.2,0.8)
p-value	0.239			0.275
UMEC/VI 125/25 vs. Column Difference	0.5			0.5
95% CI	(0.0,1.1)			(0.0,1.1)
p-value	0.046			0.057
Day 84				
n [a]	193	199	192	188
n [b]	179	192	182	180
LS mean (SE)	1.9 (0.20)	2.2 (0.19)	2.3 (0.20)	2.0 (0.20)
UMEC/VI 62.5/25 vs. Column Difference	0.2			0.2
95% CI	(-0.3,0.8)			(-0.3,0.7)
p-value	0.383			0.451
UMEC/VI 125/25 vs. Column Difference	0.4			0.3
95% CI	(-0.2,0.9)			(-0.2,0.9)
p-value	0.205			0.250
Day 168				
n [a]	193	199	192	188
n [b]	159	177	164	171
LS mean (SE)	2.1 (0.23)	2.3 (0.22)	2.9 (0.23)	2.4 (0.23)
UMEC/VI 62.5/25 vs. Column Difference	0.2			-0.1
95% CI	(-0.4,0.8)			(-0.7,0.5)
p-value	0.494			0.721
UMEC/VI 125/25 vs. Column Difference	0.8			0.5
95% CI	(0.2,1.5)			(-0.2,1.1)
p-value	0.013			0.135

Data Source: Table 6.53

Abbreviations: BDI= baseline dyspnea index; CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; TDI=Transitional Dyspnea Index; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, BDI focal score, smoking status, center group, Day, Day by BDI focal score, and Day by treatment interactions.

a. Number of subjects with analyzable data for one or more visits.

b. Number of subjects with analyzable data at the current visit.

Study DB2113374

Trough FEV1 at Day 169: Primary Endpoint

The primary efficacy endpoint was trough FEV1 on Day 169. Trough FEV1 on Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168 (i.e., at the Week 24 Visit).

The least squares (LS) mean change from baseline trough FEV1 was 0.223 L for the UMEC/VI 125/25 mcg group, 0.208 L for the UMEC/VI 62.5/25 mcg group, 0.186 L for the UMEC 125 mcg group, and 0.149 L for the TIO group (see table below).

The UMEC/VI 125/25 mcg treatment group showed statistically significant improvement in LS mean change from baseline trough FEV1 compared with TIO at Day 169 (0.074 L; see table below).

The comparison of UMEC/VI 125/25 mcg against UMEC 125 mcg did not achieve statistical significance at the 5% level for the primary endpoint of trough FEV1 at Day 169; 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.

The UMEC/VI 62.5/25 mcg treatment group showed a greater improvement in LS mean change from baseline trough FEV1 compared with the TIO treatment group at Day 169.

No treatment difference was observed for the comparison of UMEC/VI 62.5/25 mcg vs. UMEC 125 mcg (see table below).

Table 59. Primary Efficacy Analysis: Trough FEV1 (L) at Day 169 (DB2113374 ITT Population)

Day 169	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215
n [a]	219	212	213	213
n [b]	163	161	164	175
LS mean (SE)	1.332 (0.0178)	1.355 (0.0180)	1.369 (0.0179)	1.295 (0.0176)
LS mean change (SE)	0.186 (0.0178)	0.208 (0.0180)	0.223 (0.0179)	0.149 (0.0176)
UMEC/VI 62.5/25 vs. Column				
Difference	0.022			0.060
95% CI	(-0.027, 0.072)			(0.010, 0.109)
p-value	0.377			0.018
UMEC/VI 125/25 vs. Column				
Difference	0.037			0.074
95% CI	(-0.012, 0.087)			(0.025, 0.123)
p-value	0.142			0.003

Data Source: Table 6.05

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 min and 5 min 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 one or more time points.
b. Number of subjects with analyzable data at the current time point.

Weighted Mean FEV1 over 0 to 6 hours Postdose at Day 168 (Secondary Endpoint), Day 1, and Day 84

The secondary efficacy endpoint was the 0 to 6 hour postdose weighted mean FEV1 on Day 168.

The UMEC/VI 62.5/25 mcg and UMEC/VI 125/25 mcg treatment groups showed greater improvements in LS mean change from baseline in 0 to 6 hour weighted mean FEV1 compared with both TIO and UMEC 125 mcg at Day 168 (secondary endpoint), as well as at Day 1 and Day 84 (see table below).

Table 60. Statistical Analysis: 0 to 6 hour weighted Mean FEV1 (L) (DB2113374 ITT Population)

Day	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215
Day 1				
n [a]	220	215	215	214
n [b]	218	214	214	214
LS mean (SE)	1.312 (0.0091)	1.352 (0.0092)	1.359 (0.0092)	1.288 (0.0092)
LS mean change (SE)	0.167 (0.0091)	0.207 (0.0092)	0.214 (0.0092)	0.143 (0.0092)
UMEC/VI 62.5/25 vs.				
Column Difference	0.040			0.064
95% CI	(0.015, 0.066)			(0.039, 0.090)
p-value	0.002			<0.001
UMEC/VI 125/25 vs.				
Column Difference	0.047			0.071
95% CI	(0.022, 0.073)			(0.046, 0.097)
p-value	<0.001			<0.001
Day 84				
n [a]	220	215	215	214
n [b]	178	179	180	183
LS mean (SE)	1.353 (0.0160)	1.424 (0.0161)	1.438 (0.0160)	1.314 (0.0159)
LS mean change (SE)	0.207 (0.0160)	0.279 (0.0161)	0.293 (0.0160)	0.169 (0.0159)
UMEC/VI 62.5/25 vs.				
Column Difference	0.071			0.110
95% CI	(0.027, 0.116)			(0.065, 0.154)
p-value	0.002			<0.001
UMEC/VI 125/25 vs.				
Column Difference	0.085			0.123
95% CI	(0.041, 0.130)			(0.079, 0.168)
p-value	<0.001			<0.001

Day	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215
Day 168: Secondary endpoint				
n [a]	220	215	215	214
n [b]	161	161	164	172
LS mean (SE)	1.351 (0.0167)	1.422 (0.0168)	1.427 (0.0167)	1.326 (0.0165)
LS mean change (SE)	0.206 (0.0167)	0.276 (0.0168)	0.282 (0.0167)	0.180 (0.0165)
UMEC/VI 62.5/25 vs.				
Column Difference	0.070			0.096
95% CI	(0.024, 0.117)			(0.050, 0.142)
p-value	0.003			<0.001
UMEC/VI 125/25 vs.				
Column Difference	0.076			0.101
95% CI	(0.029, 0.122)			(0.055, 0.147)
p-value	0.001			<0.001

Data Source: Table 6.17

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 min and 5 min 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 one or more time points.

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

Transition Dyspnea Index Focal Score at Day 28, 84, and 168

Statistical analysis of TDI focal scores at Days 28, 84, and 168 is presented in the table below.

Table 61. TDI Focal Score (DB2113374 ITT Population)

Day	UMEC 125 mcg N=222	UMEC/VI 62.5/25 mcg N=217	UMEC/VI 125/25 mcg N=215	TIO N=215
Day 28				
n [a]	203	194	198	194
n [b]	202	193	196	194
LS mean (SE)	0.9 (0.21)	2.0 (0.22)	2.0 (0.21)	1.3 (0.22)
UMEC/VI 62.5/25 vs. Column Difference	1.0			0.7
95% CI	(0.5, 1.6)			(0.1, 1.3)
p-value	<0.001			0.022
UMEC/VI 125/25 vs. Column Difference	1.1			0.8
95% CI	(0.5, 1.7)			(0.2, 1.4)
p-value	<0.001			0.010
Day 84				
n [a]	203	194	198	194
n [b]	183	179	181	185
LS mean (SE)	1.8 (0.22)	2.2 (0.23)	2.3 (0.22)	1.5 (0.22)
UMEC/VI 62.5/25 vs. Column Difference	0.5			0.7
95% CI	(-0.2, 1.1)			(0.1, 1.3)
p-value	0.149			0.029
UMEC/VI 125/25 vs. Column Difference	0.5			0.8
95% CI	(-0.1, 1.1)			(0.1, 1.4)
p-value	0.098			0.016
Day 168				
n [a]	203	194	198	194
n [b]	163	162	167	175
LS mean (SE)	1.9 (0.25)	2.3 (0.25)	2.4 (0.25)	2.1 (0.25)
UMEC/VI 62.5/25 vs. Column Difference	0.4			0.2
95% CI	(-0.3, 1.1)			(-0.5, 0.9)
p-value	0.249			0.548
UMEC/VI 125/25 vs. Column Difference	0.5			0.3
95% CI	(-0.2, 1.2)			(-0.4, 1.0)
p-value	0.152			0.381

Data Source: Table 6.53

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; TDI=Transitional Dyspnea Index; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (mean of the two assessments made 30 min and 5 min 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 one or more time points.

c. Number of subjects with analyzable data at the current time point.

Studies DB2114417 and DB2114418

Studies DB2114417 and DB2114418 are two phase IIIa, multicenter, randomized, double-blind, placebo-controlled, combination and component, 2-period (12 weeks per period), incomplete block design cross-over exercise endurance studies to evaluate the effects of treatment of COPD patients witha dual bronchodilator: GSK573719/GW642444.

Methods

Study Participants

Inclusion criteria

Subjects eligible for enrolment in the study must have met all of the following criteria:

1. **Type of subject:** Outpatient
2. **Informed Consent:** A signed and dated written informed consent prior to study participation
3. **Age:** 40 years of age or older at Visit 1
4. **Gender**: Male or female subjects
5. **Diagnosis:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society (ATS)/European Respiratory Society [Celli, 2004] as follows:

   Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking. Although COPD affects the lungs, it also produces significant systemic consequences.
6. **Smoking History:** Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years [number of pack years = (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years]. Former smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1.
7. **Severity of Disease:** A post-salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 and a post-salbutamol FEV1 of ≥35% and ≥70% of predicted normal values calculated using the National Health and Nutrition Examination survey (NHANES) III reference equations at Visit 1 [Hankinson, 1999; Hankinson, 2010].
8. **Dyspnea:** A score of ≥2 on the Modified Medical Research Council (mMRC) Dyspnea Scale at Visit 1
9. **Resting Lung Volumes:** A resting FRC of ≥120% of predicted normal FRC at Visit 1. Predicted values for FRC and total lung capacity (TLC) were obtained using predicted normal values from [Stocks, 1995].

Exclusion criteria

Subjects meeting any of the following criteria must not have been enrolled in the study:

1. **Pregnancy:** Women who were pregnant or lactating or were planning on becoming pregnant during the study
2. **Asthma:** A current diagnosis of asthma
3. **Other Respiratory Disorders:** Known respiratory disorders other than COPD including but not limited to α-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease. Allergic rhinitis was not exclusionary.
4. **Other Diseases/Abnormalities:** Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or hematological abnormalities that were uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that had been resected for cure was not exclusionary).

Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study. Any physical or mental abnormality which would affect the subject carrying out exercise tests including peripheral vascular disease should have been excluded at the investigators discretion.

5. **Chest X-Ray:** A chest X-ray or computed tomography (CT) scan that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must have been taken at Visit 1 if a chest X-ray or CT scan was not available within 6 months prior to Visit 1. For subjects in Germany, if a chest X-ray (or CT scan) was not available in the 6 months prior to Visit 1, the subject was not eligible for the study.
6. **Contraindications:** A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate, or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction that, in the opinion of the study physician, contraindicated study participation or use of an inhaled anticholinergic.
7. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Screening (Visit 1).
8. **Lung Resection:** Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1).
9. **12-Lead ECG:** An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead ECG which caused the underlying rhythm and ECG to be obscured. Investigators were provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. Specific ECG findings that precluded subject eligibility are listed in Appendix 3 of the protocol. The study investigator determined the medical significance of any ECG abnormalities not listed in Appendix 3 of the protocol.
10. **Screening Labs:** Significantly abnormal finding from clinical chemistry and hematology tests at Visit 1.
11. **Medication Prior to Spirometry:** Unable to withhold salbutamol for the 4-hour period required prior to spirometry testing at each study visit.
12. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e., ≤12 hours per day) was not exclusionary.
13. **Nebulized Therapy:** Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., salbutamol) via nebulized therapy.
14. **Pulmonary Rehabilitation Program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.
15. **Drug or Alcohol Abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.

Treatments

The Applicant provided the study drug for use in this study. All blinded study drug was delivered via a NDPI. The NDPI provided a total of 30 doses. Each NDPI comprised 1 or 2 double-foil, laminate, blister strips.

The NDPIs containing study drug were identical in appearance. Subjects were instructed to take 1 inhalation each morning from their NDPI.

All subjects received supplemental salbutamol (metered-dose inhaler [MDI] and/or nebules) to be used on an as-needed basis (rescue medication) throughout the study.

Salbutamol was sourced from local commercial stock. If not available locally, the Applicant sourced it centrally.

Ipratropium bromide MDI for additional responsiveness testing at Visit 1 was sourced from local commercial stock. If not available locally, then the Applicant sourced it centrally.

Objectives

The primary objective of the study 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 forced expiratory volume in 1 second (FEV1) and over 12 weeks in subjects with COPD.

The secondary objective of the study was to evaluate the effect of UMEC/VI, its components, and placebo administered once-daily on lung volume measures and postdose lung function over 12 weeks in subjects with COPD.

Outcomes / endpoints

The co-primary efficacy endpoints were:

- EET postdose at Week 12, defined as the EET obtained 3 hours after dosing at Week 12 and
- Clinic visit trough (pre-bronchodilator and predose) FEV1 at Week 12 (Treatment Day 85), defined as the FEV1 value obtained 24 hours after dosing on Treatment Day 84.

The secondary efficacy endpoints were:

- Measures of lung volume (IC, FRC, and RV) at Week 12 (trough and 3-hour Postdose)
- Clinic visit 3-hour postdose FEV1 at Week 12.

Sample size

The sample size calculations used an estimate of residual standard deviation (SD) for the EET of 114 seconds. For the purposes of converting this between-subject SD from a parallel group study to an estimate of a within-subject SD for a cross-over study, the SD has been divided by a factor of square root of 2; this assumes a correlation of 0.5 between measurements on the same subject. This value was based on data from a previous ESWT study [Revill, 1999] indicating that a reasonable estimate of SD for EET in a parallel group study was 160 seconds. A study with 208 evaluable subjects has 94% power to detect a 70 second difference in EET between either of the UMEC/VI doses and placebo at the two-sided 5% significance level. A difference of 70 seconds was considered a clinically important difference for within-subject comparisons of EET (Brouillard, 2007).

This difference is therefore considered appropriate for the comparison of active treatments with placebo. With this number of evaluable subjects, the study has 64% power to detect a difference of 70 seconds between the UMEC doses and placebo and 77% power to detect a difference of 70 seconds between the VI group and placebo. In a recent publication the MCID for the ESWT was determined to be 45 to 85 seconds (or 60-115 meters) after bronchodilation is likely to be perceived by patients (Pepin, 2011).

The sample size calculations for trough FEV_1 used an estimate of residual SD based upon a Phase IIb study for UMEC in COPD subjects (AC4113073). From this study, the residual within-subject SD was 168 mL; therefore, this value was used for the sample size calculations for trough FEV_1. A study with 208 evaluable subjects has 92% power to detect a 100 mL difference in trough FEV_1 between either dose of UMEC/VI and placebo at the two-sided 5% significance level. A 100 mL difference is considered appropriate for comparisons of UMEC/VI and its components versus placebo for trough FEV_1.

In a mixed model repeated measures (MMRM) analysis, all available post-baseline assessments up to the endpoint are utilized in the analysis; however, data for subjects who withdrew prematurely from the study were not explicitly imputed. Hence, to allow for a 30% withdrawal rate, 312 subjects were randomized. Twelve subjects were to be randomized to each treatment sequence.

Assuming 50% of screened subjects would not be eligible for randomization, approximately 624 subjects were planned to be screened for this study.

Randomisation

Subjects were assigned to study treatment in accordance with the randomization schedule. The randomization code was generated by the Applicant using a validated computerized system RandAll version 2.5. Subjects were randomized using RAMOS, an Interactive Voice Response System (IVRS). This is a telephone based system used by the investigator or designee. Once a randomization number had been assigned to a subject, the same number could not be reassigned to any other subject in the study.

Randomization to blinded study drug occurred at Visit 4 after the spirometry, lung volumes, diffusion capacity, and ESWT procedures were completed, and were stratified by use of the Oxycon mobile system (use or no use) to ensure treatment allocation was balanced within these groups.

At Visit 4, eligible subjects were randomized to one of the sequences. The sequences were selected to optimize power for comparisons between UMEC/VI and placebo and therefore the number of subjects in each treatment was unbalanced.

The duration of treatment for each subject in each period was 12 weeks. On the morning of each clinic study visit, subjects were to refrain from taking their morning dose of study drug until instructed to do so by clinic personnel. Study drug was given at the clinic at approximately the same time of day as Day 1 (Visit 4 or Visit 9). On the other days during the Treatment Period (i.e., "non-clinic days"), subjects were instructed to take their study drug each morning at approximately the same time of day as the dose time on Day 1 (Visit 4 or Visit 9).

This study utilized an Interactive Voice Response System (IVRS) which provided a means for central allocation of drug. Each investigator was supplied with sufficient supplies to conduct the trial. Additional treatment packs were supplied as needed to the sites.

Blinding (masking)

Study drug taken during the two 12-week Treatment Periods was administered in a double-blind fashion. Neither the subject nor the study physician knew which study drug the subject was receiving.

Statistical methods

The co-primary endpoint of 3-hour postdose EET at Week 12 was analyzed for the ITT population using a MMRM analysis [Siddiqui, 2009], including covariates of period walking speed, mean walking speed (defined in Section 9.2.15 of the RAP), period, treatment, visit, smoking status, center group, visit by period walking speed interaction, visit by mean walking speed interaction, and visit by treatment interaction, where visit was nominal. The model used all available 3-hour postdose EET values recorded on Day 2, Week 6, and Week 12. 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 3-hour postdose EET at Week 12. The response variable was change from baseline in 3-hour postdose EET.

The co-primary endpoint of trough FEV_1 at Week 12 was analyzed for the ITT population using a MMRM analysis, including covariates of period baseline, mean baseline, period, treatment, visit, smoking status, center group, visit by period baseline interaction, visit by mean baseline interaction, and visit by treatment interaction, where visit was nominal. The model used all available trough FEV_1 values recorded on Day 2, Week 6, and Week 12. 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 FEV_1 at Week 12.

Missing data were not explicitly imputed in the co-primary MMRM analyses, although there was an underlying assumption that data were missing at random. All available scheduled assessments up to endpoint were utilized and, via modeling of the within-subject correlation structure, the derived treatment differences at Week 12 were adjusted to take into account missing data.

MMRM analysis (using saturated fixed effects and an unstructured variance-covariance matrix) was considered appropriate as the primary method of analysis as it has been shown to provide sensible answers to on-treatment questions in a range of practical situations [Siddiqui, 2009].

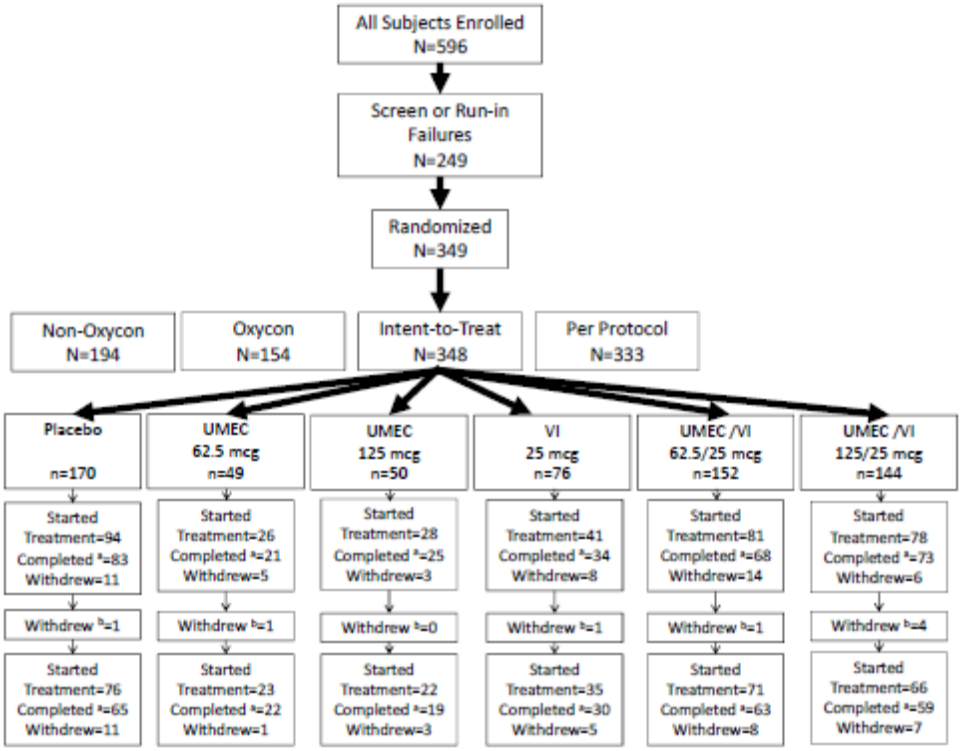
Results

Participant flow

Study DB2114417

An overview of subject disposition is shown in the figure below. A total of 596 subjects were enrolled into the study.

Figure 7. Summary of Subject Disposition (Study DB2114417)

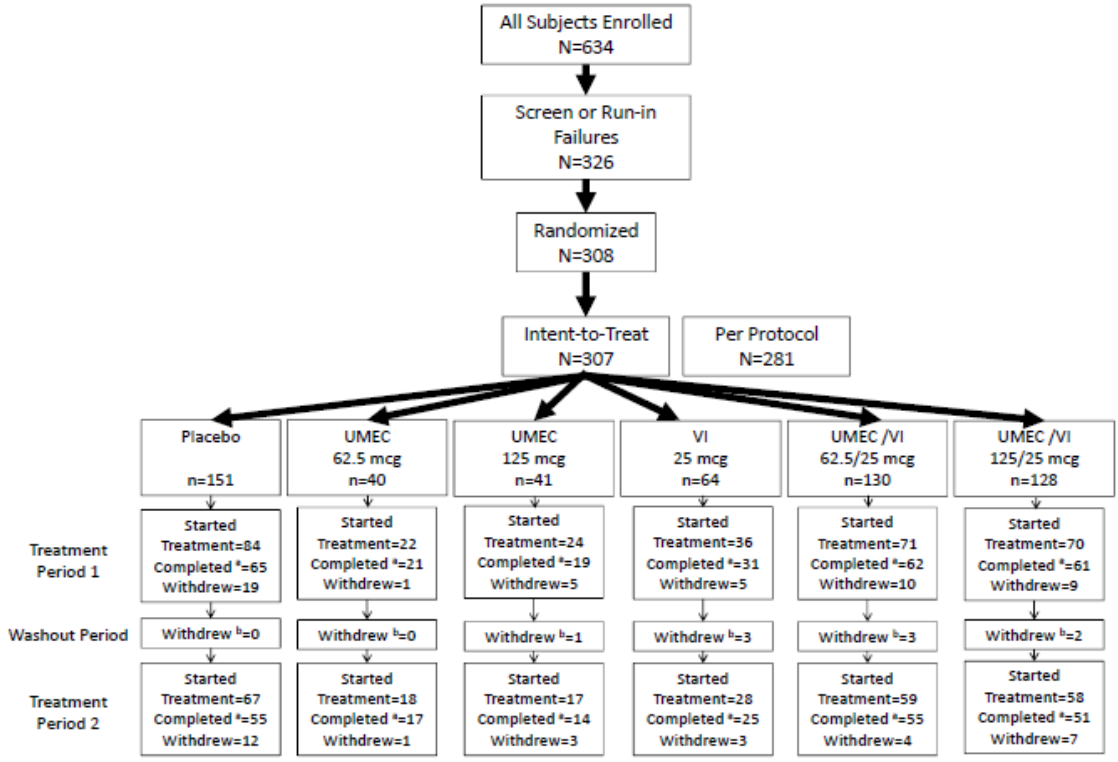


Data Source: Table 5.01 and Table 5.04
Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol
Note: Two subjects (Subjects 2423 and 3654) were included in the Run-in failure total as well as the Randomized total: Subject 2423 received study drug and recorded a reason for withdrawal and Subject 3654 did not receive study drug.
Note: Three subjects completed their Treatment Period 1 Week 12 Visit and were withdrawn on the same day; these subjects were counted in both the Withdrew During Treatment Period total and the Completed total.
a. A subject was considered to have completed the Treatment Period if they completed a Week 12 Visit for the period of interest.
b. Subjects who withdrew during the Washout Period were counted under the last treatment taken

Study DB2114418

An overview of subject disposition is shown in the figure below. A total of 634 subjects were enrolled into the study.

Figure 8. Summary of Subject Disposition (Study DB2114418)



Data Source: Table 5.01 and Table 5.04
Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol
Notes: Subject 169 was randomized but did not receive any dose of study drug. One subject completed their Treatment Period 1 Week 12 Visit and was withdrawn on the same day; this subject was counted in both the Withdrew (during Treatment Period) and Completed rows.

a. A subject was considered to have completed the Treatment Period if they completed a Week 12 visit for the period of interest.
a. Subjects who withdrew during the Washout Period were counted under the last treatment taken.

Conduct of the study

There was one amendment to the original clinical trial protocol for both studies DB2114417 and DB2114418. This amendment wa sconsidered not influencing the study results.

Baseline data

Study DB2114417

Demographics

Demographic characteristics of the ITT population are presented in the table below.

Table 62. Summary of Demographic Characteristics (DB2114417 ITT Population)

Demographic Characteristic	Total N=348
Age (years), n	348
Mean	61.6
SD	8.25
Min, Max	41, 81
Sex, n	348
Female, n (%)	153 (44)
Male, n (%)	195 (56)
Ethnicity, n	348
Hispanic/Latino, n (%)	0
Not Hispanic/Latino, n (%)	348 (100)
Race, n	348
African American/African heritage, n (%)	11 (3)
American Indian or Alaska native, n (%)	0
Asian, n (%)	0
Central/South Asian heritage, n (%)	0
Japanese/East Asian heritage/Southeast Asian heritage, n (%)	0
Native Hawaiian or other Pacific Islander, n (%)	0
White, n (%)	336 (97)
American Indian or Alaska native & White, n (%)	1 (<1)
Height (cm), n	348
Mean	169.8
SD	8.74
Min, Max	148, 193
Weight (kg), n	348
Mean	78.5
SD	18.94
Min, Max	40, 188
Body Mass Index (kg/m^2), n	348
Mean	27.11
SD	5.773
Min, Max	15.1, 62.8

Data Source: Table 5.14 and Table 5.17
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation
Note: Full detailed racial combination data are presented in Table 5.18.

Demographics were similar between the ITT and PP populations.

Smoking History and Smoking Status

Overall, subjects at screening had extensive smoking histories, with a mean of 39.0 years smoked and 48.7 pack-years (see table below). At Screening, 63% of subjects were classified as current smokers (including subjects who stopped smoking within 6 months prior to screening). No subjects reported changes in smoking status during the study.

Table 63. Summary of Smoking History and Status (DB2114417 ITT Population)

	Total N=348
Years smoked, n	348
Mean	39.0
SD	10.14
Median	40.0
Min, Max	11, 73
Smoking pack years [a], n	348
Mean	48.7
SD	25.27
Median	45.0
Min, Max	11, 146
Smoking status at Screening, n	348
Current smoker	220 (63)
Former smoker	128 (37)

Data Source: Table 5.24 and Table 5.25
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack years = (number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 64. Summary of COPD History (DB2114417 ITT Population)

	Number (%) of Subjects Total N=348
Duration of COPD, n	348
<1 year	24 (7)
≥1 to <5 years	126 (36)
≥5 to <10 years	116 (33)
≥10 to <15 years	56 (16)
≥15 to <20 years	11 (3)
≥20 to <25 years	9 (3)
≥25 years	6 (2)
COPD Type, n [a]	348
Chronic bronchitis	246 (71)
Emphysema	226 (65)

Data Source: Table 5.22
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to Visit 1, the majority of subjects (82%) reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (not involving hospitalization).

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status at screening is summarized in Table 19. All subjects were GOLD Stage II or III. A higher percentage of subjects showed reversibility after administration of salbutamol followed by ipratropium (55%) compared with reversibility to salbutamol alone (34%). Overall, 28% of subjects reported the concurrent use of ICS.

Table 65. Summary of GOLD Stage and Reversibility (DB2114417 ITT Population)

	Number (%) of Subjects
	Total N=348
GOLD Stage (percent predicted FEV_1), n	348
Stage I (≥80%)	0
Stage II (≥50% to <80%)	185 (53)
Stage III (≥30% to <50%)	163 (47)
Stage IV (<30%)	0
Reversible to Salbutamol, n [a]	348
Reversible	120 (34)
Non-reversible	228 (66)
Reversible to Salbutamol and Ipratropium, n [b]	340
Reversible	187 (55)
Non-reversible	153 (45)
ICS Use, n [c]	348
ICS users	98 (28)
ICS non-users	250 (72)

Data Source: Table 5.28

Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

a. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

b. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Study DB2114418

Demographics

Demographic characteristics of the ITT population are presented in the table below.

Table 66. Summary of Demographic Characteristics (DB2114418 ITT Population)

Demographic Characteristic	Total N=307
Age (years), n	307
Mean	62.6
SD	7.88
Min, Max	43, 84
Sex, n	307
Female, n (%)	139 (45)
Male, n (%)	168 (55)
Ethnicity, n	307
Hispanic/Latino, n (%)	0
Not Hispanic/Latino, n (%)	307 (100)
Race, n	307
African American/African heritage, n (%)	6 (2)
American Indian or Alaska native, n (%)	1 (<1)
Asian, n (%)	1 (<1)
Central/South Asian heritage, n (%)	0
Japanese/East Asian heritage/Southeast Asian heritage, n (%)	1 (<1)
Native Hawaiian or other Pacific Islander, n (%)	0
White, n (%)	298 (97)
American Indian or Alaska native & White, n (%)	1 (<1)
Height (cm), n	307
Mean	169.2
SD	9.48
Min, Max	148, 193
Weight (kg), n	307
Mean	77.7
SD	18.85
Min, Max	34, 142
Body Mass Index (kg/m^2), n	307
Mean	27.02
SD	5.702
Min, Max	15.2, 47.5

Data Source: Table 5.14 and Table 5.17
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation
Note: Full detailed racial combination data are presented in Table 5.18.

Demographics were similar between the ITT and PP populations.

Smoking History and Smoking Status

Overall, subjects at screening had extensive smoking histories, with a mean of 39.9 years smoked and 47.4 pack-years (see table below). At screening, 61% of subjects were classified as current smokers (including subjects who stopped smoking within 6 months prior to screening). Few subjects reported changes in smoking status during the study.

Table 67. Summary of Smoking History and Status (DB2114418 ITT Population)

	Total N=307
Years smoked, n	307
Mean	39.9
SD	9.67
Median	40.0
Min, Max	10, 62
Smoking pack years [a], n	307
Mean	47.4
SD	24.73
Median	42.0
Min, Max	10, 183
Smoking status at Screening, n	307
Current smoker	186 (61)
Former smoker	121 (39)

Data Source: Table 5.24 and Table 5.25
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack years = (number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 68. Summary of COPD History (DB2114418 ITT Population)

	Number (%) of Subjects
	Total N=307
Duration of COPD, n	305
<1 year	29 (10)
≥1 to <5 years	98 (32)
≥5 to <10 years	103 (34)
≥10 to <15 years	49 (16)
≥15 to <20 years	14 (5)
≥20 to <25 years	10 (3)
≥25 years	2 (<1)
COPD Type, n [a]	305
Chronic bronchitis	195 (64)
Emphysema	204 (67)

Data Source: Table 5.22
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to Visit 1, the majority of subjects (72%) reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (not involving hospitalization).

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status at screening is summarized in the table below. The majority of subjects were GOLD Stage II or III. A higher percentage of subjects showed reversibility after administration of salbutamol followed by ipratropium (66%) compared with reversibility to salbutamol alone (39%). Overall, 39% of subjects reported the concurrent use of ICS at screening.

Table 69. Summary of GOLD Stage, Reversibility, and ICS Use at Screening (DB2114418 ITT Population)

	Number (%) of Subjects
	Total N=307
GOLD Stage (percent predicted FEV_1), n	304
Stage I (≥80%)	2 (<1)
Stage II (≥50% to <80%)	158 (52)
Stage III (≥30% to <50%)	143 (47)
Stage IV (<30%)	1 (<1)
Reversible to Salbutamol, n [a]	303
Reversible	118 (39)
Non-reversible	185 (61)
Reversible to Salbutamol and Ipratropium, n [b]	302
Reversible	198 (66)
Non-reversible	104 (34)
ICS Use, n [c]	307
ICS users	121 (39)
ICS non-users	186 (61)

Data Source: Table 5.28

Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat

a. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

b. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV_1.

c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Numbers analysed

Study DB2114417

A summary of subject populations is presented in the table below.

Table 70. Summary of Subject Populations (DB2114417 ITT Population)

Population	Placebo	UMEC 62.5 mcg	UMEC 125 mcg	VI 25 mcg	UMEC/VI 62.5/25 mcg	UMEC/VI 125/25 mcg	Total
All Subjects Enrolled (ASE), n							596
Screen or Run-in Failures, n (%) [a]							249 (42)
Randomized, n	170	49	50	76	152	145	349
Intent-to-treat (ITT), n	170	49	50	76	152	144	348
Per Protocol (PP), n (%) [b]	161 (95)	47 (96)	48 (96)	66 (87)	145 (95)	135 (94)	333 (96)
Oxycon (OX), n (%) [b]	70 (41)	21 (43)	23 (46)	33 (43)	63 (41)	66 (46)	154 (44)
Non-Oxycon (NOX), n (%) [b]	100 (59)	28 (57)	27 (54)	43 (57)	89 (59)	78 (54)	194 (56)

Data Source: Table 5.01

Abbreviations: ASE=all subjects enrolled; ITT=intent-to-treat; NOX=non-Oxycon; OX=Oxycon; PP=per protocol; UMEC=umeclidinium bromide; VI=vilanterol

Note: Subjects 2423 and 3654 were included in the Randomized total as well as the Screen or Run-in Failures total.

Note: Subject 3654 was randomized but did not receive any dose of study drug.

ASE: All subjects who were screened and for whom a record exists on the study database.

ITT: All randomized subjects who received at least a single dose of study drug.

PP: All subjects in the ITT population who were not identified as full protocol deviators.

OX: Subjects in the ITT population for whom Oxycon data were collected.

NOX: Subjects in the ITT population for whom Oxycon data were not collected.

a. Percentages are based on the ASE population.

b. Percentages are based on the ITT population.

Study DB2114418

A summary of subject populations is presented in the table below.

Table 71. Summary of Subject Populations (DB2114418 ITT Population)

Population	Placebo	UMEC 62.5 mcg	UMEC 125 mcg	VI 25 mcg	UMEC/VI 62.5/25 mcg	UMEC/VI 125/25 mcg	Total
All Subjects Enrolled (ASE), n							634
Screen or Run-in Failures, n (%) [a]							326 (51)
Randomized, n	151	41	41	64	130	128	308
Intent-to-treat (ITT), n	151	40	41	64	130	128	307
Per Protocol (PP), n (%) [b]	136 (90)	35 (88)	36 (88)	59 (92)	119 (92)	117 (91)	281 (92)

Data Source: Table 5.01
Abbreviations: ASE=all subjects enrolled; ITT=intent-to-treat; PP=per protocol; UMEC=umeclidinium bromide; VI=vilanterol
Note: Subject 169 was randomized but did not receive any dose of study drug.
ASE: All subjects who were screened and for whom a record exists on the study database.
ITT: All randomized subjects who received at least a single dose of study drug.
PP: All subjects in the ITT population who were not identified as full protocol deviators.
a. Percentages are based on the ASE population.
b. Percentages are based on the ITT population.

Outcomes and estimation

Study DB2114417

Exercise Endurance Time at Week 12: Co-Primary Endpoint

Results of a repeated measures analysis of 3-hour postdose EET at Week 12 are summarized in the table below. Because the restrictions of the step-down closed testing procedure were not met, the results of all further statistical analyses are not strictly inferential.

Table 72. Primary Efficacy Analysis: 3-hour Postdose EET(s) at Week 12 (DB2114417 ITT Population)

Week 12	Placebo N=170	UMEC 62.5 mcg N=49	UMEC 125 mcg N=50	VI 25 mcg N=76	UMEC/VI 62.5/25 mcg N=152	UMEC/VI 125/25 mcg N=144
n [a]	169	49	50	74	151	142
n [b]	145	43	44	63	131	130
LS Mean Change (SE)	36.7 (13.17)	63.2 (23.93)	49.8 (23.77)	26.7 (19.72)	58.6 (13.82)	69.1 (13.99)
Column vs. Placebo Difference		26.5	13.1	-10.0	21.9	32.4
95% CI		(-25.9,78.9)	(-38.9,65.1)	(-55.5,35.4)	(-14.2,58.0)	(-3.9,68.8)
p-value		0.321	0.620	0.665	0.234	0.080
UMEC/VI 62.5/25 vs. Column Difference		-4.6		31.9		
95% CI		(-57.6,48.4)		(-14.1,77.9)		
p-value		0.865		0.174		
UMEC/VI 125/25 vs. Column Difference			19.3	42.4		
95% CI			(-33.4,71.9)	(-3.8,88.7)		
p-value			0.472	0.072		

Data Source: Table 6.06
Abbreviations: CI=confidence interval; EET=exercise endurance time; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis performed using a repeated measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, center group, visit by period walking speed, visit by mean walking speed, and visit 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 points.

Trough FEV1 at Week 12: Co-Primary Endpoint

Both the UMEC/VI 62.5/25 and 125/25 mcg treatments demonstrated greater LS mean changes from baseline in trough FEV1 at Week 12 compared with placebo (see table below).

Table 73. Primary Efficacy Analysis: Trough FEV1 (L) at Week 12 (DB2114417 ITT Population)

Week 12	Placebo N=170	UMEC 62.5 mcg N=49	UMEC 125 mcg N=50	VI 25 mcg N=76	UMEC/VI 62.5/25 mcg N=152	UMEC/VI 125/25 mcg N=144
n [a]	170	49	50	76	150	142
n [b]	148	43	44	64	130	132
LS Mean (SE)	1.404 (0.0149)	1.491 (0.0264)	1.544 (0.0263)	1.503 (0.0218)	1.615 (0.0156)	1.573 (0.0158)
LS Mean Change (SE)	-0.032 (0.0149)	0.054 (0.0264)	0.108 (0.0263)	0.067 (0.0218)	0.178 (0.0156)	0.136 (0.0158)
Column vs. Placebo Difference		0.087	0.140	0.099	0.211	0.169
95% CI		(0.030, 0.143)	(0.084, 0.196)	(0.050, 0.148)	(0.172, 0.249)	(0.129, 0.209)
p-value		0.003	<0.001	<0.001	<0.001	<0.001
UMEC/VI 62.5/25 vs. Column Difference		0.124		0.111		
95% CI		(0.067, 0.181)		(0.062, 0.161)		
p-value		<0.001		<0.001		
UMEC/VI 125/25 vs. Column Difference			0.029	0.070		
95% CI			(-0.028, 0.086)	(0.019, 0.120)		
p-value			0.320	0.007		

Data Source: Table 6.18
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis performed using a repeated measures model with covariates of period baseline, mean baseline, period, treatment, visit, smoking status, center group, visit by period baseline, visit by mean baseline, and visit 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 points.

Study DB2114418

Exercise Endurance Time at Week 12: Co-Primary Endpoint

Statistically significantly greater least squares (LS) mean changes from baseline in 3-hour postdose EET were demonstrated for both UMEC/VI treatments compared with placebo at Week 12 (see table below).

Table 74. Primary Efficacy Analysis: 3-hour Postdose EET(s) at week 12 (DB2114418 ITT Population)

Week 12	Placebo N=151	UMEC 62.5 mcg N=40	UMEC 125 mcg N=41	VI 25 mcg N=64	UMEC/VI 62.5/25 mcg N=130	UMEC/VI 125/25 mcg N=128
n [a]	147	39	40	61	129	125
n [b]	117	37	32	54	115	109
LS Mean Change (SE)	0.1 (16.66)	25.1 (30.18)	74.8 (31.58)	30.7 (24.79)	69.5 (17.09)	65.9 (17.48)
Column vs. Placebo Difference		25.0	74.7	30.6	69.4	65.8
95% CI		(-41.0, 91.0)	(6.0, 143.4)	(-26.8, 88.0)	(24.5, 114.4)	(20.3, 111.3)
p-value		0.456	0.033	0.295	0.003	0.005
UMEC/VI 62.5/25 vs. Column Difference		44.4		38.8		
95% CI		(-21.8, 110.6)		(-18.9, 96.5)		
p-value		0.188		0.187		
UMEC/VI 125/25 vs. Column Difference			-8.9	35.2		
95% CI			(-77.8, 60.1)	(-22.7, 93.1)		
p-value			0.801	0.233		

Data Source: Table 6.06
Abbreviations: CI=confidence interval; EET=exercise endurance time; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis performed using a repeated measures model with covariates of period walking speed, mean walking speed, period, treatment, visit, smoking status, center group, visit by period walking speed, visit by mean walking speed, and visit 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 points.

Trough FEV1 at Week 12: Co-Primary Endpoint

The UMEC/VI 62.5/25 and 125/25 mcg treatments demonstrated statistically significantly greater LS mean changes from baseline in trough FEV1 at Week 12 compared with placebo (see table below).

Table 75. Primary Efficacy Analysis: Trough FEV1 (L) at Week 12 (DB2114418 ITT Population)

Week 12	Placebo N=151	UMEC 62.5 mcg N=40	UMEC 125 mcg N=41	VI 25 mcg N=64	UMEC/VI 62.5/25 mcg N=130	UMEC/VI 125/25 mcg N=128
n [a]	149	40	41	64	130	126
n [b]	119	38	33	56	117	112
LS Mean (SE)	1.277 (0.0156)	1.421 (0.0267)	1.532 (0.0287)	1.388 (0.0222)	1.520 (0.0156)	1.538 (0.0159)
LS Mean Change (SE)	-0.043 (0.0156)	0.101 (0.0267)	0.212 (0.0287)	0.069 (0.0222)	0.200 (0.0156)	0.218 (0.0159)
Column vs. Placebo						
Difference		0.144	0.255	0.112	0.243	0.261
95% CI		(0.086, 0.203)	(0.193, 0.318)	(0.061, 0.163)	(0.202, 0.284)	(0.220, 0.303)
p-value		<0.001	<0.001	<0.001	<0.001	<0.001
UMEC/VI 62.5/25 vs. Column						
Difference		0.099		0.132		
95% CI		(0.041, 0.157)		(0.081, 0.183)		
p-value		<0.001		<0.001		
UMEC/VI 125/25 vs. Column						
Difference			0.006	0.150		
95% CI			(-0.055, 0.067)	(0.098, 0.201)		
p-value			0.849	<0.001		

Data Source: Table 6.18

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

Note: Analysis performed using a repeated measures model with covariates of period baseline, mean baseline, period, treatment, visit, smoking status, center group, visit by period baseline, visit by mean baseline, and visit 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 points.

Study DB2113359

Study DB2113359 was a phase IIIa 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).

Methods

Study Participants

Inclusion criteria

Subjects eligible for enrolment in the study must have met all of the following criteria:

1. **Type of Subject**: Outpatient
2. **Informed Consent**: A signed and dated written informed consent prior to study participation
3. **Age**: Subjects 40 years of age or older at Visit 1
4. **Gender**: Male or female subjects
5. **Diagnosis:** An established clinical history of COPD in accordance with the definition by the American Thoracic Society (ATS)/European Respiratory Society [Celli, 2004]
6. **Smoking History:** Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years at Visit 1 [number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Former smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1.
7. **Severity of Disease:** A post-salbutamol FEV1/FVC ratio of <0.70 and a post-salbutamol FEV1 of ≥35 and ≥80% of predicted normal values at Visit 1 (Screening) calculated using Nutrition Health and Examination Survey (NHANES) III reference equations [Hankinson, 1999].

Exclusion criteria

Subjects meeting any of the following criteria must not have been enrolled in the study:

1. **Pregnancy:** Women who were pregnant or lactating or were planning on becoming pregnant during the study
2. **Asthma:** A current diagnosis of asthma
3. **Other Respiratory Disorders:** Known respiratory disorders other than COPD including but not limited to □-1 antitrypsin deficiency, active tuberculosis, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, and interstitial lung disease. Allergic rhinitis was not exclusionary.
4. **Other Diseases/Abnormalities:** Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease) or hematological abnormalities that were uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that had been resected for cure was not exclusionary). Significance was defined as any disease that, in the opinion of the investigator, put the safety of the subject at risk through participation, or that affected the safety analysis if the disease/condition exacerbated during the study.
5. **Chest X-ray:** A chest X-ray or computed tomography (CT) scan that revealed evidence of clinically significant abnormalities not believed to be due to the presence of COPD. A chest X-ray must have been taken at Visit 1 if a chest X-ray or CT scan was not available within 6 months prior to Visit 1.
6. **Contraindications:** A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate, or a medical condition such as of narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction that, in the opinion of the study physician, contraindicated study participation or use of an inhaled anticholinergic
7. **Hospitalization:** Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
8. **Lung Resection:** Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1)
9. **12-Lead ECG:** An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead ECG that caused the underlying rhythm and ECG to be obscured. Investigators were provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility. Specific ECG findings that precluded subject eligibility are listed in Appendix 1 of the protocol. The study investigator determined the medical significance of any ECG abnormalities not listed in Appendix 1 of the protocol.
10. **Holter Monitoring:** An abnormal and significant finding from 24-hour Holter monitoring at Visit 1. Investigators were provided Holter reviews conducted by an independent cardiologist to assist in evaluation of subject eligibility. Specific findings that precluded subject study eligibility are listed in Appendix 2 of the protocol. The study investigator determined the medical significance of any Holter abnormalities not listed in Appendix 2 of the protocol.
11. **Screening Labs:** Significantly abnormal finding from clinical chemistry or hematology tests at Visit 1
12. **Medication Prior to Spirometry:** Unable to withhold salbutamol and/or ipratropium bromide for the 4-hour period required prior to spirometry testing at each study visit

13. **Oxygen:** Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e., ≥12 hours per day) was not exclusionary.
14. **Nebulized Therapy:** Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., salbutamol, ipratropium bromide) via nebulized therapy
15. **Positive Pressure Ventilation:** Use of continuous positive airway pressure (CPAP), nocturnal positive pressure, or non-invasive positive pressure ventilation (NIPPV), including use for sleep apnea.
16. **Pulmonary Rehabilitation Program:** Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.
17. **Drug or Alcohol Abuse:** A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.

Treatments

The following double-blind study drugs were used in this study:

- Dry powder formulations of UMEC/VI in the NDPI administered once-daily (in the morning)
- Dry powder formulations of UMEC in the NDPI administered once-daily (in the morning)
- Matching placebo in the NDPI once-daily (in the morning).

The UMEC/VI in the NDPI contained 2 strips. One strip contained a blend of micronized UMEC (as the quaternary ammonium bromide salt, GSK573719A), lactose monohydrate and magnesium stearate. The second strip contained a blend of micronized GW642444X (as the triphenylacetate salt, GW642444M), lactose monohydrate, and magnesium stearate. Similarly, the placebo product consisted of 2 strips each containing lactose monohydrate and magnesium stearate. The NDPI delivered, when actuated, the contents of a single blister simultaneously from each of the 2 blister strips. The LAMA monotherapy product consisted of a single strip containing UMEC (as the quarternary ammonium bromide salt, GSK573719A), lactose monohydrate, and magnesium stearate.

Objectives

The objective of this study was to evaluate the safety and tolerability of UMEC/VI Inhalation Powder 125/25 mcg and UMEC Inhalation Powder 125 mcg compared with placebo administered once-daily. All products were to be delivered via the novel dry powder inhaler (NDPI) over 52 weeks in subjects with COPD.

Outcomes/endpoints

There were no efficacy endpoints specified in this safety and tolerability study. COPD exacerbations, rescue salbutamol and/or ipratropium use, trough FEV_1, and trough FVC were measured as safety parameters in this long-term safety study.

The study endpoints included:

- Incidence of AEs

- AEs of special interest (cardiovascular, effects on glucose, effects on potassium, tremor, urinary retention, ocular effects, gallbladder disorders, pneumonia, intestinal obstruction, and anticholinergic syndrome)
- Clinical chemistry and hematology parameters
- Vital signs, 12-lead ECGs, and 24-hour Holter ECGs
- Incidence of COPD exacerbations
- Time to first COPD exacerbation
- Supplemental use of salbutamol and/or ipratropium bromide
- Percentage of rescue-free days
- Trough FEV_1 and FVC.

Sample size

The sample size was determined based on meeting ICH guidelines (ICH E1A) and based on practical considerations. Two hundred (200) subjects were planned to be randomized to UMEC/VI 125/25 mcg, 200 subjects were planned to be randomized to UMEC 125 mcg, and 100 subjects were planned to be randomized to placebo, of which it was expected that at least 120 subjects in each active treatment group and 60 subjects in the placebo group would have exposure data for the full 52 weeks, assuming at maximum a 40% withdrawal rate during the 52-week Treatment Period.

Since the sample size was based on practical considerations, no sample size sensitivity was performed.

No sample size re-estimation was planned.

Randomisation

Subjects were assigned to study treatment in accordance with the randomization schedule, which was center-based. Once a randomization number was assigned to a subject, the same number could not be reassigned to any other subject in the study. The code was generated by the Applicant using Randall version 2.5, a validated computerized system.

The randomization used blocking, and one or more blocks were allocated to each center. Subjects were randomized using RAMOS (Randomization and Medication Ordering System), an Interactive Voice Response System (IVRS). This is a telephone-based system that was used by the investigator or designee to register the subject, randomize the subject, and provide medication assignment information.

All subjects were dispensed salbutamol via MDI during the Run-in and Treatment Periods to use as needed. Following the completion of the Run-in Period, eligible subjects were randomized in a 2:2:1 ratio to one of the following double-blind treatment groups administered as 1 inhalation each morning for 52 weeks:

- UMEC/VI 125/25 mcg once-daily
- UMEC 125 mcg once-daily
- Placebo once-daily.

Blinding (masking)

Study drug was double-blind. Neither the subjects nor the study site personnel knew the treatment assignments.

Statistical methods

All planned analyses were performed after the database freeze had taken place. Once this had been achieved, unblinding of the subjects occurred and analyses were performed. No interim analyses were planned or conducted.

The following treatment comparisons were performed:

- UMEC/VI vs. placebo
- UMEC vs. placebo.

No interim analysis was planned or performed.

In this study, subjects were centrally randomized. It was likely that many centers would enroll a very small number of subjects; rather than adjusting for center in the statistical analyses, a center group was used. This consisted of all centers within the same geographical region. All center groups were finalized and documented prior to unblinding the treatment codes.

Interaction with treatment was explored by fitting a model with an additional treatment by center group interaction term; any interaction found to be statistically significant at the 10% level was further investigated and characterized.

No examinations of subgroups were performed for this study.

No multiplicity adjustment was required for this study as no formal hypothesis tests were performed.

There were no efficacy endpoints specified in this safety and tolerability study. COPD exacerbations, rescue salbutamol and/or ipratropium use, trough FEV1, and trough FVC were measured as safety parameters in this long-term safety study.

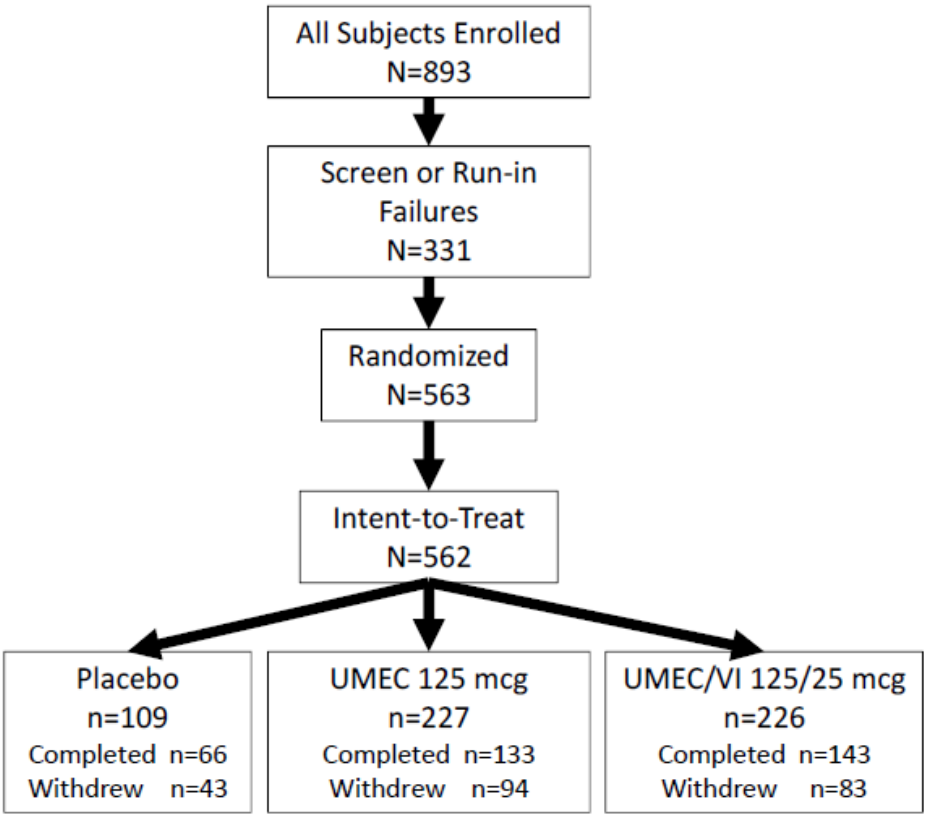
Formal statistical analyses were performed on vital signs, rescue salbutamol and/or ipratropium use, time to first COPD exacerbation, and trough FEV1 and FVC. No formal statistical analyses were performed for other safety parameters.

Results

Participant flow

An overview of subject disposition is shown in the figure below.

Figure 9. Subject Disposition (Study DB2113359)



Data Source: Table 5.01 and Table 5.03
Abbreviations: UMEC=umeclidinium bromide; VI=vilanterol
Notes: Randomized includes all subjects who were randomized and given a randomization number.
Subjects were considered to have completed if they completed the last clinic visit (Visit 7) excluding follow-up.
Subject 1962 was randomized in error but did not receive study drug and was therefore not included in the ITT population; this subject is included in the Randomized total as well as the Screen and Run-in Failures total.

Conduct of the study

There was one amendment to the original clinical trial protocol. This amendment was considered not influencing the study results.

Baseline data

Demographics

Demographic characteristics in the ITT population were generally similar across treatment groups (see table below). The majority of subjects were White (94%) and male (67%); the mean age was 61.3 years. Eight percent of the population was of Hispanic or Latino ethnicity. The mean BMI of 27.91 kg/m2 indicated that subjects tended to be slightly overweight.

Table 76. Summary of Demographic Characteristics (DB2113359 ITT Population)

Demographic Characteristic	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226	Total N=562
Age (years)				
Mean	60.1	61.7	61.4	61.3
SD	8.28	9.10	9.01	8.92
Min, Max	41, 82	40, 85	40, 84	40, 85
Sex				
Female, n (%)	36 (33)	82 (36)	70 (31)	188 (33)
Male, n (%)	73 (67)	145 (64)	156 (69)	374 (67)
Ethnicity				
Hispanic/Latino, n (%)	7 (6)	17 (7)	19 (8)	43 (8)
Not Hispanic/Latino, n (%)	102 (94)	210 (93)	207 (92)	519 (92)
Race				
White, n (%)	104 (95)	214 (94)	211 (93)	529 (94)
African American/African heritage, n (%)	3 (3)	13 (6)	14 (6)	30 (5)
American Indian or Alaska native, n (%)	0	0	0	0
Asian, n (%)	2 (2)	0	1 (<1)	3 (<1)
Central/South Asian heritage	0	0	0	0
Japanese/East Asian heritage/Southeast Asian heritage	2 (2)	0	1 (<1)	3 (<1)
Native Hawaiian or other Pacific Islander, n (%)	0	0	0	0
Height (cm)				
Mean	169.8	168.0	168.3	168.5
SD	9.85	8.67	9.51	9.26
Min, Max	148, 196	143, 188	143, 190	143, 196
Weight (kg				
Mean	79.68	78.98	79.00	79.12
SD	17.996	16.420	17.453	17.123
Min, Max	37.3, 137.3	46.6, 130.0	36.0, 136.0	36.0, 137.3
Body Mass Index (kg/m²), n				
Mean	27.65	28.05	27.89	27.91
SD	5.885	5.881	5.859	5.864
Min, Max	13.6, 43.3	17.3, 54.6	16.4, 51.3	13.6, 54.6

Data Source: Table 5.11 and Table 5.13
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Full detailed racial combination data are presented in Table 5.14.

Smoking History

Smoking history and smoking status were similar across treatment groups at screening (see table below). Overall, subjects had extensive smoking histories, with a mean of 37.1 years smoked and 41.7 pack-years and 63% of subjects were classified as current smokers (including subjects who stopped smoking within 6 months prior to screening). Few subjects (≤5%) reported changes in smoking status at either Month 6 or Month 12 during the study.

Table 77. Summary of Smoking History and Status (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226	Total N=562
Years smoked				
Mean	36.2	36.6	38.1	37.1
SD	9.18	11.49	11.38	11.05
Median	37.0	38.0	39.0	38.0
Min, Max	10, 54	10, 70	10, 67	10, 70
Smoking pack-years [a]				
Mean	42.8	39.2	43.7	41.7
SD	24.71	21.24	27.49	24.63
Median	39.0	38.0	39.0	38.5
Min, Max	10, 150	8, 144	10, 236	8, 236
Smoking status at Screening				
Current smoker	71 (65)	148 (65)	135 (60)	354 (63)
Former smoker	38 (35)	79 (35)	91 (40)	208 (37)

Data Source: Table 5.21 and Table 5.22
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack-years = (number of cigarettes smoked per day/20) x number of years smoked prior to screening.

COPD History

COPD history was similar across the treatment groups at Screening; 13%, 39%, 26%, and 23% of subjects had COPD diagnosed <1 year, ≥1 to <5 years, ≥5 to <10 years, and ≥10 years, respectively, prior to study entry (see table below). Seventy percent of subjects had a diagnosis of chronic bronchitis and 67% had a diagnosis of emphysema. Subjects could have had a diagnosis of both chronic bronchitis and emphysema.

Table 78. Summary of COPD History (DB2113359 ITT Population)

	Number (%) of Subjects			
	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226	Total N=562
Duration of COPD				
<1 year	15 (14)	33 (15)	25 (11)	73 (13)
≥1 to <5 years	42 (39)	88 (39)	89 (39)	219 (39)
≥5 to <10 years	26 (24)	64 (28)	56 (25)	146 (26)
≥10 to <15 years	14 (13)	20 (9)	27 (12)	61 (11)
≥15 to <20 years	7 (6)	7 (3)	17 (8)	31 (6)
≥20 to <25 years	5 (5)	10 (4)	7 (3)	22 (4)
≥25 years	0	5 (2)	5 (2)	10 (2)
COPD Type [a], **n**	109	227	225	561
Chronic bronchitis	74 (68)	162 (71)	159 (71)	395 (70)
Emphysema	71 (65)	149 (66)	154 (68)	374 (67)

Data Source: Table 5.19
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to Screening, the majority of subjects across treatment groups reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics (64% to 69%) and no COPD exacerbations requiring hospitalization (83% to 86%).

Screening and Baseline Lung Function

Subjects had moderate to severe airflow obstruction at screening and lung function parameters were similar across treatment groups (see table below). The overall mean post-salbutamol percent predicted FEV1 was 54.7% (range: 54.2% to 55.1% across treatment groups).

Table 79. Summary of Screening Lung Function Test Results (DB2113359 ITT Population)

Parameter	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226	Total N=562
Pre-bronchodilator FEV_1 (L), n	108	225	225	558
Mean	1.579	1.432	1.498	1.487
SD	0.5714	0.5120	0.5255	0.5311
Median	1.510	1.330	1.460	1.410
Min, Max	0.46, 3.28	0.55, 3.12	0.44, 2.80	0.44, 3.28
Post-salbutamol FEV_1 (L), n	109	225	224	558
Mean	1.724	1.594	1.647	1.641
SD	0.5691	0.4884	0.5138	0.5164
Median	1.620	1.480	1.630	1.580
Min, Max	0.69, 3.22	0.73, 3.25	0.63, 2.97	0.63, 3.25
Pre-bronchodilator FVC (L), n	108	225	225	558
Mean	3.048	2.864	2.927	2.925
SD	0.9302	0.8650	0.8514	0.8735
Median	2.935	2.780	2.900	2.840
Min, Max	1.07, 5.14	1.04, 4.92	1.26, 5.08	1.04, 5.14
Post-salbutamol FVC (L), n	109	225	224	558
Mean	3.272	3.129	3.181	3.178
SD	0.9544	0.8542	0.8551	0.8749
Median	3.240	3.070	3.105	3.100
Min, Max	1.37, 5.64	1.37, 5.59	1.25, 5.05	1.25, 5.64
Pre-bronchodilator FEV_1/FVC (L), n	108	225	225	558
Mean	52.044	50.384	51.316	51.081
SD	10.4915	10.5805	10.6390	10.5869
Median	52.600	50.000	51.300	51.250
Min, Max	28.60, 72.30	25.60, 75.60	25.80, 75.10	25.60, 75.60
Post-salbutamol FEV_1/FVC, n	109	225	224	558
Mean	53.197	51.681	52.187	52.180
SD	10.1012	10.5522	9.9999	10.2422
Median	54.200	51.300	52.750	52.850
Min, Max	29.20, 69.60	26.20, 69.80	24.30, 69.50	24.30, 69.80
Post-salbutamol Percent Predicted FEV_1 (%), n	109	225	224	558
Mean	55.1	54.2	55.0	54.7
SD	11.68	11.81	12.10	11.89
Median	53.9	53.1	53.8	53.7
Min, Max	36, 80	35, 80	35, 80	35, 80
Percent Reversibility to Salbutamol (%), n	108	224	223	555
Mean	11.9	14.2	12.7	13.1
SD	14.89	18.32	14.83	16.33
Median	8.6	10.5	10.1	9.9
Min, Max	-12, 75	-29, 159	-37, 70	-37, 159
Reversibility to Salbutamol (mL), n	108	224	223	555
Mean	151.2	158.7	151.6	154.4
SD	186.90	191.57	182.43	186.73
Median	137.0	155.0	145.0	147.0
Min, Max	-261, 904	-759, 869	-745, 770	-759, 904

Data Source: Table 5.23

Abbreviations: FEV_1=forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage and reversibility status at Screening is summarized in the table below. Nearly all subjects (>99%) were GOLD Stage II or III. The proportions of subjects who showed reversibility after

administration of salbutamol (UMEC 125: 32%; UMEC/VI 125/25: 35%; placebo: 33%) and who reported the use of ICS at Screening (UMEC 125: 32%; UMEC/VI 125/25: 35%; placebo: 37%) were broadly similar across treatment groups.

Table 80. Summary of GOLD Stage, Reversibility, and ICS Use (DB2113359 ITT Population)

	Number (%) of Subjects			
	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226	Total N=562
GOLD Stage (percent predicted FEV_1), n	109	225	224	558
Stage I (≥80%)	1 (<1)	0	0	1 (<1)
Stage II (≥50% to <80%)	71 (65)	129 (57)	137 (61)	337 (60)
Stage III (≥30% to <50%)	37 (34)	96 (43)	87 (39)	220 (39)
Stage IV (<30%)	0	0	0	0
Reversible to Salbutamol, n [a]	108	224	223	555
Reversible	36 (33)	72 (32)	78 (35)	186 (34)
Non-reversible	72 (67)	152 (68)	145 (65)	369 (66)
ICS use, n [b]	109	227	226	562
ICS users	40 (37)	73 (32)	80 (35)	193 (34)
ICS non-users	69 (63)	154 (68)	146 (65)	369 (66)

Data Source: Table 5.25
Abbreviations: FEV1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol
a. Reversible was an increase in FEV1 of ≥12% and ≥200 mL following administration of salbutamol. Non-reversible was an increase in FEV1 of <200 mL or a ≥200 mL increase that was <12% from pre-salbutamol FEV1.
b. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Numbers analysed

A summary of subject populations is presented in the table below.

Table 81. Summary of Subject Populations (DB2113359 ASE Population)

	Number (%) of Subjects			
Population	Placebo	UMEC 125 mcg	UMEC/VI 125/25 mcg	Total
All Subjects Enrolled (ASE), n				893
Screen or Run-in Failures (SRF), n (%)[a]				331 (37)
Randomized, n	109	227	227	563
Intent-to-treat (ITT), n	109	227	226	562

Data Source: Table 5.01
Abbreviations: ASE=all subjects enrolled; eCRF=electronic case report form; SRF=Screen or Run-in Failures; UMEC=umeclidinium bromide; VI=vilanterol
Notes: Randomized includes all subjects who were randomized and given a randomized number. Subject 1962 was randomized in error and is included in the Randomized row as well as the Screen and Run-in Failures row.
ASE: All subjects who were screened and for whom a record exists on the study database.
SRF: All subjects in the ASE population who were recorded as Screen failures or Run-in failures in the eCRF.
ITT: All randomized subjects who received at least a single dose of study drug.
a. Percentage was based on the ASE population.

Outcomes and estimation

There were no efficacy endpoints specified in this safety and tolerability study. The following parameters, however, were included as safety assessments: COPD exacerbations, rescue salbutamol and/or ipratropium use, trough FEV1, and trough FVC.

COPD Exacerbation

No pre-treatment COPD exacerbations were reported.

The proportion of subjects reporting at least one on-treatment COPD exacerbation was higher in the placebo group (24%) compared with the UMEC 125 (15%) or UMEC/VI 125/25 (13%) treatment groups (see tebale below).

Table 82. Summary of On-treatment COPD Exacerbations (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
Number of subjects with a COPD exacerbation, n (%) [a]	26 (24)	33 (15)	29 (13)
Number of COPD exacerbations, n (%) [a]			
0	83 (76)	194 (85)	197 (87)
1	22 (20)	17 (7)	23 (10)
2	3 (3)	11 (5)	5 (2)
>2	1 (<1)	5 (2)	1 (<1)
Total number of exacerbations, n	33	61	36
Withdrawn due to an exacerbation, n (%) [b]	5 (15)	2 (3)	1 (3)
Treatment, n (%) [b,c]			
Took oral/systemic corticosteroids	28 (85)	49 (80)	28 (78)
Took antibiotics	25 (76)	50 (82)	31 (86)
Hospitalized	4 (12)	4 (7)	2 (6)
Outcome, n (%) [b]			
Resolved	32 (97)	61 (100)	35 (97)
Fatal	0	0	0
Not resolved	1 (3)	0	1 (3)
Primary cause, n (%) [b]			
Cold air/cold weather	3 (9)	4 (7)	8 (22)
Tobacco smoke	0	0	2 (6)
Upper respiratory infection	10 (30)	17 (28)	7 (19)
Air pollution	0	1 (2)	1 (3)
Allergy	0	0	0
Exercise	0	0	0
Stress/emotions	0	3 (5)	1 (3)
Withholding or reducing COPD meds	0	2 (3)	0
Unknown etiology	13 (39)	18 (30)	13 (36)
Lack of efficacy	3 (9)	1 (2)	0
Lower respiratory infection	4 (12)	15 (25)	4 (11)
Duration of exacerbation (days) [d]			
n	32	61	35
Mean	14.2	14.0	11.7
SD	13.03	7.35	8.28
Median	9.5	12.0	10.0
Min, Max	2, 67	4, 49	1, 37

Data Source: Table 7.25

Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

a. Percentages calculated using N as the denominator.
b. Percentages calculated using the number of exacerbations as the denominator.
c. Subjects could have reported more than 1 option for a single exacerbation.
d. Duration was only calculated for exacerbations that had a resolution date recorded. The duration of the exacerbation was calculated as (exacerbation resolution date or date of death - exacerbation onset date + 1).

Four subjects reported a post-treatment COPD exacerbation (2 [2%] in the placebo group and 1 [<1%] each in the UMEC 125 and UMEC/VI 125/25 groups).

Analysis of time to first COPD exacerbation indicated that treatment with UMEC 125 resulted in a lower risk of COPD exacerbation compared with placebo (hazard ratio [HR] 0.6; CI: 0.3, 1.0, risk reduction 40%). Treatment with UMEC 125/25 also resulted in a lower risk of COPD exacerbation compared with placebo (HR 0.4, CI: 0.3, 0.8, risk reduction 60%) (see table below).

Table 83. Summary and Analysis of Time to First On-treatment COPD Exacerbation (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
Number of subject s with event, n (%)	26 (24)	33 (15)	29 (13)
Number of subjects censored, n (%)	83 (76)	194 (85)	197 (87)
Probability of having event (%)	28.3	17.5	16.0
95% CI	(20.1, 38.9)	(12.6, 23.8)	(11.3, 22.5)
Median time to onset (days)	NA	NA	NA
Column vs. Placebo			
Hazard ratio		0.6	0.4
95% CI		(0.3, 1.0)	(0.3, 0.8)

Data Source: Table 7.27

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

Notes: Probability of having an event, 95% CI, and the median are taken from the Kaplan-Meier analysis. If greater than 50% of data were censored, then the median was NA. Hazard ratios and CIs are from a Cox proportional hazards model with covariates of treatment, smoking status, and center group.

Rescue Salbutamol and/or Ipratropium Use

The mean daily use of rescue salbutamol/ipratropium was 2.9, 3.1, and 3.3 puffs/day for the UMEC 125, UMEC/VI 125/25, and placebo treatment groups, respectively, at baseline.

Greater differences from baseline in the mean number of puffs of rescue medication per day over Weeks 1 to 52 were reported for subjects in both the UMEC 125 (-4.0 puffs/day; 95% CI: -0.9,0.1) and UMEC 125/25 (-1.0 puffs/day; 95% CI: (-1.4,-0.5) treatment groups compared with placebo (see table below).

Table 84. Analysis of Mean Number of Puffs of Rescue Medication per Day over Weeks 1 to 52 (DB2113359 ITT Population)

Weeks 1-52	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
n	75	158	168
LS mean (SE)	2.6 (0.20)	2.2 (0.14)	1.6 (0.13)
LS mean change (SE)	-0.4 (0.20)	-0.8 (0.14)	-1.4 (0.13)
Column vs. Placebo Difference		-0.4	-1.0
95% CI		(-0.9,0.1)	(-1.4,-0.5)

Data Source: Table 7.50

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using an ANCOVA model with covariates of treatment, baseline (mean during the week prior to Day 1), smoking status, and center group.

The percentages of rescue-free days at baseline were 27.3, 25.8, and 24.6 for UMEC 125, UMEC/VI 125/25, and placebo, respectively. The mean change from baseline in the percentage of rescue-free days over Weeks 1 to 52 was largest for the UMEC/VI 125/25 treatment group (UMEC 125: 13.1%; UMEC/VI 125/25: 23.2%; placebo: 11.1%) (see table below).

Table 85. Summary of Percentage of Rescue-free Days (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
Baseline			
Rescue-free Days (%), n	107	221	217
Mean	24.6	27.3	25.8
SD	34.61	37.16	35.56
Median	0.0	0.0	0.0
Min, Max	0, 100	0, 100	0, 100
Week 1-52			
Rescue-free days (%), n	76	160	171
Mean	38.2	43.5	48.1
SD	39.82	41.46	40.00
Median	24.2	28.7	45.9
Min, Max	0, 100	0, 100	0, 100
Change from Baseline, n	75	158	168
Mean	11.1	13.1	23.2
SD	30.06	37.35	39.27
Median	0.0	1.1	11.8
Min, Max	-48, 96	-98, 100	-100, 100

Data Source: Table 7.48
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Baseline was the percentage during the week prior to Day 1.

Trough FEV1

Baseline FEV1 was 1.445 L; 1.506 L, and 1.557 L for the UMEC 125, UMEC/VI 125/25, and placebo groups, respectively (see table below).

Table 86. Summary of Baseline FEV1 (L) (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
n	109	225	225
Mean	1.557	1.445	1.506
SD	0.5746	0.4950	0.5505
Median	1.420	1.380	1.460
Min, Max	0.60, 3.23	0.53, 3.30	0.29, 3.10

Data Source: Table 7.51
Abbreviations: FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Baseline was the assessment made immediately predose on Day 1.

The UMEC/VI 125/25 and UMEC 125 treatment groups demonstrated greater LS mean changes from baseline in trough FEV1 compared with placebo at 6 months (UMEC 125: 0.160 L; CI: 0.083, 0.236; UMEC/VI 125/25: 0.197 L; CI: 0.121, 0.272) and 12 months (UMEC 125: 0.178 L; CI: 0.098, 0.258; UMEC/VI 125/25: 0.231 L; CI: 0.153, 0.310) (see table below).

Table 87. Trough FEV1 (L) at Months 6 and 12 (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
Month 6			
n [a]	103	215	216
n [b]	79	163	178
LS mean (SE)	1.489 (0.0320)	1.649 (0.0221)	1.686 (0.0214)
LS mean change (SE)	-0.015 (0.0320)	0.144 (0.0221)	0.181 (0.0214)
Column vs. Placebo Difference		0.160	0.197
95% CI		(0.083,0.236)	(0.121,0.272)
Month 12			
n [a]	103	215	216
n [b]	66	132	143
LS mean (SE)	1.459 (0.0332)	1.637 (0.0232)	1.691 (0.0224)
LS mean change (SE)	-0.045 (0.0332)	0.133 (0.0232)	0.186 (0.0224)
Column vs. Placebo Difference		0.178	0.231
95% CI		(0.098,0.258)	(0.153,0.310)

Data Source: Table 7.53

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

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (assessment made immediately predose on Day 1), smoking status, center group, Month, Month by baseline, and Month 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 current time point.

Trough FVC

Baseline FVC was 2.883 L; 2.938 L, and 2.993 L for the UMEC 125, UMEC/VI 125/25, and placebo groups, respectively (see table below).

Table 88. Summary of Baseline FVC (L) (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
n	109	225	225
Mean	2.993	2.883	2.938
SD	0.9368	0.8364	0.8562
Median	2.950	2.840	2.900
Min, Max	1.26, 5.15	1.19, 5.17	0.94, 5.19

Data Source: Table 7.54

Abbreviations: FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

Note: Baseline was the assessment made immediately predose on Day 1.

The UMEC/VI 125/25 and UMEC 125 treatment groups demonstrated greater LS mean changes from baseline in trough FVC compared with placebo at 6 months (UMEC 125: 0.209 L; CI: 0.095, 0.323; UMEC/VI 125/25: 0.240 L; CI: 0.127, 0.353) and 12 months (UMEC 125: 0.194 L; CI: 0.076, 0.312; UMEC/VI 125/25: 0.252 L; CI: 0.135, 0.368) (see table below).

Table 89. Trough FVC (L) at Months 6 and 12 (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 mcg N=227	UMEC/VI 125/25 mcg N=226
Month 6			
n [a]	103	215	216
n [b]	79	163	178
LS mean (SE)	2.944 (0.0478)	3.152 (0.0330)	3.183 (0.0320)
LS mean change (SE)	-0.002 (0.0478)	0.206 (0.0330)	0.237 (0.0320)
Column vs. Placebo Difference		0.209	0.240
95% CI		(0.095,0.323)	(0.127,0.353)
Month 12			
n [a]	103	215	216
n [b]	66	132	143
LS mean (SE)	2.907 (0.0491)	3.101 (0.0343)	3.159 (0.0333)
LS mean change (SE)	-0.039 (0.0491)	0.155 (0.0343)	0.213 (0.0333)
Column vs. Placebo Difference		0.194	0.252
95% CI		(0.076,0.312)	(0.135,0.368)

Data Source: Table 7.56

Abbreviations: CI=confidence interval; FVC=forced vital capacity; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with covariates of treatment, baseline (assessment made immediately predose on Day 1), smoking status, center group, Month, Month by baseline, and Month 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 current time point.

Summary of main studies

The following tables summarise the efficacy results from the 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).

Table 90. Summary of efficacy for study 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	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 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	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 consisted of the treatment comparisons for UMEC/VI 125/25 mcg vs. PLA, UMEC 125 mcg vs. PLA, and VI 25 mcg vs. PLA, then UMEC/VI 125/25 mcg vs. VI 25 mcg and UMEC/VI 125/25 mcg vs. UMEC 125 mcg performed in this order for the primary (trough FEV_1 on Day 169), followed by the key secondary (TDI focal score at Day 168), and then weighted mean FEV_1 over 0 to 6 hours at Day 168. 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 obtained for comparisons of UMEC/VI 125/25 mcg with placebo, but not for UMEC 125 mcg compared with placebo. Therefore, the results of all further statistical analyses should be interpreted only descriptively.				
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 125	VI 25	UMEC/VI 125/25

estimate variability	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.				

Table 91. Summary of efficacy for study 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	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 consisted of the treatment comparisons for UMEC/VI 62.5/25 mcg vs. PLA, UMEC 62.5 mcg vs. PLA, and VI 25 mcg vs. PLA, then UMEC/VI 62.5/25 mcg vs. VI 25 mcg and UMEC/VI 62.5/25 mcg vs. UMEC 62.5 mcg performed in this order for the primary (trough FEV_1 on Day 169), followed by the key secondary (TDI focal score at Day 168), and then weighted mean FEV_1 over 0 to 6 hours at Day 168. 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/VI 62.5/25 mcg, UMEC 62.5 mcg, and VI 25 mcg with placebo but not for UMEC/VI 62.5/25 compared with VI 25 mcg (or UMEC 62.5 mcg). Therefore, the results of all further statistical analyses should be interpreted only descriptively.				
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 62.5	VI 25	UMEC/VI 62.5/25
	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.				

Table 92. Summary of efficacy for study DB2113360

Title: A Multicenter Trial Comparing the Efficacy and Safety of GSK573719/GW642444 with GW642444 and with Tiotropium over 24 Weeks in Subjects with COPD		
Study identifier	DB2113360 (EUdraCT #: 2010-021800-72)	
Design	Multicenter, randomized (1:1:1:1), double-blind, double-dummy, parallel-group	
	Duration of Main phase	24 weeks
	Duration of Run-in phase	7 to 10 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 over tiotropium (TIO) and contribution of UMEC to UMEC/VI combination	
Treatments groups	VI 25 mcg OD	VI 25 mcg, 24 weeks, 209 randomised
	UMEC/VI 62.5/25 mcg OD	UMEC/VI 62.5/25 mcg, 24 weeks, 212 randomised
	UMEC/VI 125/25 mcg OD	UMEC/VI 125/25 mcg, 24 weeks, 216 randomised

	TIO 18 mcg OD		TIO 18mcg, 24 weeks, 209 randomised
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	25 May 2012		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	The ITT (excluding Investigator 040688) 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	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25	TIO
	Number of subjects (ITT)	205	207	208	203
	Number of subjects at Day 169 for trough FEV_1	162	177	167	173
	Trough FEV_1 (L) (LS mean change from baseline)	0.121	0.211	0.209	0.121
	SE	(0.0189)	(0.0183)	(0.0187)	(0.0186)

Effect estimate per comparison	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. TIO
		Difference	0.088
		95% CI	(0.036,0.140)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 125/25 vs. VI 25
		Difference	0.088
		95% CI	(0.036,0.140)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. TIO
		Difference	0.090
		95% CI	(0.039,0.141)
		P-value	<0.001
	Trough FEV_1 (L)	Comparison groups	UMEC/VI 62.5/25 vs. VI 25
		Difference	0.090
		95% CI	(0.039,0.142)
		P-value	<0.001
Notes	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 consisted of the treatment comparisons for UMEC/VI 125/25 mcg vs. TIO, then UMEC/VI 125/25 mcg vs. VI 25 mcg, performed in this order for the primary (trough FEV_1 on Day 169) and secondary (weighted mean FEV_1 over 0 to 6 hours at Day 168) efficacy endpoints, followed by comparisons of UMEC/VI 62.5/25 mcg vs. TIO, then UMEC/VI 62.5/25 mcg vs. VI 25 mcg on the same endpoints in the same order. All comparisons included in the testing hierarchy achieved statistical significance at the 5% level.		
Analysis description	**Secondary analysis**		

Analysis population and time point description	The ITT Population (excluding Investigator 040688) 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	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25	TIO
	Number of subjects (ITT)	205	207	208	203
	Number of subjects at Day 168 for 0-6 h weighted mean FEV_1	161	173	166	168
	0-6 h Weighted mean FEV_1 (L) (LS mean change from baseline)	0.178	0.254	0.263	0.181
	SE	(0.0189)	(0.0183)	(0.0187)	(0.0187)
Effect estimate per comparison	Weighted Mean FEV_1 (L)	Comparison groups		UMEC/VI 125/25 vs. TIO	
		Difference		0.083	
		95% CI		(0.031,0.134)	
		P-value		0.002	
	Weighted Mean FEV_1 (L)	Comparison groups		UMEC/VI 125/25 vs. VI 25	
		Difference		0.086	
		95% CI		(0.033,0.138)	
		P-value		0.001	
	Weighted Mean FEV_1 (L)	Comparison groups		UMEC/VI 62.5/25 vs. TIO	
		Difference		0.074	
		95% CI		(0.022,0.125)	
		P-value		0.005	
	Weighted Mean FEV_1 (L)	Comparison groups		UMEC/VI 62.5/25 vs. VI 25	
		Difference		0.077	
		95% CI		(0.025,0.128)	
		P-value		0.004	
Analysis description	**Other Efficacy analysis**				
Analysis population and time point description	The ITT Population (excluding Investigator 040688) 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	VI 25	UMEC/VI 62.5/25	UMEC/VI 125/25	TIO
	Number of subjects (ITT)	205	207	208	203
	Number of subjects at Day 168 for TDI focal score	159	177	164	171
	LS mean TDI focal score	2.1	2.3	2.9	2.4
	SE	(0.23)	(0.22)	(0.23)	(0.23)
Effect estimate per comparison	LS mean TDI focal score	Comparison groups		UMEC/VI 125/25 vs. TIO	
		Difference		0.5	
		95% CI		(-0.2,1.1)	
		P-value		0.135	
	LS mean TDI focal score	Comparison groups		UMEC/VI 125/25 vs. VI 25	
		Difference		0.8	
		95% CI		(0.2,1.5)	
		P-value		0.013	
	LS mean TDI focal score	Comparison groups		UMEC/VI 62.5/25 vs. TIO	
		Difference		-0.1	
		95% CI		(-0.7,0.5)	

		P-value	0.721
	LS mean TDI focal score	Comparison groups	UMEC/VI 62.5/25 vs. VI 25
		Difference	0.2
		95% CI	(-0.4,0.8)
		P-value	0.494

Table 93. Summary of efficacy for study 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	24 weeks				
	Duration of Run-in phase	7 to 10 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 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	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 consisted of the treatment comparisons for UMEC/VI 125/25 mcg vs. TIO, then UMEC/VI 125/25 mcg vs. UMEC 125 mcg, performed in this order for the primary (trough FEV_1 on Day 169) and secondary (weighted mean FEV_1 over 0 to 6 hours at Day 168) efficacy endpoints, followed by comparisons of UMEC/VI 62.5/25 mcg vs. TIO, then UMEC/VI 62.5/25 mcg vs. UMEC 125 mcg on the same endpoints in the same order. As a result of the comparison of UMEC/VI 125/25 mcg vs. UMEC 125 mcg not achieving statistical significance at the 5% level for the primary endpoint of trough FEV_1 at Day 169, the restrictions of the step-down testing procedure were not met and, therefore, the results of all further statistical analyses are not strictly inferential.		
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	Comparison groups	UMEC/VI 62.5/25 vs. UMEC 125

	(L)	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	

Table 94. Summary of efficacy for study 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	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, 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	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. 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. 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)	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 based on the results of the step-down testing hierarchy described for 3-h postdose EET.						
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)	170	49	50	76	152	144
	Number of subjects at Week 12 for Trough IC	148	43	44	64	131	132
	Trough IC (L) (LS mean change from baseline)	-0.002	0.025	0.187	0.067	0.196	0.168
	SE	(0.0255)	(0.0457)	(0.0457)	(0.0377)	(0.0269)	(0.0270)
Effect estimate per comparison	Trough IC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.170		
		95% CI			(0.103,0.237)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.198		
		95% CI			(0.131,0.265)		
		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	148	43	44	64	131	131
	3-h postdose IC (L) (LS mean change from baseline)	0.028	0.142	0.249	0.160	0.267	0.250
	SE	(0.0259)	(0.0463)	(0.0462)	(0.0382)	(0.0274)	(0.0275)
Effect estimate per comparison	3-h postdose IC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.222		
		95% CI			(0.154, 0.290)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.238		
		95% CI			(0.171, 0.306)		
		P-value			<0.001		
Notes	The results of statistical analyses for IC should be interpreted only descriptively based on the results of the step-down testing hierarchy described for 3-h postdose EET.						
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)	170	49	50	76	152	144
	Number of subjects at Week 12 for Trough FRC	148	43	44	64	131	132
	Trough FRC (L) (LS mean change from baseline)	0.020	-0.262	-0.241	-0.109	-0.219	-0.350
	SE	(0.0494)	(0.0899)	(0.0890)	(0.0738)	(0.0523)	(0.0524)
Effect estimate per comparison	Trough FRC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.369		
		95% CI			(-0.504,-0.235)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.238		
		95% CI			(-0.373,-0.104)		
		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	148	43	44	64	131	131
	3-h postdose FRC (L) (LS mean change from baseline)	-0.081	-0.358	-0.456	-0.229	-0.384	-0.548
	SE	(0.0495)	(0.0893)	(0.0885)	(0.0734)	(0.0523)	(0.0526)
Effect estimate per comparison	3-h postdose FRC (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.467		
		95% CI			(-0.600, -0.334)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.302		
		95% CI			(-0.434, -0.170)		
		P-value			<0.001		
Notes	The results of statistical analyses for FRC should be interpreted only descriptively based on the results of the step-down testing hierarchy described for 3-h postdose EET.						
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)	170	49	50	76	152	144
	Number of subjects at Week 12 for Trough RV	148	43	44	64	131	132
	Trough RV (L) (LS mean change from baseline)	0.039	-0.337	-0.249	-0.138	-0.255	-0.423
	SE	(0.0521)	(0.0948)	(0.0940)	(0.0779)	(0.0552)	(0.0553)
Effect estimate per comparison	Trough RV (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.463		
		95% CI			(-0.604,-0.321)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.295		
		95% CI			(-0.436,-0.154)		
		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	148	43	44	64	131	131
	3-h postdose RV (L) (LS mean change from baseline)	-0.086	-0.375	-0.451	-0.253	-0.437	-0.625
	SE	(0.0526)	(0.0955)	(0.0945)	(0.0784)	(0.0556)	(0.0560)
Effect estimate per comparison	3-h postdose RV (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			-0.539		
		95% CI			(-0.681, -0.396)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			-0.351		
		95% CI			(-0.493, -0.209)		
		P-value			<0.001		
Notes	The results of statistical analyses for RV should be interpreted only descriptively based on the results of the step-down testing hierarchy described for 3-h postdose EET.						
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)	170	49	50	76	152	144
	Number of subjects at Week 12 for 3-h postdose FEV_1	147	43	44	64	130	130
	3-h postdose FEV_1 (L) (LS mean change from baseline)	-0.007	0.122	0.156	0.115	0.254	0.217
	SE	(0.0159)	(0.0277)	(0.0275)	(0.0229)	(0.0166)	(0.0169)
Effect estimate per comparison	3-h postdose FEV_1 (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		Difference			0.224		
		95% CI			(0.183, 0.265)		
		P-value			<0.001		
		Comparison groups			UMEC/VI 62.5/25 vs. PLA		
		Difference			0.261		
		95% CI			(0.221, 0.301)		
		P-value			<0.001		
Notes	The results of statistical analyses for 3-h postdose FEV_1 should be interpreted only descriptively based on the results of the step-down testing hierarchy described for 3-h postdose EET.						

Table 95. Summary of efficacy for study 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. Only the comparison of the UMEC/VI 62.5/25 and 125/25 mcg treatments vs. PLA were powered.						
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 per comparison	Trough RV (L)	Comparison groups			UMEC/VI 125/25 vs. PLA		
		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		

Table 96. Summary of efficacy for study 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 ± 2day 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 primary efficacy studies as the designs were very similar. A separate integration was performed for the two exercise studies as the designs were identical. The primary efficacy and exercise studies were not integrated together due to differences in design and duration of treatment. Efficacy data from the long-term safety study was not integrated with those from other studies as the study was of a different duration and had a different objective. The treatment comparisons performed for each endpoint in the integrated data were: each dose of UMEC/VI and placebo, each dose of UMEC and placebo, VI and placebo, each dose of UMEC/VI and VI, and each dose of UMEC/VI and the relevant UMEC dose. In addition, for the primary efficacy studies integration, each dose of UMEC/VI was compared with TIO. No adjustment for multiplicity was made in the integrated analysis.

Studies DB2113361, DB2113373, DB2113360 and DB2113374

For the integrated analysis, both doses of UMEC/VI (62.5/25 and 125/25 mcg) and their respective components demonstrated statistically and clinically significant improvements in LS mean changes from baseline in trough FEV1 at Day 169 compared with placebo ($p<0.001$; Table below). The improvements in trough FEV1 at Day 169 were statistically significant for both doses of UMEC/VI compared with each respective dose of UMEC, VI, and TIO ($p<0.001$ for each). However except for the comparison of UMEC/VI 125/25 with VI 25, the other comparisons did not reach the level of clinical relevance of 100 ml.

Table 97. Primary Efficacy Analysis: Trough FEV1 (L) at Day 169 (Integrated Studies DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

Day 169	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
n [a]	547	830	818	416	623	1024	414
n [b]	383	668	654	322	475	778	348
LS mean (SE)	1.237 (0.0115)	1.436 (0.0090)	1.453 (0.0091)	1.371 (0.0133)	1.389 (0.0107)	1.340 (0.0081)	1.373 (0.0129)
LS mean change (SE)	-0.008 (0.0115)	0.191 (0.0090)	0.208 (0.0091)	0.126 (0.0133)	0.144 (0.0107)	0.095 (0.0081)	0.128 (0.0129)
UMEC/VI 62.5/25 vs. Column							
Difference	0.199			0.064		0.095	0.062
95% CI	(0.170, 0.228)			(0.033, 0.095)		(0.072, 0.119)	(0.032, 0.093)
p-value	<0.001			<0.001		<0.001	<0.001
UMEC/VI 125/25 vs. Column							
Difference	0.216				0.064	0.113	0.080
95% CI	(0.187, 0.245)				(0.037, 0.091)	(0.089, 0.137)	(0.049, 0.110)
p-value	<0.001				<0.001	<0.001	<0.001
UMEC 62.5 vs. Column							
Difference	0.135						
95% CI	(0.101, 0.168)						
p-value	<0.001						
UMEC 125 vs. Column							
Difference	0.152						
95% CI	(0.121, 0.183)						
p-value	<0.001						
VI 25 vs. Column Difference	0.104						
95% CI	(0.076, 0.131)						
p-value	<0.001						

Data Source: Table 3.34

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

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, 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 current time point.

Clinically meaningful TDI focal scores relative to baseline were observed for all treatment groups, including placebo, at Day 168 (see table below).

Statistically significant ($p<0.001$) and clinically meaningful differences in TDI focal scores (i.e., ≥1 unit) were demonstrated for both doses of UMEC/VI (62.5/25 and 125/25 mcg) compared with placebo

at Day 168. UMEC 62.5 mcg, UMEC 125 mcg, and VI 25 mcg demonstrated statistically significant greater TDI focal scores compared with placebo at Day 168 (p<0.006).

Statistically significant (p<0.007) improvements in TDI focal score were observed for each dose of UMEC/VI (62.5/25 and 125/25 mcg) over its respective components at Day 168, with the exception of UMEC 62.5/25 mcg over UMEC 62.5 mcg (p=0.194).

TDI focal scores at Day 168 were similar for both doses of UMEC/VI compared with TIO.

Table 98. Statistical Analysis: TDI Focal Score at Day 168 (Integrated Studies DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)

Day 168	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
n [a]	494	782	761	394	579	944	382
n [b]	390	675	655	326	476	770	346
LS mean (SE)	1.1 (0.15)	2.2 (0.12)	2.4 (0.12)	2.0 (0.18)	1.6 (0.14)	1.8 (0.11)	2.2 (0.17)
UMEC/VI 62.5/25 vs. Column Difference	1.2			0.3		0.4	0.1
95% CI	(0.8, 1.6)			(-0.1, 0.7)		(0.1, 0.7)	(-0.3, 0.5)
p-value	<0.001			0.194		0.007	0.759
UMEC/VI 125/25 vs. Column Difference	1.3				0.7	0.5	0.2
95% CI	(0.9, 1.7)				(0.4, 1.1)	(0.2, 0.9)	(-0.2, 0.6)
p-value	<0.001				<0.001	<0.001	0.397
UMEC 62.5 vs. Column Difference	0.9						
95% CI	(0.5, 1.4)						
p-value	<0.001						
UMEC 125 vs. Column Difference	0.6						
95% CI	(0.2, 1.0)						
p-value	0.006						
VI 25 vs. Column Difference	0.8						
95% CI	(0.4, 1.1)						
p-value	<0.001						

Data Source: Table 3.52
Abbreviations: BDI=baseline dyspnea index; CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; TDI=transition dyspnea index; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis used a repeated measures model with terms for study, treatment, smoking status at Screening, baseline (BDI score), day, geographical region, 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 current time point.

For the integrated analysis, both doses of UMEC/VI (62.5/25 and 125/25 mcg) and their respective components demonstrated statistically significant improvements in LS mean changes from baseline in 0 to 6 hour weighted mean FEV1 at Day 168 compared with placebo (p<0.001). The improvements in 0 to 6 hour weighted mean FEV1 at Day 168 were statistically significant for both doses of UMEC/VI compared with each respective dose of UMEC, VI, and TIO (p<0.001 for each).

Table 99. Statistical Analysis: 0 to 6 hour Weighted Mean FEV1 (L) (Integrated Studies DB2113361, DB2113373, DB2113360 and BD2113374 ITT Population)

	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
Day 168							
n [a]	553	834	822	414	625	1028	416
n [b]	386	667	646	319	472	770	340
LS mean (SE)	1.239 (0.0112)	1.500 (0.0088)	1.513 (0.0090)	1.402 (0.0130)	1.418 (0.0105)	1.381 (0.0080)	1.423 (0.0128)
LS mean change (SE)	-0.006 (0.0112)	0.255 (0.0088)	0.268 (0.0090)	0.157 (0.0130)	0.173 (0.0105)	0.136 (0.0080)	0.178 (0.0128)
UMEC/VI 62.5/25 vs. Column Difference	0.261			0.098		0.119	0.077
95% CI	(0.233, 0.289)			(0.068, 0.129)		(0.096, 0.143)	(0.047, 0.107)
p-value	<0.001			<0.001		<0.001	<0.001
UMEC/VI 125/25 vs. Column Difference	0.274				0.095	0.132	0.089
95% CI	(0.246, 0.302)				(0.068, 0.121)	(0.108, 0.156)	(0.059, 0.120)
p-value	<0.001				<0.001	<0.001	<0.001
UMEC 62.5 vs. Column Difference	0.163						
95% CI	(0.130, 0.196)						
p-value	<0.001						
UMEC 125 vs. Column Difference	0.179						
95% CI	(0.149, 0.210)						
p-value	<0.001						
VI 25 vs. Column Difference	0.142						
95% CI	(0.115, 0.169)						
p-value	<0.001						

Data Source: Table 3.64

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

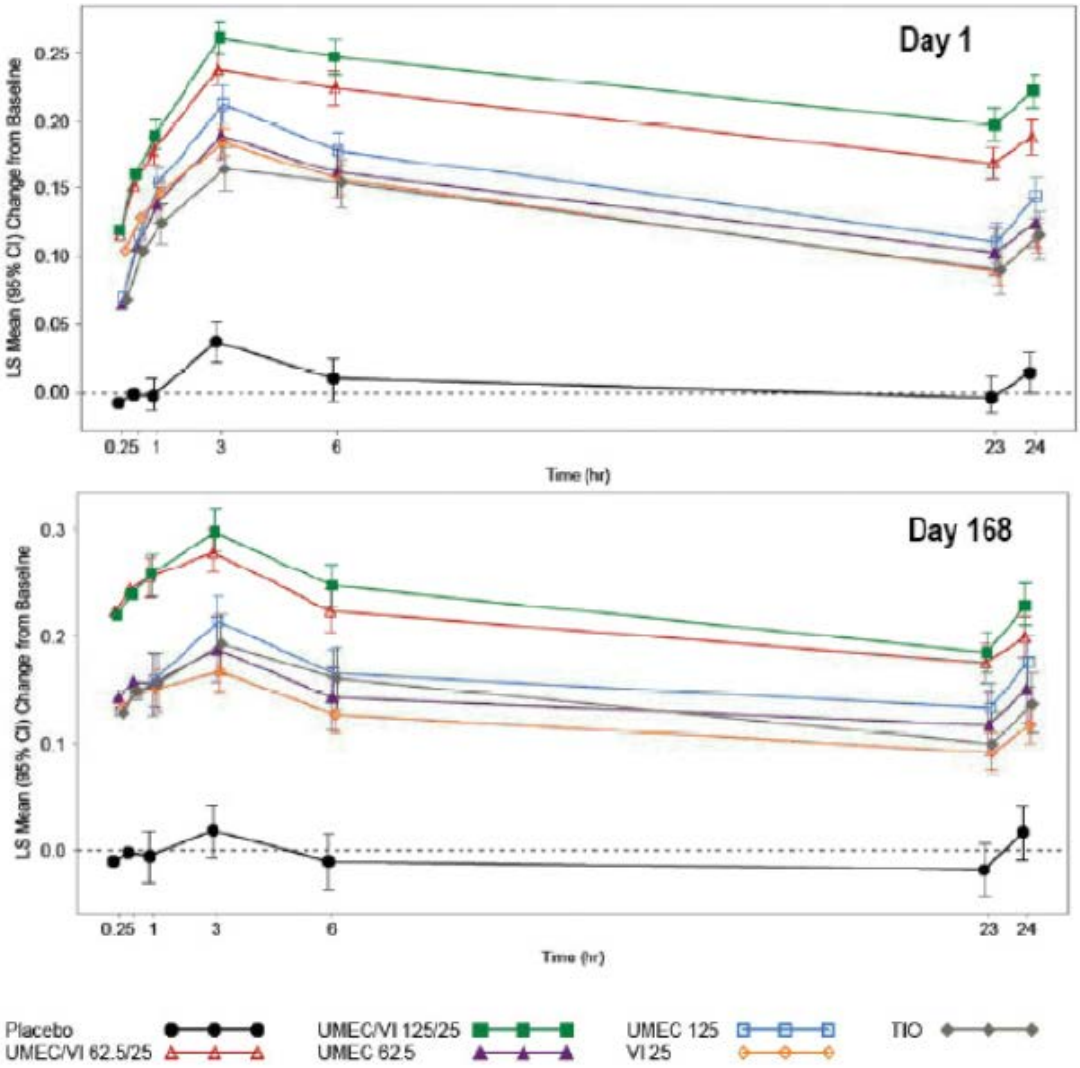
Note: Analysis used a repeated measures model with terms for study, treatment, smoking status at Screening, baseline FEV_1 (mean of 30 and 5 minutes predose on Day 1), day, geographical region, day by baseline, and day by treatment interactions.

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

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

For the integrated analysis, both doses of UMEC/VI (125/25 and 62.5/25 mcg) and their respective components demonstrated statistically significant postdose improvements in LS mean changes from baseline in serial FEV1 compared with placebo at all time points assessed on all days studied ($p<0.001$). The post dose improvements in serial FEV1 were statistically significant for each dose of UMEC/VI compared with its respective components ($p\leq0.035$) and for both doses of UMEC/VI compared with TIO ($p<0.001$) for all time points assessed on all days studied (Days 1 and 168 presented in the figure below).

Figure 10. Least Squares Mean (95% CI) Change from Baseline in Serial FEV1 (L) (Integrated Studies DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)



Data Source: Figure 3.40 and Figure 3.43
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
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, day by baseline, and day by treatment interactions.

For the integrated analysis, statistically significant greater reductions from baseline in the mean number of puffs of rescue medication per day were demonstrated for both doses of UMEC/VI, UMEC 125 mcg, and VI 25 mcg ($p<0.001$; see table below), but not UMEC 62.5 mcg, over placebo at Weeks 1 to 24. Statistically significant ($p<0.001$) greater reductions from baseline in the mean number of puffs of rescue medication per day over Weeks 1 to 24 were demonstrated for UMEC 125/25 mcg compared with UMEC 125 mcg and VI 25 mcg and for UMEC/VI 62.5/25 mcg compared with UMEC 62.5 mcg ($p<0.001$) but not VI 25 mcg. Both doses of UMEC/VI demonstrated statistically significant greater reductions from baseline in the mean number of puffs of rescue medication per day over Weeks 1 to 24 compared with TIO ($p\leq0.007$). Reductions from baseline in rescue medication use were generally consistent between treatment groups across all 4-week increments, starting with Weeks 1 to

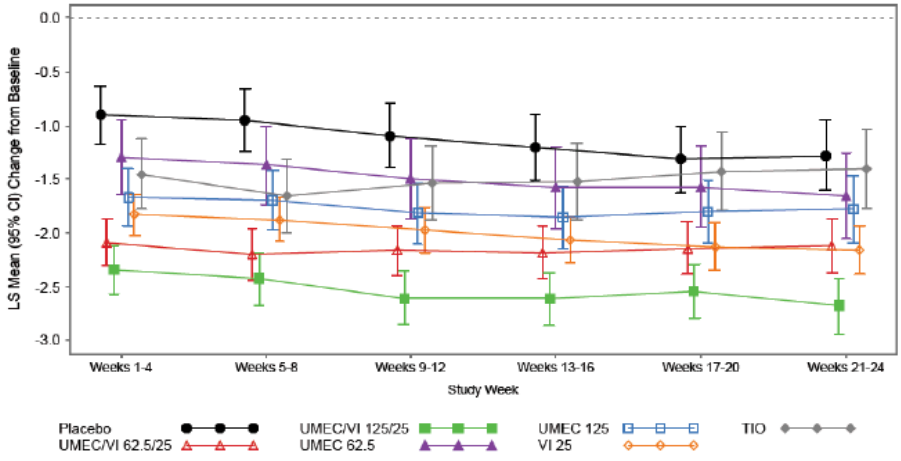
4 (as shown in the figure below). Most treatment groups exhibited a general decrease in rescue medication use from baseline over time.

Table 100. Analysis of Mean Number of Puffs of Rescue Medication Per day over Weeks 1 to 24 (Integrated Studies DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
Baseline							
Mean puffs/day, n	547	826	814	410	623	1014	414
Mean	5.3	5.3	4.8	5.5	5.3	5.0	5.1
SD	5.88	5.39	5.08	5.71	5.81	5.21	4.58
Median	3.8	3.7	3.6	4.0	3.6	3.6	4.0
Min, Max	0, 37	0, 35	0, 41	0, 37	0, 33	0, 34	0, 28
Weeks 1 to 24							
n	440	717	696	345	529	857	363
LS mean (SE)	3.88 (0.142)	2.86 (0.112)	2.46 (0.116)	3.55 (0.176)	3.19 (0.136)	3.00 (0.100)	3.39 (0.167)
LS mean change (SE)	-1.12 (0.142)	-2.14 (0.112)	-2.54 (0.116)	-1.45 (0.176)	-1.81 (0.136)	-2.00 (0.100)	-1.61 (0.167)
UMEC/VI 62.5/25 vs. Column Difference	-1.02			-0.68		-0.14	-0.53
95% CI	(-1.38, -0.66)			(-1.08, -0.29)		(-0.44, 0.16)	(-0.91, -0.14)
p-value	<0.001			<0.001		0.362	0.007
UMEC/VI 125/25 vs. Column Difference	-1.42				-0.73	-0.54	-0.93
95% CI	(-1.79, -1.05)				(-1.05, -0.40)	(-0.85, -0.23)	(-1.31, -0.55)
p-value	<0.001				<0.001	<0.001	<0.001
UMEC 62.5 vs. Column Difference	-0.33						
95% CI	(-0.75, 0.09)						
p-value	0.126						
UMEC 125 vs. Column Difference	-0.69						
95% CI	(-1.08, -0.30)						
p-value	<0.001						
VI 25 vs. Column Difference	-0.88						
95% CI	(-1.21, -0.54)						
p-value	<0.001						

Data Source: Table 3.78 and Table 3.79
Abbreviations: ANCOVA=analysis of covariance; ITT=intent-to-treat; LS=least squares; Max=maximum; Min=minimum; SD=standard deviation; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Baseline was the percentage during the week prior to Day 1.
Note: Analysis was performed using a ANCOVA model with covariates of study, treatment, smoking status at Screening, baseline mean puffs of rescue medication, and geographic region.

Figure 11. Least Squares Mean (95% CI) Change from Baseline in Mean Number of Puffs of Rescue Medication (Integrated Studies DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)



Data Source: Figure 3.70
Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; ITT=intent-to-treat; LS=least squares; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis used an ANCOVA model with covariates for study, treatment, smoking status at Screening, baseline mean puffs of rescue medication, and geographic region.

Clinically meaningful improvements in mean SGRQ total scores from baseline at Day 168 were observed for all treatment groups except placebo (as shown in the figure below)

For the integrated analysis, both doses of UMEC/VI (125/25 mcg and 62.5/25 mcg) and their respective components demonstrated a statistically significant greater decrease in LS mean change

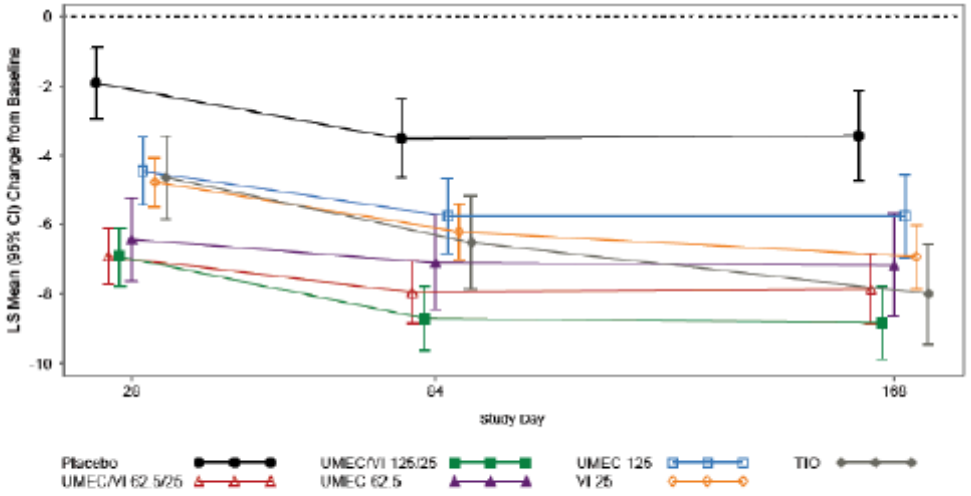
from baseline in mean SGRQ total score at Day 168 compared with placebo (p≤0.011) (see table below). The improvements in mean SGRQ total score at Day 168 were statistically significant for UMEC/VI 125/25 mcg over components (p≤0.008) but were not statistically significant for UMEC/VI 62.25 mcg over components or for either dose of UMEC/VI over TIO.

Table 101. Analysis of SRGQ Total Score at Day 168 (integrated Studies DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)

	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418
Day 168							
n [a]	473	764	739	388	562	920	388
n [b]	357	640	612	312	452	730	327
LS mean (SE)	45.33 (0.671)	40.92 (0.513)	39.93 (0.529)	41.58 (0.767)	42.99 (0.621)	41.83 (0.469)	40.74 (0.749)
LS mean change (SE)	-3.43 (0.671)	-7.85 (0.513)	-8.84 (0.529)	-7.18 (0.767)	-5.78 (0.621)	-6.93 (0.469)	-8.02 (0.749)
UMEC/VI 62.5/25 vs. Column Difference	-4.42			-0.67		-0.92	0.17
95% CI	(-6.08, -2.75)			(-2.43, 1.10)		(-2.28, 0.45)	(-1.58, 1.93)
p-value	<0.001			0.459		0.189	0.846
UMEC/VI 125/25 vs. Column Difference	-5.41				-3.06	-1.90	-0.82
95% CI	(-7.11, -3.70)				(-4.61, -1.52)	(-3.31, -0.50)	(-2.57, 0.94)
p-value	<0.001				<0.001	0.008	0.362
UMEC 62.5 vs. Column Difference	-3.75						
95% CI	(-5.70, -1.81)						
p-value	<0.001						
UMEC 125 vs. Column Difference	-2.34						
95% CI	(-4.15, -0.54)						
p-value	0.011						
VI 25 vs. Column Difference	-3.50						
95% CI	(-5.09, -1.92)						
p-value	<0.001						

Data Source: Table 3.86
Abbreviations: CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; SGRQ=St. George's Respiratory Questionnaire; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis performed using a repeated measures model with terms for study, treatment, smoking status at Screening, baseline total score, day, geographical region, and day by baseline, and day by treatment interactions.
a. Number of subjects with analyzable data for 1 or more time points.
a. Number of subjects with analyzable data at the current time point.

Figure 12. Least Squares Mean (95% CI) Change from Baseline in SGRQ Total Score (Integrated Studies DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)



Data Source: Figure 3.44
Abbreviations: CI=confidence interval; ITT=intent-to-treat; LS=least squares; SGRQ=St. George's Respiratory Questionnaire; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Analysis performed using a repeated measures model with terms for study, treatment, smoking status at Screening, baseline total score, day, geographical region, day by baseline, and day by treatment interactions.

In the placebo-controlled studies (DB2113361 and DB2113373), on-treatment COPD exacerbations were reported more frequently in the placebo treatment group (13% to 14%) compared with the UMEC/VI, UMEC, and VI treatment groups (6% to 9%) (see table below).

In the TIO controlled studies DB2113360 and DB2113374, the incidence of on-treatment COPD exacerbations ranged from 5% to 12% across the UMEC/VI, UMEC, and VI treatment groups compared with 5% to 7% in the TIO treatment group.

For the integrated analysis, COPD exacerbations were reported more frequently in the placebo treatment group (13%) compared with the UMEC/VI, UMEC, and VI treatment groups (6% to 9%).

Table 102. Summary of On-treatment COPD Exacerbations (Individual and Integrated Studies DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)

Number of subjects with a COPD exacerbation, n (%) [a]	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Integrated, N n (%)	555 73 (13)	837 67 (8)	826 50 (6)	418 33 (8)	629 58 (9)	1030 88 (9)	418 25 (6)
DB2113361, N n (%)	275 38 (14)		403 23 (6)		407 32 (8)	404 32 (8)	
DB2113373, N n (%)	280 35 (13)	413 27 (7)		418 33 (8)		421 39 (9)	
DB2113360, N n (%)		207 14 (7)	208 11 (5)			205 17 (8)	203 11 (5)
DB2113374, N n (%)		217 26 (12)	215 16 (7)		222 26 (12)		215 14 (7)

Data Source: Table 3.90; CSR DB2113361, Table 6.89; CSR DB2113373, Table 6.89; CSR DB2113360, Table 6.79; CSR DB2113374, Table 6.79

Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Percentages calculated using N as the denominator.

Integration of exercise studies

For the integrated analysis, treatment with either dose of UMEC/VI (62.5/25 and 125/25 mcg) resulted in a statistically significant increase in LS mean changes from baseline in 3-hour postdose EET at Week 12 compared with placebo ($p<0.002$; see table below). The comparisons of effect of treatment on EET as compared to placebo was clinically relevant (defined as 45-65 sec improvement) only for UMEC/VI 125/25.

Table 103. Statistical Analysis of 3-Hour Postdose EET (seconds) at Week 12 (Integrated Studies DB2114417 and DB2114418 ITT Population)

Week 12	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
n [a]	316	280	267	88	90	135
n [b]	262	246	239	80	76	117
LS Mean Change (SE)	19.2 (10.39)	62.9 (10.80)	66.7 (10.99)	44.6 (18.85)	59.2 (19.20)	27.9 (15.52)
Column vs. Placebo						
Difference		43.7	47.5	25.4	40.0	8.8
95% CI		(15.5, 72.0)	(19.0, 76.1)	(-15.88, 66.6)	(-1.8, 81.8)	(-27.0, 44.5)
p-value		0.002	0.001	0.226	0.061	0.631
UMEC/VI 62.5/25 vs. Column Difference				18.3		35.0
95% CI				(-23.2, 59.9)		(-1.2, 71.1)
p-value				0.387		0.058
UMEC/VI 125/25 vs. Column Difference					7.5	38.8
95% CI					(-34.7, 49.7)	(2.5, 75.1)
p-value					0.727	0.036

Data Source: Table 3.109

Abbreviations: CI=confidence interval; EET=exercise endurance time; ITT=intent-to-treat; LS=least squares; SE=standard error; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using a repeated measures model with terms for study, period, treatment, smoking status at Screening, geographical region, day, mean walking speed, period walking speed, and day by mean walking speed, day by period walking speed, 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.

For the integrated analysis, statistically significant greater LS mean changes from baseline in trough FEV1 were demonstrated for both doses of UMEC/VI (62.5/25 and 125/25 mcg) compared with placebo at Week 12 ($p<0.001$; see table below).

Table 104. Primary Efficacy Analysis: Trough FEV1 (L) at Week 12 (Integrated Studies DB2114417 and DB2114418 ITT Population)

Week 12	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
n [a]	319	280	268	89	91	140
n [b]	267	247	244	81	77	120
LS Mean (SE)	1.348 (0.0108)	1.572 (0.0110)	1.559 (0.0112)	1.459 (0.0188)	1.536 (0.0193)	1.453 (0.0155)
LS Mean Change (SE)	-0.035 (0.0108)	0.189 (0.0110)	0.176 (0.0112)	0.076 (0.0188)	0.153 (0.0193)	0.070 (0.0155)
Column vs. Placebo Difference		0.224	0.211	0.111	0.187	0.104
95% CI		(0.196, 0.252)	(0.182, 0.239)	(0.070, 0.151)	(0.146, 0.229)	(0.069, 0.140)
p-value		<0.001	<0.001	<0.001	<0.001	<0.001
UMEC/VI 62.5/25 vs. Column Difference				0.113		0.119
95% CI				(0.072, 0.154)		(0.084, 0.155)
p-value				<0.001		<0.001
UMEC/VI 125/25 vs. Column Difference					0.023	0.106
95% CI					(-0.018, 0.065)	(0.071, 0.142)
p-value					0.269	<0.001

Data Source: Table 3.121

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

Note: Analysis performed using a repeated measures model with terms for study, period, treatment, smoking status at Screening, geographical region, day, mean baseline, period baseline, and day by mean baseline, day by period 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.

Sub-group analyses

The results of the subgroup analyses that included the intrinsic factors of age, gender, and race and the extrinsic factors of smoking status, treatment naïve status and GOLD class (I/II and III/IV) indicated that there was no impact of these factors on treatment effect. The response to treatment was in the same direction and of similar magnitude for each category of subgroup and in the overall COPD population. Notably, the bronchodilator response was evident in both GOLD I/II and III/IV subgroups. Interactions with treatment were observed for the factors of geographical region and ICS use for the primary endpoint of trough FEV1. However, for each of these subgroup categories (ICS use and geographical region) the response to treatment was in the same direction and any differences in magnitude were not considered clinically relevant. For these intrinsic and extrinsic factors, no differential in response to UMEC/VI 125/25 and UMEC/VI 62.5/25 mcg was observed.

Analysis by reversibility to salbutamol

For the intrinsic factor of reversibility defined as post salbutamol improvements in FEV1 ≥12% and ≥200 mL from baseline, interactions for the primary endpoint of trough FEV1 at Day 169 were found to be statistically significant in the integrated analysis of the primary efficacy studies. Although response to treatment was in the same direction for each category within each subgroup, the reversible subjects showed a greater difference from placebo for UMEC/VI 125/25 mcg (0.282 L improvement over placebo at Day 169) compared with UMEC/VI 62.5/25 mcg (0.225 L over placebo at Day 169). The

greater improvements in trough FEV1 were observed at Day 2 and maintained for the duration of the study.

Greater benefit with UMEC/VI 125/25 mcg than with UMEC/VI 62.5/25 mcg in the reversible subgroup was also apparent for TDI focal scores (1.7 and 1.4 unit improvement over placebo at Day 169 for UMEC /VI 125/25 and 62.5/25 mcg), SGRQ scores (-5.99 and -5.50 reduction over placebo at Day 169 for UMEC /VI 125/25 and 62.5/25 mcg), and rescue salbutamol use (-1.82 and -1.18 puffs/day reduction over placebo at Day 169 for UMEC /VI 125/25 and 62.5/25 mcg).

Both UMEC/VI doses of 62.5/25 and 125/25 mcg provided similar improvements in the broad COPD subject population enrolled in these studies. Greater improvements in efficacy including lung function and reductions in rescue salbutamol use were observed with UMEC 125/25 mcg than those observed with UMEC/VI 62.5/25 mcg in COPD patients who demonstrated reversibility to salbutamol at screening (≥200 mL and ≥12% increase in FEV1). In addition greater improvements with UMEC/VI 125/25 mcg than UMEC/VI 62.5/25 mcg over TIO in TDI and reductions in rescue use were seen in the overall study population. Therefore the Applicant initially proposed both doses of UMEC/VI for registration.

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. A summary of the number of subjects by different sub-groups is given in the table below which gives an idea of the mix of the study population.

Table 105. Summay of Number of Subjects (Integrated Studies DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)

	Number (%) of Subjects							
Subgroups	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418	Total N=4713
Sex, n	555	837	826	418	629	1030	418	4713
Female	185 (33)	246 (29)	268 (32)	120 (29)	211 (34)	340 (33)	127 (30)	1497 (32)
Male	370 (67)	591 (71)	558 (68)	298 (71)	418 (66)	690 (67)	291 (70)	3216 (68)
Age (years), n	555	837	826	418	629	1030	418	4713
≤64	335 (60)	449 (54)	439 (53)	217 (52)	335 (53)	589 (57)	208 (50)	2572 (55)
65 to 74	170 (31)	299 (36)	309 (37)	148 (35)	232 (37)	345 (33)	160 (38)	1663 (35)
75 to 84	49 (9)	85 (10)	78 (9)	50 (12)	61 (10)	93 (9)	48 (11)	464 (10)
≥85	1 (<1)	4 (<1)	0	3 (<1)	1 (<1)	3 (<1)	2 (<1)	14 (<1)
Race, n	555	837	826	418	629	1030	418	4713
African American/ African heritage	18 (3)	29 (3)	21 (3)	14 (3)	10 (2)	19 (2)	14 (3)	125 (3)
American Indian or Alaska native	1 (<1)	16 (2)	22 (3)	3 (<1)	0	24 (2)	19 (5)	85 (2)
Asian	49 (9)	73 (9)	77 (9)	35 (8)	77 (12)	76 (7)	38 (9)	425 (9)
Native Hawaiian or other Pacific Islander	0	2 (<1)	0	0	0	0	0	2 (<1)
White	475 (86)	689 (82)	684 (84)	354 (85)	533 (85)	898 (87)	336 (80)	3979 (84)
Mixed Race	12 (2)	28 (3)	12 (1)	12 (3)	9 (1)	13 (1)	11 (3)	97 (2)
n	555	837	826	418	629	1030	418	4713
East Asian	26 (5)	58 (7)	55 (7)	20 (5)	56 (9)	41 (4)	36 (9)	292 (6)
Not East Asian	529 (95)	779 (93)	771 (93)	398 (95)	573 (91)	989 (96)	382 (91)	4421 (94)
Geographic regions [a], n	555	837	826	418	629	1030	418	4713
United States	135 (24)	228 (27)	193 (23)	118 (28)	145 (23)	254 (25)	103 (25)	1176 (25)
European Union	268 (48)	237 (28)	384 (46)	124 (30)	311 (49)	468 (45)	122 (29)	1914 (41)
Other	152 (27)	372 (44)	249 (30)	176 (42)	173 (28)	308 (30)	193 (46)	1623 (34)

	Number (%) of Subjects							
Subgroups	Placebo N=555	UMEC/VI 62.5/25 N=837	UMEC/VI 125/25 N=826	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1030	TIO N=418	Total N=4713
United States	135 (24)	228 (27)	193 (23)	118 (28)	145 (23)	254 (25)	103 (25)	1176 (25)
Non-United States	420 (76)	609 (73)	633 (77)	300 (72)	484 (77)	776 (75)	315 (75)	3537 (75)
Treatment naïve [b], n	555	837	826	418	629	1030	418	4713
Treatment naïve	182 (33)	301 (36)	264 (32)	128 (31)	176 (28)	354 (34)	138 (33)	1543 (33)
Not treatment naïve	373 (67)	536 (64)	562 (68)	290 (69)	453 (72)	676 (66)	280 (67)	3170 (67)
ICS use at Screening [c], n	555	837	826	418	629	1030	418	4713
ICS user	275 (50)	408 (49)	389 (47)	219 (52)	317 (50)	485 (47)	208 (50)	2301 (49)
ICS non-user	280 (50)	429 (51)	437 (53)	199 (48)	312 (50)	545 (53)	210 (50)	2412 (51)
GOLD status, n	554	834	821	417	627	1024	415	4692
I & II: FEV_1≥50% predicted	240 (43)	409 (49)	362 (44)	191 (46)	280 (45)	498 (49)	195 (47)	2175 (46)
III & IV: FEV_1<50% predicted	314 (57)	425 (51)	459 (56)	226 (54)	347 (55)	526 (51)	220 (53)	2517 (54)
History of smoking use, n	555	837	826	418	629	1030	418	4713
Current smoker [d]	293 (53)	390 (47)	415 (50)	207 (50)	314 (50)	511 (50)	196 (47)	2326 (49)
Former smoker	262 (47)	447 (53)	411 (50)	211 (50)	315 (50)	519 (50)	222 (53)	2387 (51)
Reversibility to Salbutamol [e], n	553	834	821	415	625	1022	412	4682
Not reversible	385 (70)	586 (70)	549 (67)	294 (71)	418 (67)	697 (68)	306 (74)	3235 (69)
Reversible	168 (30)	248 (30)	272 (33)	121 (29)	207 (33)	325 (32)	106 (26)	1447 (31)
Reversibility to Salbutamol and Ipratropium [f], n	543	827	819	411	618	1014	410	4642
Not reversible	255 (47)	380 (46)	381 (47)	188 (46)	263 (43)	489 (48)	205 (50)	2161 (47)
Reversible	288 (53)	447 (54)	438 (53)	223 (54)	355 (57)	525 (52)	205 (50)	2481 (53)

Data Source: Table 3.04

Abbreviations: COPD=chronic obstructive pulmonary disease; FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteriod; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

a. Other region included Argentina, Australia, Canada, Chile, Japan, Korea, Mexico, Philippines, Peru, Russia, Thailand, Ukraine, and South Africa.
b. Treatment-naïve subjects reported taking no COPD medication apart from short-acting bronchodilators in the 30 days prior to Screening.
c. ICS users reported taking a ICS at Screening; ICS non-users did not report taking a ICS at Screening.
d. Subjects were classed as a current smoker unless they had not smoked in the 6 months prior to Screening.
e. Reversibility to salbutamol was defined as an increase in FEV_1 of ≥12% and ≥200 mL following administration of 4 puffs of salbutamol.
f. Reversibility to salbutamol and ipratropium was defined as an increase in FEV_1 of ≥12% and ≥200mL following administration of both salbutamol and ipratropium.

There are no studies in any particular special populations like very severe COPD patients or COPD patients with severe cardiovascular disease. However such studies are not required as the targeted indication is not at any such specific special populations.

Supportive studies

Study ZEP117115

This was a phase IIIb multicenter, randomized, double-dummy, parallel group study to evaluate the efficacy and safety of UMEC/VI Inhalation Powder (62.5/25 mcg once-daily) when administered via the Novel DPI (NDPI, ELLIPTA™ DPI) compared with tiotropium (18 mcg once-daily) when administered via the HandiHaler™ over a treatment period of 24 weeks in subjects with COPD.

Methods

Study Participants

Inclusion criteria

Subjects eligible for enrollment in the study must have met all of the following criteria:

1. **Type of subject:** Outpatient.
2. **Informed Consent:** A signed and dated written informed consent prior to study participation.
3. **Age**: Subjects 40 years of age or older at Visit 1.
4. **Gender**: Male or female subjects.
5. **Diagnosis**: An established clinical history of COPD in accordance with the definition by the American Thoracic Society (ATS)/European Respiratory Society [Celli, 2004] as follows:

   Chronic obstructive pulmonary disease is a preventable and treatable disease state characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

   Although COPD affects the lungs, it also produces significant systemic consequences.
6. **Smoking History**: Current or former cigarette smokers with a history of cigarette smoking of ≥10 pack-years [number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers were defined as those who had stopped smoking for at least 6 months prior to Visit 1.
7. **Severity of Disease**: A post-albuterol/salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 and a post-albuterol/salbutamol FEV1 of ≤70% of predicted normal values calculated using National Health and Nutritional Examination survey (NHANES) III reference equations at Visit 1 [Hankinson, 1999; Hankinson, 2010]
8. **Dyspnea:** A score of ≥2 on the modified Medical Research Council (mMRC) Dyspnea Scale at Visit 1.

Exclusion criteria

Subjects meeting any of the following criteria must not have been enrolled in the study:

1. **Pregnancy**: Women who were pregnant or lactating or were planning on becoming pregnant during the study
2. **Asthma**: A current diagnosis of asthma
3. **Other Respiratory Disorders**: Known α-1 antitrypsin deficiency, active lung infections (such as tuberculosis), and lung cancer were absolute exclusionary conditions. A subject who, in the opinion of the investigator, had any other significant respiratory conditions in addition to COPD was to be excluded. Examples may include clinically significant bronchiectasis, pulmonary hypertension, sarcoidosis, or interstitial lung disease.
4. **Other Diseases/Abnormalities**: Subjects with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, endocrine (including uncontrolled diabetes or thyroid disease), or hematological abnormalities that were

uncontrolled and/or a previous history of cancer in remission for <5 years prior to Visit 1 (localized carcinoma of the skin that has been resected for cure is not exclusionary). Significant was defined as any disease that, in the opinion of the investigator, would put the safety of the subject at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

5. **Contraindications:** A history of allergy or hypersensitivity to any anticholinergic/muscarinic receptor antagonist, beta2-agonist, lactose/milk protein or magnesium stearate, or a medical condition such as narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction that, in the opinion of the study physician, contraindicated study participation or use of an inhaled anticholinergic.
6. **Hospitalization**: Hospitalization for COPD or pneumonia within 12 weeks prior to Visit 1
7. **Lung Resection**: Subjects with lung volume reduction surgery within the 12 months prior to Screening (Visit 1)
8. **12-lead ECG**: An abnormal and significant ECG finding from the 12-lead ECG conducted at Visit 1, including the presence of a paced rhythm on a 12-lead electrocardiogram (ECG) which caused the underlying rhythm and ECG to be obscured. Investigators were provided with ECG reviews conducted by a centralized independent cardiologist to assist in evaluation of subject eligibility.
9. **Medication Prior to Spirometry**: Unable to withhold albuterol/salbutamol for the 4-hour period required prior to spirometry testing at each study visit
10. **Oxygen**: Use of long-term oxygen therapy (LTOT) described as oxygen therapy prescribed for greater than 12 hours a day. As-needed oxygen use (i.e., ≤12 hours per day) was not exclusionary.
11. **Nebulized Therapy**: Regular use (prescribed for use every day, not for as-needed use) of short-acting bronchodilators (e.g., albuterol/salbutamol) via nebulized therapy.
12. **Pulmonary Rehabilitation Program**: Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1. Subjects who were in the maintenance phase of a pulmonary rehabilitation program were not excluded.
13. **Drug or Alcohol Abuse**: A known or suspected history of alcohol or drug abuse within 2 years prior to Visit 1.

Treatments

The Applicant provided the study drug for use in this study. The following study drugs were used in this study:

- UMEC/VI 62.5/25 mcg once-daily via NDPI + placebo once-daily via HandiHaler
- TIO 18 mcg once-daily via HandiHaler + placebo once-daily via NDPI.

Subjects were instructed to take one dose each morning from both the NDPI and the HandiHaler.

On the morning of each clinic study visit, subjects refrained from taking their morning dose of study drug until instructed to do so by clinic personnel. Study drug was given at the clinic at approximately the same time of day as Day 1 (Visit 2). On the other days during the Treatment Period (i.e., "non-clinic days"), subjects were instructed to take their study drug each morning at approximately the same time of day as the dose time on Day 1 (Visit 2).

UMEC/VI, and matching placebo (identical in appearance to the inhaler containing active study drug) were administered via an NDPI for oral inhalation. The NDPI for UMEC/VI and placebo contained two, double-foil, laminate, blister strips within the NDPI. The NDPI provided a total of 30 doses (60 blisters) and delivered, when actuated, the contents of a single blister simultaneously from each of the 2 blister strips.

Objectives

The primary objective was to compare the efficacy of UMEC/VI Inhalation Powder (62.5/25 mcg) once-daily with tiotropium (18 mcg) once-daily over 24 weeks for the treatment of subjects with COPD.

Secondary objectives were to compare effects of UMEC/VI Inhalation Powder (62.5 /25 mcg) once-daily with tiotropium (18 mcg) once-daily on safety over 24 weeks in subjects with COPD.

Outcomes/endpoints

The primary endpoint was the clinic visit trough FEV1 on Treatment Day 169. Trough FEV1 on Treatment Day 169 was defined as the mean of the FEV1 values obtained at 23 and 24 hours after dosing on Day 168 (i.e., at Week 24).

The secondary efficacy endpoint was the weighted mean 0-6 hour FEV1 obtained post dose on Day 168.

Sample size

The sample size calculations used a 2-sided 5% significance level and an estimate of residual standard deviation (SD) for trough FEV1 of 240 mL. The estimate of SD was based on Mixed Model Repeated Measures (MMRM) analyses of previous Phase IIIA studies in COPD subjects (studies DB2113360, DB2113361, DB2113373 and DB2113374). A study with 337 evaluable subjects per arm has 90% power to detect a 60 mL difference between treatments in trough FEV1.

It was estimated that approximately 25% of subjects could withdraw without providing a Week 24 assessment. Although, in MMRM, all available post-baseline assessments up to the endpoint for subjects in the ITT population are utilized in the analysis, data for subjects who withdrew prematurely from the study were not explicitly imputed. Hence, to allow for a 25% withdrawal rate, approximately 450 subjects were planned to be randomized to each treatment arm. Assuming 30% of screened subjects would not be eligible for randomization, approximately 1300 subjects were planned to be screened to randomize 900 for this study.

Randomisation

Subjects were assigned to study treatment in accordance with the randomization schedule. The randomization code was generated by the Applicant using a validated computerized system RandAll version 2.5. Subjects were randomized 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.

Blinding (masking)

The investigator or treating physician may have unblinded a subject's treatment assignment only in the case of an emergency, when knowledge of the study treatment was essential for the appropriate clinical management or welfare of the subject.

Statistical methods

All planned analyses were performed after the database freeze had taken place. Once this had been achieved, unblinding of the subjects occurred and analyses were performed. No interim analyses were planned or conducted.

The primary treatment comparison of UMEC/VI 62.5/25 mcg with tiotropium was performed on trough FEV_1 on Day 169 and on 0-6 hour weighted mean at Day 168, for the ITT Population.

Treatment comparison of UMEC/VI 62.5/25 mcg with tiotropium was performed for all the other efficacy endpoints, for the ITT Population. No further adjustment for multiciplicity was applied.

No interim analysis was planned or performed.

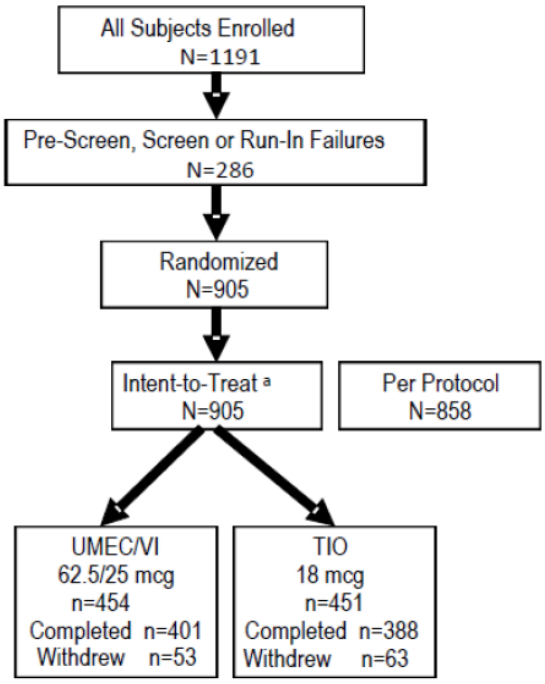
The primary endpoint of trough FEV_1 on Day 169 was analyzed for the ITT population using a MMRM analysis [Siddiqui, 2009], including covariates of baseline FEV_1, smoking status, Day, center group, treatment, Day by baseline interaction, and Day by treatment interaction, where Day is nominal. The model used all available trough FEV_1 values recorded on Days 2, 28, 56, 84, 112, 140, 168, and 169. 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 FEV_1 on Day 169. Two models were fitted; one with a response variable of trough FEV_1, and one with a response variable of change from baseline in trough FEV_1.

Results

Participant flow

An overview of subject disposition is shown in the figure below.

Figure 13. Subject Disposition (Study ZEP117115)



Data Source: Table 5.01 and Table 5.03
Abbreviations: ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Subjects were considered to have completed if they completed the last clinic visit (Visit 10) excluding follow-up.
Note: Randomized subjects included all subjects who were randomized and given a randomization number.
a. The ITT population was used as the primary population for all study population, efficacy, safety and health outcomes analyses. Additional information is provided in Section 5.2 and Section 5.3.

Conduct of the study

There was one amendment to the original clinical trial protocol. This amendment was considered not influencing the study results.

Baseline data

Demographics

Demographic characteristics in the ITT population were similar between treatment groups (see table below).

Table 106. Summary of Demographic Characteristics (ZEP117115 ITT Population)

Demographic Characteristic	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451	Total N=905
Age (years), n	454	451	905
Mean	61.9	62.7	62.3
SD	8.41	8.50	8.46
Median	62.0	63.0	62.0
Min, Max	40, 88	40, 85	40, 88
Sex, n	454	451	905
Female, n (%)	144 (32)	148 (33)	292 (32)
Male, n (%)	310 (68)	303 (67)	613 (68)
Ethnicity, n	454	451	905
Hispanic/Latino, n (%)	1 (<1)	0	1 (<1)
Not Hispanic/Latino, n (%)	453 (>99)	451 (100)	904 (>99)
Race, n	454	451	905
African American/African Heritage, n (%)	13 (3)	7 (2)	20 (2)
American Indian or Alaska Native, n (%)	1 (<1)	1 (<1)	2 (<1)
Asian, n (%)	0	0	0
Central/South Asian Heritage	0	0	0
Japanese/East Asian Heritage/South East Asian Heritage	0	0	0
Native Hawaiian or other pacific islander	0	0	0
White, n (%)	439 (97)	442 (98)	881 (97)
African American/African Heritage & White, n (%)	1 (<1)	1 (<1)	2 (<1)
Height (cm), n	454	451	905
Mean	170.1	170.2	170.1
SD	9.50	9.45	9.47
Median	170.0	170.0	170.0
Min, Max	148, 197	128, 200	128, 200
Weight (kg), n	454	451	905
Mean	80.76	77.90	79.34
SD	19.125	17.983	18.610
Median	79.00	77.00	78.00
Min, Max	43.0, 161.2	36.9, 140.0	36.9, 161.2
Body mass index (kg/m²), n	454	451	905
Mean	27.85	26.80	27.32
SD	5.887	5.466	5.702
Median	27.10	26.40	26.70
Min, Max	17.0, 50.5	14.4, 45.4	14.4, 50.5

Data Source: Table 5.09 and Table 5.12
Abbreviations: ITT=intent-to-treat; max=maximum; min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Full detailed race and racial combination data are provided in Table 5.13.

Demographics were similar between the ITT and PP populations.

Smoking History

At screening, 57% of subjects overall were classified as current smokers (including subjects who stopped smoking within 6 months prior to screening; see table below). During the course of the study, one subject in the TIO treatment group changed their smoking status from the previous visit. The subject started smoking between the screening Visit and the visit at Day 84.

Mean smoking pack-years at screening was similar between treatment groups (see table below).

The percentage of current smokers in the UMEC/VI 62.5/25 mcg treatment group was slightly higher compared with the TIO treatment group.

Table 107. Summary of Smoking History and Status (ZEP117115 ITT Population)

Smoking History/Status	UMEC/VI 62.5/25 mcg N=454	TIO 18mcg N=451	Total N=905
Years smoked, n	454	451	905
Mean	37.6	38.2	37.9
SD	10.79	11.50	11.15
Median	39.5	40.0	40.0
Min, Max	12, 70	10, 68	10, 70
Cigarettes/day, n	454	451	905
Mean	23.3	23.1	23.2
SD	10.35	10.34	10.34
Median	20.0	20.0	20.0
Min, Max	6, 80	5, 80	5, 80
Smoking pack-years [a], n	454	451	905
Mean	44.1	44.4	44.2
SD	24.44	25.03	24.72
Median	40.0	40.0	40.0
Min, Max	10, 176	10, 156	10, 176
Smoking status at Screening, n	454	451	905
Current smoker	270 (59)	243 (54)	513 (57)
Former smoker	184 (41)	208 (46)	392 (43)

Data Source: Table 5.19 and Table 5.20
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: A subject was classed as a current smoker at a visit unless they had not smoked in the 6 months prior to that visit.
a. Smoking pack-years=(number of cigarettes smoked per day/20) x number of years smoked.

COPD History

A summary of COPD history is provided in the table below.

Table 108. Summary of COPD History (ZEP117115 ITT Population)

	Number (%) of Subjects		
	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451	Total N=905
Duration of COPD, n	454	451	905
<1 year	21 (5)	17 (4)	38 (4)
≥1 to <5 years	160 (35)	149 (33)	309 (34)
≥5 to <10 years	153 (34)	152 (34)	305 (34)
≥10 to <15 years	90 (20)	81 (18)	171 (19)
≥15 to <20 years	11 (2)	27 (6)	38 (4)
≥20 to <25 years	9 (2)	15 (3)	24 (3)
≥25 years	10 (2)	10 (2)	20 (2)
COPD type [a], n	454	451	905
Chronic bronchitis	344 (76)	325 (72)	669 (74)
Emphysema	293 (65)	297 (66)	590 (65)

Data Source: Table 5.17
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Subjects could select 'chronic bronchitis,' 'emphysema,' or both for COPD type.

In the 12 months prior to screening, the majority of subjects (85% and 82% in the UMEC/VI treatment group and the TIO group, respectively) reported no COPD exacerbations requiring oral/systemic corticosteroids and/or antibiotics or hospitalization. In addition, the percentage of subjects who did not have a COPD exacerbation resulting in hospitalization in the 12 months prior to screening was similar in both treatment groups (93% and 94% in the UMEC/VI treatment group and the TIO group, respectively).

Screening and Baseline Lung Function

Overall, subjects had moderate to very severe airflow obstruction at screening, and lung function parameters were similar across treatment groups (see table below).

Summary of Screening Lung Function Test Results (ZEP117115 ITT Population)

Parameter	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451	Total N=905
Pre-bronchodilator FEV_1 (L), n	454	451	905
Mean	1.261	1.262	1.262
SD	0.4603	0.4773	0.4686
Median	1.205	1.180	1.190
Min, Max	0.35, 2.67	0.35, 3.14	0.35, 3.14
Post-salbutamol FEV_1 (L), n	454	451	905
Mean	1.409	1.414	1.411
SD	0.4854	0.5036	0.4943
Median	1.380	1.350	1.370
Min, Max	0.39, 2.85	0.47, 3.13	0.39, 3.13
Post-ipratropium FEV_1 (L), n [a]	452	449	901
Mean	1.511	1.509	1.510
SD	0.5170	0.5400	0.5283
Median	1.480	1.440	1.460
Min, Max	0.39, 3.15	0.50, 3.25	0.39, 3.25
Pre-bronchodilator FVC (L), n	454	451	905
Mean	2.711	2.750	2.730
SD	0.8405	0.8546	0.8473
Median	2.670	2.670	2.670
Min, Max	0.93, 5.33	0.98, 5.48	0.93, 5.48
Post-salbutamol FVC (L), n	454	451	905
Mean	2.972	3.006	2.989
SD	0.8848	0.8756	0.8799
Median	2.875	2.890	2.890
Min, Max	1.04, 6.29	1.01, 5.78	1.01, 6.29
Post-ipratropium FVC (L), n	452	449	901
Mean	3.153	3.142	3.147
SD	1.2042	0.8899	1.0587
Median	3.045	3.030	3.040
Min, Max	1.00, 19.85	1.22, 5.93	1.00, 19.85
Pre-bronchodilator FEV_1/FVC, n	454	451	905
Mean	46.845	46.229	46.538
SD	10.5482	10.9394	10.7434
Median	46.300	45.800	46.000
Min, Max	18.20, 72.30	16.90, 69.80	16.90, 72.30
Post-salbutamol FEV_1/FVC, n	454	451	905
Mean	47.820	47.396	47.609
SD	10.7846	10.9173	10.8470
Median	47.400	47.100	47.300
Min, Max	15.90, 69.60	19.60, 70.00	15.90, 70.00
Post-salbutamol percent predicted FEV_1 (%), n	454	451	905
Mean	46.2	46.5	46.4
SD	13.02	12.76	12.89
Median	46.8	46.9	46.8
Min, Max	11, 71	17, 73	11, 73
Percent reversibility to salbutamol (%), n	454	451	905
Mean	13.2	13.6	13.4

Parameter	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451	Total N=905
SD	13.36	13.09	13.22
Median	10.7	12.5	11.3
Min, Max	-24, 79	-33, 73	-33, 79
Reversibility to salbutamol (mL), n	454	451	905
Mean	147.5	152.2	149.8
SD	149.92	155.04	152.43
Median	123.5	139.0	133.0
Min, Max	-339, 743	-484, 1016	-484, 1016
Percent reversibility to salbutamol and ipratropium (%), n	452	449	901
Mean	22.1	21.8	22.0
SD	18.29	18.24	18.25
Median	18.9	20.1	19.3
Min, Max	-16, 151	-20, 123	-20, 151
Reversibility to salbutamol and ipratropium (mL), n	452	449	901
Mean	252.5	247.5	250.0
SD	199.24	202.96	201.01
Median	220.0	230.0	230.0
Min, Max	-130, 1590	-230, 1390	-230, 1590

Data Source: Table 5.21

Abbreviations: FEV_1= forced expiratory volume in 1 second; FVC=forced vital capacity; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Post-ipratropium spirometry was conducted following post-albuterol/salbutamol spirometry.

Screening GOLD Stage, Percent of Subjects Demonstrating Bronchodilator Reversibility, and ICS Use

Categorization of post-albuterol/salbutamol percent predicted FEV1 by the Global Initiative for Obstructive Lung Disease (GOLD) stage, reversibility status and ICS use at Screening are summarized in the table below. The majority of subjects were GOLD II and III, approximately 30% were reversible to albuterol/salbutamol, and approximately half were on ICS.

Table 109. Summary of GOLD Stage, Reversibility, and ICS Use (ZEP117115 ITT Population)

	Number (%) of Subjects		
	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451	Total N=905
GOLD Stage (percent predicted FEV_1), n	454	451	905
Stage I (≥80%)	0	0	0
Stage II (≥50% to <80%)	185 (41)	190 (42)	375 (41)
Stage III (≥30% to <50%)	207 (46)	206 (46)	413 (46)
Stage IV (<30%)	62 (14)	55 (12)	117 (13)
Reversible to salbutamol, n [a]	454	451	905
Reversible	124 (27)	142 (31)	266 (29)
Non-reversible	330 (73)	309 (69)	639 (71)
Reversible to salbutamol and ipratropium, n [b]	452	449	901
Reversible	244 (54)	239 (53)	483 (54)
Non-reversible	208 (46)	210 (47)	418 (46)
ICS use, n [c]	454	451	905
ICS users	247 (54)	237 (53)	484 (53)
ICS non-users	207 (46)	214 (47)	421 (47)

Data Source: Table 5.23
Abbreviations: FEV_1=forced expiratory volume in 1 second; GOLD=Global Initiative for Obstructive Lung Disease; ICS=inhaled corticosteroid; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
a. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of albuterol/salbutamol. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-albuterol/salbutamol FEV_1.
b. Reversible was an increase in FEV_1 of ≥12% and ≥200 mL following administration of both albuterol/salbutamol and ipratropium. Non-reversible was an increase in FEV_1 of <200 mL or a ≥200 mL increase that was <12% from pre-albuterol/salbutamol FEV_1.
c. ICS use was defined as those subjects who were currently taking ICS medications at the Screening Visit.

Numbers analysed

A summary of subject populations is presented in the table below. The ITT population was used as the primary population for study population, efficacy, safety and health outcomes analyses.

Table 110. Summary of Subject Populations (ZEP117115 ASE Population)

	Number (%) of Subjects		
Population	UMEC/VI 62.5/25 mcg	TIO 18 mcg	Total
All Subjects Enrolled (ASE)			1191
Screen or Run-in Failures [a]			148 (14)
Randomized	454	451	905
Intent-to-Treat (ITT)	454	451	905
Per Protocol (PP) [b]	430 (95)	428 (95)	858 (95)

Data Source: Table 5.01
Abbreviations: ASE=all subjects enrolled; ITT=intent-to-treat; PP=per protocol; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
ASE: All subjects who were screened and for whom a record exists in the study database.
ITT: All randomized subjects who received at least a single dose of study drug.
PP: All subjects in the ITT population who were not identified as full protocol deviators.
a. Percentage is based on the population that attended the screening visit (N=1053).
b. Percentages are based on the ITT population

Outcomes and estimation

Trough FEV1 at Day 169: Primary Endpoint

The primary efficacy endpoint was trough FEV1 on Day 169. Trough FEV1 on Day 169 was defined as the mean of the FEV1 values obtained 23 and 24 hours after dosing on Day 168 (i.e., at the Week 24 [Day 168] Visit).

A statistically significant improvement of 112 mL in least squares (LS) mean change from baseline trough FEV1 was demonstrated for the UMEC/VI 62.5/25 mcg treatment group compared with the TIO treatment group at Day 169 (see table below).

Table 111. Primary Efficacy Analysis: Trough FEV1 (L) at Day 169 (ZEP117115 ITT Population)

Day 169	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451
n [a]	453	449
n [b]	400	388
LS mean (SE)	1.457 (0.0114)	1.345 (0.0115)
LS mean change (SE)	0.205 (0.0114)	0.093 (0.0115)
UMEC/VI 62.5/25 vs. Column		
Difference		0.112
95% CI		(0.081,0.144)
p-value		<0.001

Data Source: Table 6.05
Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
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 one or more visits.
b. Number of subjects with analyzable data at the current visit.

Weighted Mean FEV1 Over 0 to 6 Hours Postdose at Day 168 (Secondary Endpoint), Day 1, and Day 84

The secondary efficacy endpoint was the 0 to 6 hour postdose weighted mean FEV1 on Day 168.

A statistically significant improvement in LS mean change from baseline in 0 to 6 hour weighted mean FEV1 was demonstrated for the UMEC/VI 62.5/25 mcg treatment group compared with the TIO treatment group at Day 168, as well as at Days 1 and 84 (see table below).

Table 112. Statistical Analysis: 0 to 6 hour Weighted Mean FEV_1 (L) (ZEP117115 ITT Population)

Day	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451
Day 1		
n [a]	454	447
n [b]	449	445
LS mean (SE)	1.459 (0.0072)	1.401 (0.0073)
LS mean change (SE)	0.208 (0.0072)	0.149 (0.0073)
UMEC/VI 62.5/25 vs. Column Difference		0.058
95% CI		(0.038,0.079)
p-value		<0.001
Day 84		
n [a]	454	447
n [b]	418	402
LS mean (SE)	1.522 (0.0114)	1.423 (0.0116)
LS mean change (SE)	0.271 (0.0114)	0.171 (0.0116)
UMEC/VI 62.5/25 vs. Column Difference		0.100
95% CI		(0.068,0.132)
p-value		<0.001
Day 168: Secondary endpoint		
n [a]	454	447
n [b]	404	387
LS mean (SE)	1.527 (0.0124)	1.422 (0.0126)
LS mean change (SE)	0.276 (0.0124)	0.170 (0.0126)
UMEC/VI 62.5/25 vs. Column Difference		0.105
95% CI		(0.071,0.140)
p-value		<0.001

Data Source: Table 6.18

Abbreviations: CI=confidence interval; FEV_1=forced expiratory volume in 1 second; ITT=intent-to-treat; LS=least squares; SE=standard error; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

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 one or more visits.

b. Number of subjects with analyzable data at the current visit.

SGRQ total score

Total and SGRQ domain scores at baseline are provided in Table 6.51. Mean total SGRQ scores at baseline were similar across treatment groups (UMEC/VI 49.03, TIO 48.56).

The results of the analysis of the SGRQ total score at Days 28, 84, and 168 are presented in the table below.

Clinically meaningful reductions from baseline in SGRQ total scores (i.e., <-4; demonstrating an improvement in health-related quality of life [Jones, 2005]) were observed in all treatment groups at Days 28, 84, and 168. The treatment difference for UMEC/VI versus TIO was statistically significant at all assessments.

Table 113. Analysis of SGRQ Total Score (ZEP117115 ITT Population)

Day	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451
Day 28		
n [a]	445	430
n [b]	441	423
LS mean (SE)	42.45 (0.434)	44.55 (0.433)
LS mean change (SE)	-6.17 (0.434)	-4.07 (0.443)
UMEC/VI 62.5/25 vs. Column		
Difference		-2.10
95% CI		(-3.31,-0.88)
p-value		<0.001
Day 84		
n [a]	445	430
n [b]	410	392
LS mean (SE)	41.61 (0.487)	43.69 (0.497)
LS mean change (SE)	-7.02 (0.487)	-4.93 (0.497)
UMEC/VI 62.5/25 vs. Column		
Difference		-2.08
95% CI		(-3.45,-0.72)
p-value		0.003
Day 168		
n [a]	445	430
n [b]	388	374
LS mean (SE)	41.35 (0.538)	43.45 (0.548)
LS mean change (SE)	-7.27 (0.538)	-5.17 (0.548)
UMEC/VI 62.5/25 vs. Column		
Difference		-2.10
95% CI		(-3.61,-0.59)
p-value		0.006

Data Source: Table 6.56

Abbreviations: CI=confidence interval; ITT=intent-to-treat; LS=least squares; SE=standard error; SGRQ=St. George's Respiratory Questionnaire; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

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 one or more visits.

b. Number of subjects with analyzable data at the current visit.

SGRQ Responders

The proportions of subjects who were SGRQ responders (defined as a reduction from baseline in total score of 4 units or more) are presented in the table below (Day 168). The odds of being a responder versus not being a responder were statistically significant for comparisons of UMEC/VI with TIO at all assessments.

Table 114. SGRQ Responder Analysis at Day 168 (ZEP117115 ITT Population)

Day 168	UMEC/VI 62.5/25 mcg N=454	TIO 18 mcg N=451
n	445	430
Responder [a]	237 (53)	196 (46)
Non-responder	208 (47)	234 (54)
UMEC/VI 62.5/25 vs. Column		
Odds Ratio		1.4
95% CI		(1.0, 1.8)
p-value		0.022

Data Source: Table 6.57

Abbreviations: ITT=intent-to-treat; SGRQ=St. George's Respiratory Questionnaire; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: Analysis performed using logistic regression with covariates of treatment, baseline (score prior to dosing on Day 1), smoking status, and center group.

a. Response was defined as a SGRQ total score of 4 units below baseline (score prior to dosing on Day 1) or lower. Non-response was defined as a SGRQ total score higher than 4 units below baseline, or a missing change from baseline in SGRQ total score with no subsequent non-missing scores. For early withdrawals, any visit after withdrawal where SGRQ was supposed to be assessed was classified as non-response. The classification was not derived if the change from baseline in SGRQ total score was missing but subsequent change from baseline SGRQ total scores were present.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The four primary efficacy studies (studies DB2113361, DB2113373, DB2113360 and DB2113374) were all double-blind, randomized, controlled parallel group studies. Two were placebo controlled and two were active controlled studies. 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 to be in serious breach of GCP. However only 20 subjects were recruited in 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 the key secondary endpoint in all the primary efficacy studies. The treatment duration in these studies was 24 weeks. The primary efficacy studies all had at least four treatment groups and there were a number of statistical comparisons planned. Therefore to avoid multiplicity, a heirerchal system of statistical testing was pre-specified for each study.

Two exercise studies (studies DB2114417 and DB2114418) 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 (EET) 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 heirerchal system of statistical testing was pre-specified for each study.

In addition a long-term safety study (study BD2113359) which also collected data on trough FEV1 provides evidence on maintenance of treatment effects over the long-term. This was a double-blind, placebo controlled, randomized study for 52 weeks.

During the evaluation, the Applicant presented an additional 24 week active comparator study (study ZEP117115) comparing UMEC/VI 62.5/25 mcg with TIO 18 mcg.

Efficacy data and additional analyses

Lung function

In studies DB2113361 and DB2113373, a statistically significant and clinically relevant improvement in trough FEV1 was observed for both UMEC/VI 125/25 and UMEC/VI 62.5/25 as compared to placebo (238 mL and 167 mL respectively).

In study DB2113361, a statistically significant and clinically relevant improvement in trough FEV1 was observed for UMEC/VI 125/25 versus VI 25 (114 mL). However a statistically significant but not clinically relevant improvement (defined as an increase of 100 mL or more) in trough FEV1 at D169 was observed for UMEC/VI 125/25 versus UMEC 125 (79 mL). In study DB2113373, a statistically significant but and close to clinically relevant improvement in trough FEV1 was observed for UMEC/VI 62.5 mg versus VI 25 mg (95 mL) but for UMEC/VI 62.5 versus 62.5 mg (52 mL) the results were statistically significant but not clinically relevant. The comparison of both UMEC/VI 125/25 and UMEC/VI 62.5/25 over the monocomponents UMEC and VI alone in studies DB2113361 and DB213373 therefore did not show a statistically significant and also clinically relevant improvement in trough FEV1 consistently, when a change of 100 mL in trough FEV1 is considered as the minimum clinically relevant important difference (MCID). In study DB2113360, a statistically significant but not clinically relevant improvement in trough FEV1 at day 169 was observed for both UMEC/VI 125/25 and UMEC/VI 62.5/25 versus VI 25 (88 mL and 90 mL respectively). In study DB2113374, the improvement in trough FEV1 at D169 that was observed for UMEC/VI 125/25 (37 mL) and for UMEC/VI 62.5/25 (22 mL) versus UMEC 125 was neither statistically significant nor clinically relevant.To summarise, in the four primary efficacy studies (DB2113361, DB2113373, DB2113360 and DB2113374), the improvement in trough FEV1 at D169 for UMEC/VI versus UMEC alone generally failed to meet clinical relevance, when a change of 100 mL in trough FEV1 is considered as the MCID. This suggests that the contribution of VI 25 to the UMEC/VI FDC is not clinically relevant. The Applicant was therefore requested during the evaluation to justify the clinical relevance of adding VI to the UMEC/VI FDC. For the comparison of UMEC/VI versus VI alone, inconsistent results in terms of improvement in trough FEV1 have been observed amongst the studies. The Applicant was also requested to justify the inconsistent results observed.

The Applicant argued that the bronchodilator effect of UMEC/VI was large with improvements in trough FEV1 compared with placebo well in excess of 100 mL, proposed as an MCID for pre-dose trough FEV1 based on comparisons with baseline or placebo. Across the phase III studies, the treatment differences for comparisons of UMEC/VI with components consistently favoured the combination. However, the range of treatment differences was quite large and the contribution of VI to UMEC/VI 62.5/25 was more marked than for UMEC/VI 125/25.

For UMEC/VI 62.5/25, the differences for comparisons with VI were large and ranged from 90 to 132mL in the primary efficacy studies and the exercise studies (see table below). Treatment differences between UMEC/VI 62.5/25 with UMEC 62.5 were also large in the two exercise studies (99 and 124 mL) and more modest in the study DB2113373 (52mL). Overall the consistent benefits and the magnitude of response observed with UMEC/VI 62.5/25 over its components indicate that the addition of both UMEC 62.5 and VI to the combination produced clinically relevant increases in trough FEV1.

Table 115. UMEC/VI 62.5/25: Data Evaluating the Contribution of UMEC 62.5 and VI for Trough FEV1 (mL) (DB2113373, DB2113360, DB2114417 and DB2114418 ITT Populations)

	Time Point	Treatment Difference	95% CI
Contribution of VI 25: Comparison of UMEC/VI 62.5/25 vs. UMEC 62.5			
DB2113373 (primary efficacy)	Week 24	52	17, 87
DB2114417 (exercise)	Week 12	124	67, 181
DB2114418 (exercise)	Week 12	99	41, 157
Contribution of UMEC 62.5: Comparison of UMEC/VI 62.5/25 vs. VI 25			
DB2113373 (primary efficacy)	Week 24	95	60, 130
DB2113360 (primary efficacy)	Week 24	90	39, 142
DB2114417 (exercise)	Week 12	111	62, 161
DB2114418 (exercise)	Week 12	132	81,1 83

Data Source: CSR DB2113373, Table 6.05; CSR DB2113360, Table 6.05; CSR DB2114417, Table 6.18; CSR DB2114418, Table 6.18

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

For UMEC/VI 125/25, the treatment differences for comparisons with VI ranged from 70 to 150 mL in the primary efficacy and exercise studies which were supportive of a clinically relevant effect of adding UMEC 125 to the combination (see table below). Treatment differences between UMEC/VI 125/25 with UMEC 125 ranged from 6 to 79 ml (see table below). These results indicate the added benefit of VI to UMEC/VI 125/25 is more variable. However, the results are still indicative of greater benefit with the combination as all comparisons favoured UMEC/VI 125/25 over UMEC 125.

Table 116. UMEC/VI 125/25: Data Evaluating the Contribution of UMEC 125 and VI for Trough FEV1 (ml) (Individual DB2113361, DB2113360, DB2113374, DB2114417 and DB2114418 ITT Ppopulation)

	Time Point	Treatment Difference	95% CI
Contribution of UMEC 125: Comparison of UMEC 125/25 vs. VI 25			
DB2113361 (primary efficacy)	Week 24	114	81, 148
DB2113360 (primary efficacy)	Week 24	88	36, 140
DB2114417 (exercise)	Week 12	70	19, 120
DB2114418 (exercise)	Week 12	150	98, 201
Contribution of VI 25: Comparison of UMEC/VI 125/25 vs. UMEC 125			
DB2113361 (primary efficacy)	Week 24	79	46, 112
DB2113374 (primary efficacy)	Week 24	37	-12, 87
DB2114417 (exercise)	Week 12	29	-28, 86
DB2114418 (exercise)	Week 12	6	-55, 67
DB2113359 (long-term safety) [a]	Week 52	53	N/A[a]

Data Source: CSR DB2113361, Table 6.05; CSR DB2113360, Table 6.05; CSR DB2113374, Table 6.05; CSR DB2114417, Table 6.18; CSR DB2114418, Table 6.18 CSR DB2113359, Table 52

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

a. This was not a planned treatment comparison for this study. The mean difference has been calculated from the difference of each active treatment from placebo, but no confidence interval has been calculated.

The range of treatment differences for the UMEC/VI 62.5/25 versus UMEC 62.5 alone were 52, 124 and 99 mL. However the last two values are from the two exercise studies (DB2114417 and DB2114418) which have to be accepted with caution as there are unexplained inconsistencies in between the results of the two exercise studies and in between the results of the exercise studies and other pivotal studies. The range of treatment differences for the UMEC/VI 125/25 to UMEC 125 comparisons are 79, 37, 53,

29 and 6 mL. Again the last two values are from the two exercise studies (DB2114417 and DB2114418) which have to be accepted with caution. Excluding the values from the two exercise studies (DB2114417 and DB2114418), the difference for UME/VIC 125/25 to UMEC 125 comparison are in the range of 37, 53 and 79 mL and for UMEC/VI 62.5/25 to UMEC 62.5 it is 52 mL. Three of the four comparisons are less than 53 mL. Moreover the comparator arm here is UMEC alone which is not yet authorised and its clinical experience is limited to clinical studies. Comparing the observed improvement in trough FEV1 to published data on another LAMA/LABA FDC, which is reported to have better effects on trough FEV1 in the range of 70-90 mL when compared with its monocomponents (that are already authorised), the question whether the efficacy of the UMEC/VI FDC is superior (and to a clinically relevant extent) to its monocomponents, especially VI, remained.

The Applicant presented during the evaluation, data from two 3-way cross-over studies (study DB2116133 and study DB2116132). In both studies DB2116133 and DB2116132, a statistically significant improvement in trough FEV1 for UMEC/VI 62.5/25 versus UMEC 62.5 was observed (93 mL and 63 mL respectively). In a subgroup of patients who were responsive to UMEC 62.5 or VI 25 (demonstrated $\geq$ 12% and 200mL increase from baseline in the 6 hours after receiving the first dose of UMEC or VI) in study DB2116133, statistically significant improvement in trough FEV1 with UMEC/VI 62.5/25 versus UMEC 62.5 were observed (83 mL and 133 mL respectively). A potential limitation of the DB2116132 and DB2116133 studies is their relatively short duration (14 days). However, the consistency of effect on trough FEV1 from the second day of treatment through week 24 observed for UMEC/VI and UMEC in the primary efficacy studies (DB2113361, DB2113373, DB2113360 and DB213374), with the exception of the UMEC 125 response in study DB2113374, provides reassurance that the treatment comparisons from studies DB2116132 and DB2116133 are indicative of those obtained over longer time periods. In study DB2113360, a statistically significant but not clinically relevant improvement in trough FEV1 was observed for both UMEC/VI 125/25 and UMEC/VI 62.5/25 versus TIO 18 (88 mL and 90 mL respectively). In study DB2113374, a statistically significant improvement but not clinically relevant improvement in trough FEV1 versus TIO 18 was observed for UMEC/VI 125/25 (74 mL) but not for UMEC/VI 62.5/25 (60 mL). However, in study ZEP117115 submitted during the evaluation, a statistically significant and clinically relevant improvement in trough FEV1 at D169 was observed with UMEC/VI 62.5/25 versus TIO 18 (112 mL).

To summarise, the efficacy data from the four primary efficacy studies (DB2113361, DB2113373, DB2113360 and DB2113374) indicate that both doses of UMEC/VI have a statistically significant and clinically relevant improvement in trough FEV1 as compared to placebo. However the comparison of both doses of UMEC/VI over the UMEC and VI monocomponents alone did not show a clinically relevant change consistently, when a change of 100 mL was considered as the MCID. However it is agreed by the CHMP that this 100 mL MCID s for comparisons of the FDC versus placebo and may not be appropriate for the comparison of a FDC of two bronchodilators (a LAMA and a LABA) against only one bronchodilator (either a LAMA or a LABA). It is also noted that in the recently approved indacaterol/glycopyrronium bromide FDC, for the comparison of the FDC versus the mono-components alone, the reported increase in trough FEV1 was 70 and 90 mL (Bateman et al 2013; Welte et al 2013).

Based on those results, for the UMEC/VI FDC, the only comparison that generally failed to meet consistent clinical relevance was UMEC/VI versus UMEC alone. For the UMEC/VI versus UMEC alone comparison, the values that were determined (without regard to dose of UMEC) in the > 24 week treatment duration studies were 79 mL, 52 mL, 37 mL and 53 mL (studies DB2113361, DB2113373, DB2113374 and DB2113359). The Applicant justified these results based on variability between studies. Furthermore it is accepted that in order to infer on the contribution of each component to the FDC, the only method available is to compare the results of the FDC versus the mono-components alone (e.g. UMEC/VI versus UMEC), derived from parallel arms. This comparison assumes that the

mono-component (e.g.UMEC) will exert the full effect observed in the mono-component alone (UMEC) treatment arm when used in the UMEC/VI FDC as well. However it is accepted that when two bronchodilators are combined together, there will be an overall loss of some effects as a true additive effect of bronchodilation is not seen. This suggests that there will be a loss of contribution from each component of the combination and therefore the comparison made to evaluate the contribution of VI alone (UMEC/VI versus UMEC) is an under-estimate of the true effect of the contribution of VI alone. This justification was considered acceptable by the CHMP. The CHMP also noted that the magnitude of the contribution of VI 25 to UMEC/VI 62.5/25 in at least one of these studies is considered comparable to the indacaterol/glycopryrromium bromide results versus the indacaterol and glycopyrronium bromide monocomponents (90 mL and 70 mL) (Bateman et al 2013; Welte et al 2013).

To determine if the combination of UMEC/VI has a clinically meaningful addition over its mono-components, the CHMP considered that the most valid comparison presented by the Applicant during the evaluation is UMEC/VI versus TIO, as UMEC and VI alone are not yet authorised. For the comparison of UMEC/VI 62.5/25 vs TIO, an improvement in trough FEV1 with the FDC of 112 mL, 90 mL and 60 mL was observed (studies ZEP 117115, DB 2113360 and DB2113374 respectively). Looking at the effects on lung-function from baseline, the variability observed in the comparison UMEC/VI versus TIO in the three studies is due to variations in improvement in trough FEV1 in the TIO arm and not in the UMEC/VI arm. This is also explained by the fact that at maximal bronchodilation (as can be expected with the FDC) the variability is lesser. It should be noted that in study ZEP 117115, a robust study where the sample size was larger than in the other two studies DB2113360 and DB2113374, there were no issues of multiple treatment arms as only UMEC/VI 62.5/25 and TIO were compared. A clinically relevant and statistically significant superiority of UMEC/VI as compared to tiotropium on the primary endpoint of trough FEV1 was observed in study ZEP117115. These results versus TIO support the clinical relevance of lung function changes (improvement in trough FEV1) observed with UMEC/VI FDC.

It was also noted that the effect of UMEC 62.5 alone on lung function, measured as the change in trough FEV1 from baseline, in study DB2113373 was 115 mL which is comparable to the effects of TIO which were 121 mL, 149 mL and 93 mL in studies DB2113360, DB2113374 and ZEP 117115 respectively. Therefore the CHMP concluded that the the clinically meaningful superiority of the UMEC/VI FDC versus TIO is due to the additional contribution of VI.

Taking all the above observations in to consideration, the CHMP concluded that the observed improvements in trough FEV1 for UMEC/VI versus UMEC alone (79 mL, 52 mL, 37 mL and 53 mL) taken together can be considered a clinically meaningful additional contribution.

Symptomatic endpoints

In studies DB2113361 and DB2113373, a statistically significant and clinically relevant improvement in transition dyspnoea index (TDI) score at D168 versus placebo was observed for both UMEC/VI 125/25 and UMEC/VI 62.5/25 (1.0 and 1.2 respectively). In study DB2113360, no statistically significant improvement in TDI score at D168 was observed versus TIO 18 for UMEC/VI 125/25 and UMEC/VI 62.5/25 (0.5 and -0.1 respectively). In study DB2113374, no statistically significant improvement in TDI socre at D168 was observed versus TIO 18 for UMEC/VI 125/25 and UMEC/VI 62.5/25 (0.3 and 0.2 respectively).

In study DB2113361, a statistically significant improvement in TDI score at D168 was observed for UMEC/VI 125/25 versus VI 25 (0.5) and vesus UMEC 125 (0.6). In study DB2113373, no statistically significant improvement in TDI score at D168 was observed for UMEC/VI 62.5/25 verus VI 25 (0.4) and UMEC 62.5 (0.3). In study DB2113360, a statistically significant improvement in TDI score at D168 was observed versus VI 25 for only UMEC/VI 125/25 but not for UMEC/VI 62.5/25 (0.8 and 0.2

respectively). In study DB2113374, no statistically significant improvement in TDI score at D168 was observed versus UMEC 125 for both UMEC/VI 125/25 and UMEC/VI 62.5/25 (0.5 and 0.4 respectively).

The Applicant was requested during the evaluation to explain the failure to demonstrate superiority of the UMEC/VI FDC over the UMEC and VI monocomponents on the symptomatic endpoint of focal TDI score.

Evidence for the superiority of the UMEC/VI over the mono-components alone for symptom improvement is principally based on the consistency of findings of numerical superiority over the monocomponents for mean TDI scores and the proportion of responders based on TDI score across the primary efficacy studies. The Applicant also argued that as TDI focal score is not a true interval scale, the minimum clinically important difference (MCID) between active treatments cannot also be considered as 1 unit of TDI focal score. Any incremental benefit is indicative of a benefit of the FDC. Finally, according to the Applicant, the findings for TDI are in line with the results for the primary lung function measure of trough FEV1 and the secondary lung function measure of 0-6 hour weighted mean FEV1 which favoured the UMEC/VI FDC over its monocomponents. The consistency of findings favouring the UMEC/VI FDC across multiple endpoints and doses indicates the improvements with UMEC/VI are clinically relevant.

Looking at the range of results achieved for UMEC/VI on TDI, it ranges from 1.8 to 2.9 across studies. It must be borne in mind that in these studies the comparator placebo and TIO alone also had large changes in TDI focal score from baseline (1.2 with placebo and 2.2 with TIO). Considering this range, the additional benefit of 0.3 to 0.8 for the comparison of UMEC/VI FDC over its mono-components alone was not considered impressive. It is agreed that UMEC/VI FDC was consistently shown to be better than the mono-components alone, which suggests that this is not a chance observation, but a definite numerical superiority over the mono-components. However only for two comparisons across the 8 possible comparisons is the increase in TDI score greater than 0.5 and for 5 of the 8 comparisons the 95% CI encompasses 0. In the responder analysis presented by the Applicant, as well, for 5 of the 8 comparisons available for UMEC/VI versus its monocomponents, the 95% CI encompassed 1.

The Applicant presented data from other secondary endpoints of time to first COPD exacerbation, SGRQ score and rescue salbutamol use (the only endpoint in which the contribution of VI appeared to be substantial which is not surprising considering that the rescue is also a beta-agonist like VI), all these are generally supportive of the numerical superiority of UMEC/VI over the mono-components and for none of these parameters a consistently statistically significant benefit for UMEC/VI FDC over the mono-components have been shown.

In study ZEP117115, submitted during the evaluation, a clinically meaningful reduction from baseline in SGRQ total score at D168 was observed with UMEC/VI 62.5/25 versus TIO 18 (-2.10, p = 0.006). SGRQ is a disease-specific questionnaire designed to measure the impact of respiratory disease and its treatment on the subject's health-related quality of life. To establish the clinical relevance of the statistical significant results demonstrated on SGRQ in this study, the Applicant presented also a responder analysis. The responder analysis (number of patients who had a -4 change in score from baseline) showed that there were 53% responders in the UMEC/VI 62.5/25 arm as compared to the 46% responders in the TIO 18 arm. Taking in to account the results of the other endpoints measured in this study and which are also supportive, it can be concluded that a significant and clinically relevant superiority of UMEC/VI 62.5/25 as compared to TIO 18 alone has been demonstrated in study ZEP117115. The proportion of patients who responded with at least the MCID in SGRQ score (defined as a decrease of 4 units from baseline) at Week 24 was greater for UMEC/VI (49%) compared with placebo (34%) and each monotherapy component (44% for UMEC and 48% for VI).

As UMEC and VI are not currently authorised, the comparison to TIO is the best measure of clinical relevance. For the comparison of UMEC/VI 62.5/25 over TIO there are two valid comparisons: the

meta-analysis of DB2113360 and DB2113374 and study ZEP117115. In study ZEP117115, a statistically significant improvement of UMEC/VI over TIO on SGRQ (-2.10; p=0.006) was shown. Whereas in the meta-analysis, the improvement with the UMEC/VI FDC was not significant over TIO on TDI (0.1; p=0.817). However it should be noted that the results of ZEP117115 are considered more robust as this study had only two treatment arms which avoids any issues of multiplicity. In the meta-analysis, the data from two separate studies were combined and both these studies had 4 treatment arms.

Taking the overall data available, it is accepted that both doses of UMEC/VI showed a clinically meaningful and statistically significant improvement on symptomatic endpoint (TDI score) as compared to placebo. For the comparison of UMEC/VI versus its mono-components, there is a consistent numerical superiority and the failure to demonstrate statistical significance is probably due to the fact that these studies were not powered to demonstrate a smaller magnitude of improvement.

Of note in the recently approved glycopyrronium/indacaterol FDC, a statistically significant improvement in TDI score was observed over TIO and fluticasone/salmeterol but not over the mono-components glycopyrronium and indacaterol (Bateman et al 2013; Welte et al 2013). The above results of UMEC/VI are along similar lines in that a statistically significant superiority over TIO for SGRQ in study ZEP117115 has been demonstrated but not for TDI in the comparison over the mono-components/Tio in the other studies.

For the comparison of UMEC/VI over monocomponents (UMEC or VI) on the symptomatic endpoint of TDI, the results show only numerical superiority that was not statistically significant. It is accepted that superiority of the FDC over its mono-components is generally difficult to demonstrate on TDI score and that the magnitude of improvement considered clinically relevant for such a comparison is not currently established. Therefore, the consistent demonstration of a numerical superiority (although not statistically significant) of UMEC/VI FDC over the mono-components in change in TDI score and also the responder analysis is considered acceptable evidence to demonstrate efficacy of the UMEC/VI FDC on symptomatic endpoint.

Highest strength

A distinct and clinically relevant improvement in lung function (trough FEV) between UMEC/VI 125/25 and UMEC/VI 62.5/25 was not observed in the four main efficacy studies. The comparison of both UMEC/VI 125/25 and UMEC/VI 62.5/25 over TIO in studies DB2113360 and DB2113374 also did not show a clinically relevant improvement in trough FEV1 at D169, although a consistent numerical improvement was shown. The lack of clinically significant and conclusive dose-response between the two doses of UMEC in the phase III studies does not support the need for two different doses of UMEC in the UMEC/VI FDC. Moreover the lack of data to provide rational guidance on ‘when and who’ should be treated with the higher dose of UMEC does not support the proposed UMEC/VI 125/25 dose. The reasons for the recommendation to use the higher strength FDC in patients responsive to salbutamol were considered unclear. The Applicant was requested during the evaluation to justify the need for a higher strength of UMEC/VI and the population which would benefit from it. A statistically significant treatment by reversibility to salbutamol interaction was observed for the primary efficacy endpoint of trough FEV1 on D169 in the integrated analysis of the primary efficacy studies. The reversible subjects showed greater improvements in bronchodilation as measured by trough FEV1 with UMEC/VI 125/25 mcg (282m L improvement over placebo at D169) compared with UMEC/VI 62.5/25 mcg (225 mL over placebo at D169). The sub-group analysis did show for all the compared parameters that the higher dose UMEC/VI 125/25 was better than the lower dose UMEC/VI 62.5/25. For the primary endpoint, a difference in trough FEV1 of 57ml was seen between the two doses. For the key secondary endpoint of TDI focal scores, the difference was 0.3 between the two doses in the sub-group of reversible patients. This difference was not considered very compelling. Even if the sub-group analysis is considered

appropriate this is only a suggestive inference which must be confirmed in appropriately designed trials. In the current clinical practice, patients are not generally assessed for reversibility before starting treatments and so the higher dose is unlikely to be appropriately used even if it is considered useful in the sub-group. If patients who do not respond adequately are tried a higher dose without testing for reversibility (as is likely to occur in clinical practice), it is likely that two-thirds of patients will receive a higher dose unnecessarily, as only one third are expected to be reversible. A distinct and clinically relevant improvement in lung function or TDI focal score between the two doses of UMEC/VI was not observed. The comparison of both doses of UMEC/VI over active comparator (TIO) also did not show a clinically relevant change on trough FEV1, although a consistent numerical superiority was shown in response. As the clinical benefit of the UMEC/VI 125/25 dose was not considered conclusively demonstrated by the CHMP, the Applicant decided to withdraw this strength during the evaluation. The Applicant's decision to only pursue the UMEC/VI 62.5/25 lower dose was supported by the CHMP.

Long term study

In study DB2113359, treatment with UMEC 125/25 resulted in a lower risk of COPD exacerbation compared with placebo (HR 0.4, CI: 0.3, 0.8, risk reduction 60%). Trough FEV1 at 6 months: UMEC/VI 125/25 demonstrated greater mean LS change from baseline in trough FEV1 compared to placebo at 6 and 12 months (the difference versus placebo was 197 mL and 231 mL respectively).

Exercise endurance studies

In study DB2114417, no statistically significant improvement in exercise endurance time (EET) at week 12 was observed versus placebo for both UMEC/VI 125/25 and UMEC/VI 62.5/25 (32.4 and 32.9 respectively). However in study DB2114418, statistically significant improvement in EET at week 12 was observed versus placebo for both UMEC/VI 125/25 and UMEC/VI 62.5/25 (65.8 and 69.4 respectively).

In study DB2114417, no statistically significant improvement in EET at week 12 was observed versus UMEC 125 and VI 25 for UMEC/VI 125/25 (19.3 and 42.4 respectively). Also no statistically significant improvement in EET at week 12 was observed versus UMEC 62.5 and VI 25 for UMEC/VI 62.5/25 (-4.6 and 31.9 respectively). In study DB2114418, no statistically significant improvement in EET at week 12 was observed versus UMEC 125 and VI 25 for UMEC/VI 125/25 (-8.9 and 35.2 respectively). Also no statistically significant improvement in EET at week 12 was observed versus UMEC 62.5 and VI 25 for UMEC/VI 62.5/25 (44.4 and 38.8 respectively).

In study DB2114417, a statistically significant and clinically relevant improvement in trough FEV1 at Week 12 was observed versus placebo for both UMEC/VI 125/25 and UMEC/VI 62.5/25 (169 mL and 211 mL respectively). In study DB2114418, a statistically significant and clinically relevant improvement in trough FEV1 at Week 12 was observed versus placebo for both UMEC/VI 125/25 and UMEC/VI 62.5/25 (261 mL and 243 mL respectively).

In study DB2114417, no statistically significant nor clinically relevant improvement in trough FEV1 at week 12 was observed for UMEC/VI 125/25 versus UMEC 125 and VI 25 (29 mL and 70 mL respectively). For UMEC/VI 62.5/25, a statistically significant and clinically relevant improvement in trough FEV1 at week 12 was oberserved versus UMEC 62.5 and VI 25 (124 mL and 111 mL respectively).

In study DB2114418, a statistically significant and clinically relevant improvement in trough FEV1 at week 12 was observed for UMEC/VI 125/25 versus VI 25 (150 mL) but not versus UMEC 125 (6 mL). For UMEC/VI 62.5/25, a statistically significant and clinically relevant improvement in trough FEV1 at week 12 was observed versus UMEC 62.5 and VI 25 (99 mL and 132 mL respectively).

The results of the exercise endurance studies DB2114417 and DB2114418 are inconsistent with each other and a number of inconsistencies within the results of each individual study have been observed. In study DB2114417, no statistical significant or clinically relevant improvement in EET at week 12 for both UMEC/VI arms as compared to placebo (first step of the heirerchal testing) was shown and hence this study was a failed study and no inferences can be drawn. In study DB2114418, both doses of UMEC/VI were seen to be statistically and clinically (based on MCID of 45-85 sec) better as compared to placebo. For the comparison of the UMEC/VI FDC against the mono-components alone UMEC and VI, a significant effect on EET was not seen.

In both studies, a statistically significant and clinically relevant improvement in trough FEV1 at week 12 was observerved for both UMEC/VI arms versus placebo. No consistent results have been observed in studies DB2114417 and DB2114418 on trough FEV at week 12 for both UMEC/VI stremgths versus UMEC 125 or 62.5 and VI 25 alone. Due to the difference in populations,the cross-over nature of the studies, their shorter duration (12 weeks) the hitherto unexplained inconsistent results observed on trough FEV1 in these two studies should be interpreted with caution.

Indication

As all the efficacy studies predominantly included subjects from the GOLD category B (88%) and as consequence any conclusions drawn are likely to be applicable to this subset only. However the claimed indication would allow all four GOLD categories to be treated with the combination as a first line treatment. During the evaluation the Applicant was requested to justify the indication claimed. The Applicant did clarify that the 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, 58% subjects were group D and 42% were Group B. A reasonable proportion of subjects across the grade II-IV (GOLD grading based on spirometry) was represented in the studied population. Therefore it was accepted by the CHMP that the results are likely to be relevant to the broad COPD population. The Applicant also presented an analysis of the trough FEV1 effects in patients identified as treatment naïve and compared it with the effects in patients not identified as treatment naïve. The effects in both groups are comparable. A first line indication in COPD was recently granted for the first authorised LAMA/LABA FDC. Therefore a first-line indication is considered acceptable for UMEC/VI FDC.

2.5.4. Conclusions on the clinical efficacy

The results of studies DB2113361 and DB2113373 demonstrated a clinically relevant and statistically significant improvement in both the primary endpoint (trough FEV1) and the secondary endpoint (TDI focal score) with both doses of UMEC/VI as compared to placebo.

However when UMEC/VI was compared to the mono-therapies alone (UMEC or VI) or to TIO alone, the improvement observed on trough FEV1 was quite variable. It is accepted that UMEC/VI 62.5/25 demonstrated a clinically meaningful and statistically significant improvement in lung function (trough FEV1) as compared to TIO, which is the current standard treatment of COPD: 112 mL, 90 mL and 60 mL in studies ZEP 117115, DB 2113360 and DB2113374 respectively. The major extent of variability observed in FEV1 improvement seems to be due to TIO and not to UMEC/VI. As a combination of two bronchodilators will probably be providing maximal bronchodilation, the effects of UMEC/VI are at the top-end of a dose response curve as compared to TIO alone, explaining this observed variability. Furthermore, of the three studies listed above, study ZEP 117115 submitted by the Applicant during the evaluation was considered by the CHMP the most robust as only two treatments were compared as apposed to 4 treatment arms in studies DB2113360 and DB2113374, which may cause issues of multiplicity and balancing at base line.

The comparison of UMEC/VI 62.5/25 versus VI 25 (contribution of UMEC 62.5) was 95 mL and 90 mL in studies DB2113373 and DB2113360, respectively. These improvements in lung function (trough FEV1) were considered a clinically relevant contribution considering that this is an underestimation of the actual contribution of the UMEC/VI FDC. Similarly, although there were some questions raised during the evaluation, the observed improvements in trough FEV1 for UMEC/VI versus UMEC alone (contribution of VI alone) of 79 mL, 52 mL, 37 mL and 53 mL, taken together, were considered by the CHMP as an acceptable additional contribution of clinical relevance.

With regards to improvement in symptomatic endpoints (TDI and SGRQ), three sets of data were relevant to measure the effects of UMEC/VI 62.5/25: study DB2113373, a meta-analysis of studies DB2113360 and DB2113374 and finally, ZEP117115, submitted during the evaluation. In study DB2113373, a numerical superiority in the TDI score of UMEC/VI over UMEC (0.3; p=0.244) or VI (0.4; p=0.117) was observed. In the meta-analysis of studies DB2113360 and DB2113374, a numerical superiority of UMEC/VI over UMEC (0.4; p=0.147), VI (0.2; p=0.475) or TIO (0.1; p=0.817) was shown. In study ZEP117115, a statistically significant superiority in SGRQ of UMEC/VI over TIO (-2.10; p=0.006) was demonstrated. To establish the clinical relevance of the numerical superiority, the Applicant presented a responder analysis (number of patients who had a -4 change in score from baseline). It showed that there were 53% responders in the UMEC/VI arm as compared to the 46% responders in the TIO arm. Taking into account the results of all the endpoints from this study, it can be accepted that a significant and clinically relevant superiority of UMEC/VI as compared to TIO alone was shown. TIO is a well established monotherapy in the treatment of COPD and is the widely used and established LAMA. Based on the results of study ZEP117115, it was concluded by the CHMP that a clinically relevant symptomatic benefit with the UMEC/VI FDC as compared to tiotropium was considered demonstrated.

Taking into account that initially conducted active-controlled studies had smaller sample size and there were multiple treatment arms in those studies which complicated treatment comparisons and inferences, it can be accepted that study ZEP117115 is more reliable. Furthermore, the initially conducted studies did show numerical superiority of UMEC/VI over TIO although not to a clinically relevant extent. Therefore based on the results of all three active controlled studies taken together, it can still be accepted that UMEC/VI has a clinically meaningful better effects on symptomatic endpoint than TIO and the monocomponents alone.

A distinct and clinically relevant improvement in lung function or TDI focal score between the two doses of UMEC/VI was not observed. The comparison of both doses of UMEC/VI over active comparator (TIO) also did not show a clinically relevant change on trough FEV1, although a consistent numerical superiority was shown in response. As the clinical benefit of the UMEC/VI 125/25 dose was not considered conclusively demonstrated by the CHMP, the Applicant decided to withdraw this strength during the evaluation. The Applicant's decision to only pursue the UMEC/VI 62.5/25 lower dose was supported by the CHMP.

2.6. Clinical safety

The four 6-month Primary Efficacy Studies underpin the conclusions about the safety data supporting the use of UMEC/VI in the treatment of COPD. Given the similarity in study design and duration, safety data from the Primary Efficacy Studies were integrated. These integrated data comprise the majority of the safety information and are the focus of the data in this report.

Data on the long-term safety of UMEC/VI 125/25 mcg and UMEC 125 mcg was obtained in the 52-week placebo-controlled long-term safety study (study DB2113359) and is also discussed as this is the only data available on the long-term safety of UMEC/VI.

Additional safety information was obtained from a separate integration of the two 3-month Exercise studies. Additional studies of at least 4 weeks duration were included in an integrated analysis along with the studies described above to provide further safety information on UMEC monotherapy (studies AC4115408 and AC4113589) and VI monotherapy (studies B2C111045, HZC112206, and HZC112207) (All COPD Studies, integration of 14 studies). Only the relevant highlights from these studies will be discussed in the report.

Safety data from clinical pharmacology studies and phase II studies of UMEC and UMEC/VI, studies of VI in COPD and asthma also provide additional safety information. These data did not reveal any new adverse effects or any marked changes in severity, duration or frequency of adverse effects and therefore not discussed in detail in this report.

The safety concerns with UMEC/VI relate to pharmacological effects often associated with muscarinic antagonists and beta agonists. Pharmacologic class effects that have been associated with muscarinic antagonists 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, cough, etc.

Pharmacologic class effects that have been associated with beta agonists include cardiovascular effects (increased heart rate, prolonged QT interval, cardiac rhythm abnormalities, palpitations, and myocardial ischemia), metabolic effects (low potassium and elevated glucose), and tremor. In addition, pneumonia and lower respiratory tract infections (LRTIs) are commonly reported in patients with COPD. The potential for UMEC/VI treatment to result in these effects has been evaluated in the UMEC/VI clinical development program through evaluation of Adverse Events of Special Interest (AESI), 12-lead electrocardiogram (ECG) and Holter assessments, vital signs, and clinical chemistry and hematology laboratory measures.

In pre-clinical studies, gallbladder distension accompanied by myofibre degeneration/regeneration was observed in one 14 day dog study. This was not observed in longer term studies in dog.

Patient exposure

As of 22 August 2012, a total of 2454 COPD subjects were treated with UMEC/VI (62.5/25 or 125/25 mcg) in the UMEC/VI clinical development program. A total of 1124 COPD subjects were treated with UMEC/VI 62.5/25 mcg and 1330 COPD subjects were treated with UMEC/VI 125/25 mcg. In addition, 576 subjects received UMEC 62.5 and 1087 subjects received UMEC 125 mcg, and 2501 subjects received VI 25 mcg compared with 1637 subjects receiving placebo and 423 subjects receiving TIO in all of the integrated COPD studies (14 studies). The summary of subject exposure (all COPD clinical studies ITT population) is provided in the table below.

Table 117. Summary of Subject Exposure (All COPD Clinical Studies ITT Population)

Study Grouping/ Study Number	Number of Subjects							
	Treated [a,b]	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	Placebo	TIO
Primary Efficacy Studies								
DB2113361 DB2113373 DB2113360 DB2113374	4733	842	832	418	629	1034	555	423
Long-term Studies								
DB2113359	562	NA	226	NA	227	NA	109	NA
HZC102871 HZC102970	818	NA	NA	NA	NA	818	NA	NA
Exercise Studies [c,d]								
DB2114417 DB2114418	655	282	272	89	91	140	321	NA
Other Studies Integrated with All COPD Clinical Studies								
AC4115408	206	NA	NA	69	69	NA	68	NA
AC4113589	142	NA	NA	NA	71	NA	71	NA
B2C111045	202	NA	NA	NA	NA	101	101	NA
HZC112206 HZC112207	820	NA	NA	NA	NA	408	412	NA
All COPD Clinical Studies	8138	1124	1330	576	1087	2501	1637	423

Data Source: Table 1.02, Table 1.04, Table 8.19, Table 8.20; CSR DB2113359 Table 7.01; CSR AC4115408 Table 7.01, CSR AC4113589 Table 7.01, and CSR B2C111045 Table 8.01

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

a. Number of subjects treated with at least 1 dose of study drug.
b. Total number of subjects treated in 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.

As seen from the above table, only the primary efficacy studies, long-term safety study and the exercise studies involved use of the combination UMEC/VI.

In the 14 integrated COPD studies, exposure to study drug for >48 weeks was reported for 146 (11%) subjects in the UMEC/VI 125/25 mcg treatment group, 133 (12%) subjects in the UMEC 125 mcg treatment group, and 590 (24%) subjects in the VI 25 mcg treatment group. This exposure came primarily from the long-term safety study (study DB2113359) and the exacerbation studies (studies HZC102871 and HZC102970). The summary of exposure from all COPD studies is presented in the table below.

Table 118. Summary of Exposure (All COPD Clinical Studies ITT Population)

	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Exposure (days)							
n	1637	1124	1330	576	1087	2501	423
Mean	119.3	132.6	157.3	128.3	152.7	185.7	149.5
SD	77.85	49.33	87.71	50.62	97.48	112.78	45.75
Median	110.0	166.0	167.0	165.0	166.0	168.0	167.0
Min.	1	1	1	1	1	1	1
Max.	372	177	371	179	375	384	176
Total Subject-years							
Exposure	534.77	408.05	572.68	202.38	454.36	1271.25	173.09
Range of Exposure							
n	1637	1124	1330	576	1087	2501	423
>4 weeks	1366 (83)	1066 (95)	1262 (95)	548 (95)	954 (88)	2296 (92)	395 (93)
>8 weeks	1251 (76)	1034 (92)	1212 (91)	522 (91)	900 (83)	2153 (86)	382 (90)
>12 weeks	1103 (67)	932 (83)	1129 (85)	450 (78)	827 (76)	2045 (82)	374 (88)
>24 weeks	394 (24)	326 (29)	462 (35)	154 (27)	370 (34)	1147 (46)	116 (27)
>36 weeks	73 (4)	0	160 (12)	0	154 (14)	622 (25)	0
>48 weeks	66 (4)	0	146 (11)	0	133 (12)	590 (24)	0
>52 weeks	19 (1)	0	37 (3)	0	35 (3)	209 (8)	0

Data Source: Table 1.02
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Subjects in cross-over studies were counted once under each treatment received.

Of the data from the COPD studies, the data from the primary efficacy studies are the controlled data and is the most important data to assess the safety profile of UMEC/VI in comparison to placebo and the monocomponents. The summary of exposure in the primary efficacy studies is given in the table below.

Table 119. Summary of Expousre of the Primary Efficacy Studies (DB2113361, DB2113373, DB2113360 and DB2113374 ITT Population)

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

Data Source: Table 1.03
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Only one study provided long-term safety data (beyond 24 weeks) for the combination of UMEC/VI. The summary of exposure in this long-term study DB2113359 is provided in the table below.

Table 120. Summary of Exposure (DB2113359 ITT Population)

	Placebo N=109	UMEC 125 N=227	UMEC/VI 125/25 N=226
Exposure (days), n	109	227	226
Mean	269.4	269.0	285.3
SD	127.54	125.52	114.18
Median	357.0	357.0	357.5
Min, Max	1, 372	1, 375	1, 371
Length of Exposure (days)	**Number (%) of Subjects**		
1-91	18 (17)	30 (13)	19 (8)
92-182	13 (12)	31 (14)	31 (14)
183-273	7 (6)	20 (9)	25 (11)
274-364	52 (48)	111 (49)	114 (50)
>364	19 (17)	35 (15)	37 (16)

Data Source: CSR DB2113359 Table 7.01
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol

Two exercise studies (studies DB2114417 and DB2114418) provide good quality safety data for exposure durations of up to 12 weeks in a controlled setting The summary of exposure in the exercise studies are presented in the table below.

Table 121. Summary of Exposure (DB2114417 and DB2114418 ITT Population)

	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
Exposure (days)						
n	321	282	272	89	91	140
Mean	77.8	80.5	80.4	81.4	77.7	78.5
SD	20.17	16.23	16.50	12.73	21.07	19.39
Median	85.0	85.0	85.0	85.0	85.0	85.0
Min.	1	1	1	11	2	2
Max.	96	103	101	91	95	112
Total Subject-years						
Exposure	68.36	62.13	59.90	19.84	19.35	30.07
Range of Exposure						
n	321	282	272	89	91	140
>4 weeks	302 (94)	273 (97)	262 (96)	88 (99)	85 (93)	133 (95)
>8 weeks	284 (88)	260 (92)	252 (93)	83 (93)	80 (88)	123 (88)
>12 weeks	199 (62)	183 (65)	189 (69)	60 (67)	57 (63)	93 (66)

Data Source: Table 1.04
Abbreviations: ITT=intent-to-treat; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium bromide; VI=vilanterol
Note: Subjects in cross-over studies are counted once under each treatment received.

The data discussed below are from the primary efficacy controlled studies and allows drawing robust inferences on safety.

Adverse events

An overall summary of AE data in the primary efficacy studies is provided in the below table.

Table 122. Summary of Adverse Events (DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

Events	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any on-treatment AEs	264 (48)	447 (53)	438 (53)	216 (52)	348 (55)	518 (50)	208 (49)
Any drug related AEs [a]	31 (6)	52 (6)	62 (7)	34 (8)	62 (10)	68 (7)	23 (5)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study [a]	26 (5)	50 (6)	47 (6)	31 (7)	41 (7)	59 (6)	20 (5)
Any on-treatment SAEs	26 (5)	50 (6)	43 (5)	27 (6)	37 (6)	59 (6)	22 (5)
Any post-treatment SAEs	2 (<1)	5 (<1)	6 (<1)	5 (1)	2 (<1)	7 (<1)	0
Any drug related SAEs [a]	0	1 (<1)	0	1 (<1)	2 (<1)	4 (<1)	0
Any on-treatment or post-treatment fatal AEs	2 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)

Data Source: Table 2.02, Table 2.19, Table 2.36, Table 2.53, Table 2.92, Table 2.107, Table 7.03
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; UMEC=umeclidinium bromide; VI=vilanterol
a. Includes both on-treatment and post-treatment AEs.

Approximately half of the subject population reported at least 1 on-treatment AE across all treatment groups (ranging from 50% to 55% for the UMEC/VI, UMEC, and VI treatment groups, 48% for placebo, and 49% for TIO). The incidences of fatal AEs and other SAEs, as well as AEs leading to permanent discontinuation or withdrawal were low and similar across all UMEC/VI and component treatment groups when compared with placebo and TIO. The incidence of drug-related AEs was low across the UMEC/VI and component treatment groups (UMEC/VI 62.5/25 mcg (6%), UMEC/VI 125/25 mcg (7%), UMEC 62.5 mcg (8%), VI 25 mcg (7%) and the placebo (6%) and TIO (5%) treatment groups.

For the long-term safety study, the summary of adverse events is presented in the below table. The incidence of on- and post-treatment drug-related AEs (12% to 13%) and on-treatment SAEs (6% to 7%) was similar across all treatment groups including placebo. Adverse events leading to permanent discontinuation or withdrawal were reported for 9% and 8%, respectively, in the UMEC 125 mcg and UMEC/VI 125/25 mcg treatment groups compared with 12% for placebo. Fatal AEs were reported for 4 subjects in the UMEC 125 mcg treatment group (2%) and 1 subject (<1%) in the placebo group.

Table 123. Summary of Adverse Events (DB2113359 ITT Population)

Events	Number (%) of Subjects		
	Placebo N=109	UMEC 125 N=227	UMEC/VI 125/25 N=226
Any on-treatment AEs	57 (52)	132 (58)	120 (53)
Any post-treatment AEs	2 (2)	5 (2)	5 (2)
Any drug-related AEs [a]	14 (13)	28 (12)	26 (12)
Any AEs leading to permanent discontinuation of study treatment or withdrawal from study [a]	13 (12)	21 (9)	17 (8)
Any on-treatment SAEs	7 (6)	17 (7)	14 (6)
Any post-treatment SAEs	1 (<1)	3 (1)	0
Any drug-related SAEs [a]	0	1 (<1)	0
Any on-treatment fatal AEs	0	2 (<1)	0
Any post-treatment fatal AEs	1 (<1)	2 (<1)	0

Data Source: CSR DB2113359 Table 7.02
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; UMEC=umeclidinium bromide; VI=vilanterol
a. Includes both on-treatment and post-treatment AEs.

The summary of adverse events from the exercsise studies is presented the table below. This is in line with the previous two sets, where there is comparability of incidences with placebo in all classes of adverse events.

Table 124. Summary of Adverse Events (DB2114417 and DB2114418 ITT Population)

Events	Number (%) of Subjects					
	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
Any on-treatment AEs	105 (33)	92 (33)	98 (36)	18 (20)	36 (40)	45 (32)
Any drug related AEs [a]	14 (4)	12 (4)	10 (4)	0	4 (4)	5 (4)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study [a]	17 (5)	10 (4)	7 (3)	2 (2)	3 (3)	7 (5)
Any on-treatment SAEs	10 (3)	7 (2)	9 (3)	1 (1)	4 (4)	9 (6)
Any post-treatment SAEs	2 (<1)	1 (<1)	2 (<1)	0	0	3 (2)
Any drug related SAEs [a]	0	0	0	0	0	1 (<1)
Any on-treatment or post-treatment fatal AEs	0	1 (<1)	0	0	1 (1)	0

Data Source: Table 2.03, Table 2.20, Table 2.37, Table 2.54, Table 2.93, Table 2.108, Table 7.04
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; UMEC=umeclidinium bromide; VI=vilanterol
a. Includes both on-treatment and post-treatment AEs.

The summary of adverse events in all integrated COPD studies is presented in the table below.

Table 125. Summary of Adverse Events (All COPD Clinical Studies ITT Population)

Events	Placebo N=1637 SY=535	UMEC/VI 62.5/25 N=1124 SY=408	UMEC/VI 125/25 N=1330 SY=573	UMEC 62.5 N=576 SY=202	UMEC 125 N=1087 SY=454	VI 25 N=2501 SY=1271	TIO N=423 SY=173
Incidence	Number (%) of Subjects						
Any on-treatment AEs	698 (43)	539 (48)	656 (49)	261 (45)	562 (52)	1367 (55)	208 (49)
Any AEs leading to permanent discontinuation of study drug or withdrawal from study	97 (6)	60 (5)	71 (5)	34 (6)	68 (6)	151 (6)	20 (5)
Any on-treatment SAEs	65 (4)	57 (5)	66 (5)	29 (5)	61 (6)	225 (9)	22 (5)
Any on-treatment or post-treatment fatal AEs [a]	5 (<1)	6 (<1)	1 (<1)	3 (<1)	7 (<1)	22 (<1)	2 (<1)
Exposure-Adjusted Frequency	Number of Subjects with Events per 1000 Subject-Years						
Any on-treatment AEs	1305.2	1320.9	1145.5	1289.7	1236.9	1075.3	1201.7
Any AEs leading to permanent discontinuation of study drug or withdrawal from study	181.4	147.0	124.0	168.0	149.7	118.8	115.5
Any on-treatment SAEs	121.5	139.7	115.2	143.3	134.3	177.0	127.1
Any on-treatment or post-treatment fatal AEs	9.3	14.7	1.7	14.8	15.4	17.3	11.6

Data Source: Table 2.01, Table 2.04, Table 2.18, Table 2.21, Table 2.35, Table 2.38, Table 2.52, Table 2.55
Abbreviations: AE=adverse event; ITT=intent-to-treat; SAE=serious adverse event; SY=subject-years; UMEC=umeclidinium bromide; VI=vilanterol
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).
a. Additionally, 1 death was reported in the VI 6.25 mcg treatment group of B2C111045 and a post-treatment death was reported after study closure for a subject in the placebo group of DB2113373.

Common adverse events

Results from the primary efficacy studies and the integrated studies will be discussed below under all relevant sections.

In the primary efficacy studies, the most frequently reported AEs were headache (6-10%) and nasopharyngitis (7 to 9%) with similar incidences across all treatment groups including placebo. These are common conditions across the general population. The common AEs (reported by ≥3% of subjects in any treatment group) are summarized in the below table.

Table 126. Summary of On-Treatment Adverse Events Reported by 3% or More of Subjects Within Any Treatment Group

	Number (%) of Subjects						
Preferred Term	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any AE	**264 (48)**	**447 (53)**	**438 (53)**	**216 (52)**	**348 (55)**	**518 (50)**	**208 (49)**
Headache	58 (10)	76 (9)	75 (9)	32 (8)	62 (10)	87 (8)	24 (6)
Nasopharyngitis	48 (9)	74 (9)	77 (9)	29 (7)	43 (7)	98 (9)	33 (8)
Cough	23 (4)	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)
URTI	21 (4)	27 (3)	24 (3)	21 (5)	23 (4)	32 (3)	22 (5)
Back pain	20 (4)	31 (4)	23 (3)	8 (2)	27 (4)	20 (2)	15 (4)
Hypertension	10 (2)	13 (2)	15 (2)	10 (2)	18 (3)	24 (2)	8 (2)
Oropharyngeal pain	9 (2)	17 (2)	17 (2)	6 (1)	12 (2)	29 (3)	5 (1)
COPD	14 (3)	19 (2)	15 (2)	12 (3)	8 (1)	14 (1)	6 (1)
Arthralgia	8 (1)	10 (1)	17 (2)	12 (3)	10 (2)	14 (1)	7 (2)
Dyspnoea	14 (3)	10 (1)	4 (<1)	4 (<1)	11 (2)	20 (2)	3 (<1)

Data Source: Table 2.02, Table 2.59

Abbreviations: AE=adverse event; COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; URTI=upper respiratory tract infection; VI=vilanterol

Cough, pharyngitis, dry mouth, and constipation were the only on-treatment AEs reported by more than 1% of subjects in any UMEC/VI treatment group and having an incidence in any UMEC/VI treatment group greater than 1% over the placebo incidence as shown in the below table.

Table 127. Summary of On-Treatment Adverse Events Reported by More than 1% of Subjects in Any UMEC/VI Group Greater than 1% Over the Placebo Incidence 9DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

	Number (%) of Subjects						
Preferred Term	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Cough	23 (4)	18 (2)	44 (5)	16 (4)	29 (5)	37 (4)	11 (3)
Pharyngitis	2 (<1)	16 (2)	5 (<1)	6 (1)	7 (1)	16 (2)	5 (1)
Dry mouth	2 (<1)	4 (<1)	14 (2)	3 (<1)	5 (<1)	6 (<1)	7 (2)
Constipation	1 (<1)	12 (1)	9 (1)	1 (<1)	7 (1)	6 (<1)	3 (<1)

Data Source: Table 2.172

Abbreviations: ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Of the AEs observed with an incidence less than 1% but greater than placebo, only atrial fibrillation and tachycardia are considered to potentially be related to UMEC/VI. All of these AEs are in the proposed prescribing information for UMEC/VI and could potentially be related to either a LAMA or a LABA.

For the integrated safety data from all COPD clinical studies, the incidence of on-treatment AEs reported by ≥3% is provided in the table below. This was similar across all treatment groups. The most frequently reported AEs were nasopharyngitis and headache, with incidences across all treatment groups ranging from 7% to 10%, and 6% to 10%, respectively (170 to 219 and 139 to 231 subjects, respectively, per 1000 subject-years of exposure).

Table 128. Summary of On-Treatment Adverse Events Reported by 3% or More of Subjects Within Any Treatment Group (All COPD Clinical Study ITT Population)

Preferred Term	Placebo N=1637 SY=535	UMEC/VI 62.5/25 N=1124 SY=408	UMEC/VI 125/25 N=1330 SY=573	UMEC 62.5 N=576 SY=202	UMEC 125 N=1087 SY=454	VI 25 N=2501 SY=1271	TIO N=423 SY=173
Incidence	**Number (%) of Subjects**						
Any AE	**698 (43)**	**539 (48)**	**656 (49)**	**261 (45)**	**562 (52)**	**1367 (55)**	**208 (49)**
Nasopharyngitis	117 (7)	87 (8)	98 (7)	42 (7)	77 (7)	256 (10)	33 (8)
Headache	122 (7)	82 (7)	103 (8)	38 (7)	105 (10)	191 (8)	24 (6)
URTI	39 (2)	31 (3)	30 (2)	23 (4)	33 (3)	132 (5)	22 (5)
Back pain	48 (3)	32 (3)	38 (3)	10 (2)	40 (4)	87 (3)	15 (4)
Cough	41 (3)	21 (2)	58 (4)	16 (3)	42 (4)	77 (3)	11 (3)
COPD	27 (2)	19 (2)	21 (2)	12 (2)	16 (1)	79 (3)	6 (1)
Oropharyngeal pain	21 (1)	19 (2)	18 (1)	6 (1)	16 (1)	66 (3)	5 (1)
Exposure-adjusted frequency	**Number of Subjects with Events per 1000 Subject-Years**						
Any AE	**1305.2**	**1320.9**	**1145.5**	**1289.7**	**1236.9**	**1075.3**	**1201.7**
Nasopharyngitis	218.8	213.2	171.1	207.5	169.5	201.4	190.7
Headache	228.1	201.0	179.9	187.8	231.1	150.2	138.7
URTI	72.9	76.0	52.4	113.6	72.6	103.8	127.1
Back pain	89.8	78.4	66.4	49.4	88.0	68.4	86.7
Cough	76.7	51.5	101.3	79.1	92.4	60.6	63.6
COPD	50.5	46.6	36.7	59.3	35.2	62.1	34.7
Oropharyngeal pain	39.3	46.6	31.4	29.6	35.2	51.9	28.9

Data Source: Table 2.01, Table 2.04, Table 2.58, Table 2.61
Abbreviations: AE=adverse event; COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; SY=subject-years; TIO=tiotropium; UMEC=umeclidinium bromide; URTI=upper respiratory tract infection; VI=vilanterol
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).

In study ZEP117115, headache, cough, pharyngitis and back-pain were the common on-treatment AEs reported by ≥3% of subjects in both treatment groups.

Serious adverse event / deaths / other significant events

All fatal AEs were included together regardless of relation to dose of study drug. A summary of the 46 deaths reported in COPD in relation to study and treatment arms is provided in table below.

Table 129. Summary of Deaths Reported in Studies Conducted in COPD (All ITT Population)

Study Grouping/ Study Number	Number (%) of Subjects						
	Placebo	UMEC/VI 62.5/25	UMEC/VI 125/25	UMEC 62.5	UMEC 125	VI 25	TIO
Primary Efficacy Studies							
DB2113361 DB2113373 DB2113360 DB2113374	2 (<1) [a]	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1) [b]	2 (<1)
Long-term Studies							
DB2113359	1 (<1)	NA	0	NA	4 (2)	NA	NA
HZC102871 HZC102970	NA	NA	NA	NA	NA	13 (2)	NA
Exercise Studies							
DB2114417 DB2114418	0	1 (<1)	0	0	1 (1)	0	NA
Other Studies Integrated with All COPD Clinical Studies							
AC4115408	0	NA	NA	0	0	NA	NA
AC4113589	0	NA	NA	NA	0	NA	NA
B2C111045 [c]	0	NA	NA	NA	NA	0	NA
HZC112206 HZC112207	2 (<1)	NA	NA	NA	NA	3 (<1)	NA
All COPD Clinical Studies	5 (<1)	6 (<1)	1 (<1)	3 (<1)	7 (<1)	22 (<1)	2 (<1)
Other Supportive Studies							
DB2113120	0	NA	NA	NA	NA	NA	NA
AC4113073	0	NA	NA	0	0	NA	0
AC4115321	0	NA	NA	0	0	NA	0
Overall Total (all 17 studies)	5 (<1)	6 (<1)	1 (<1)	3 (<1)	7 (<1)	22 (<1)	2 (<1)

Data Source: Table 2.52, Table 2.53, Table 2.54, Table 8.37, and Table 8.38; CSR DB2113359 Table 7.02; CSR AC4115408 Table 7.02, CSR AC4113589 Table 7.02, CSR B2C111045 Section 8.3.1; CSR DB2113120 Table 8.53, CSR AC4113073 Table 7.02, and CSR AC4115321 Table 8.02

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

Note: On-treatment or post-treatment fatal AEs are reported. Reported number (n) and percentage of subjects is calculated for each study grouping or the individual study, as applicable (see Section 1.2.2).

a. A post-treatment death reported after study closure for a subject in the placebo group of DB2113373 is not included in this table.
b. One fatal event (SAE of sudden death) in DB2113373 was considered related to treatment by the investigator.
c. One death reported in the VI 6.25 mcg treatment group of B2C111045 is not included in this table.

Primary efficacy studies (studies DB2113361, DB2113373, DB2113360 and DB2113374)

Overall, 21 of 4733 subjects (<1%) died during the treatment or post-treatment periods of the Primary Efficacy Studies. An additional post-treatment death related to worsening painful lymph nodes in the neck was reported after study closure for a subject in the placebo group of 1 study, bringing the total number of deaths to 22. The incidence of any fatal AE was similar (<1%) across all treatment groups including UMEC/VI, UMEC, VI, placebo, and TIO.

One fatal AE was considered related to treatment by the investigator, an SAE of sudden death experienced in the VI 25 mcg treatment group in one study (study DB2113373).

Each of the 22 fatalities was adjudicated by an external independent and blinded adjudication committee. The adjudication committee members were asked to indicate the primary cause of death (cardiovascular, respiratory, cancer, other cause of death, or unknown) and further select a subcategory corresponding to the primary cause of death. The incidence of adjudicated fatal serious adverse reports is given in the below table.

Table 130. Adjudicated Fatal Serious Adverse Reports (DB2113361, DB2113373, DB2113360, D2113374 ITT Population)

Fatal Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any fatal serious adverse report	3 (<1)	5 (<1)	1 (<1)	3 (<1)	2 (<1)	6 (<1)	2 (<1)
Cardiovascular – any type	1 (<1)	2 (<1)	0	0	0	2 (<1)	0
Sudden death	1 (<1)	1 (<1)	0	0	0	0	0
Myocardial infarction/ischemic heart disease	0	0	0	0	0	1 (<1)	0
Congestive heart failure	0	0	0	0	0	1 (<1)	0
Stroke – haemorrhagic	0	1 (<1)	0	0	0	0	0
Respiratory – any type	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
COPD exacerbation without evidence of pneumonia	1 (<1)	2 (<1)	0	1 (<1)	0	1 (<1)	0
Cancer – any type	0	0	0	0	2 (<1)	1 (<1)	0
Lung cancer	0	0	0	0	1 (<1)	0	0
Unknown primary	0	0	0	0	0	1 (<1)	0
Other cancer cause	0	0	0	0	1 (<1)	0	0
Other – any type	0	0	1 (<1)	1 (<1)	0	0	1 (<1)
Unknown – any type	1 (<1)	1 (<1)	0	1 (<1)	0	2 (<1)	1 (<1)
Inadequate information	1 (<1)	1 (<1)	0	1 (<1)	0	0	0
Indeterminate	0	0	0	0	0	2 (<1)	1 (<1)

Data Source: Table 2.134
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: One post-treatment death (Subject 2441 from DB2113373, placebo group, PT "lymph node pain") was reported after study closure. This subject was not included in the clinical database and so does not appear in the source tables for fatal AEs (N=22), but the case was adjudicated, so the case does appear in the source tables for adjudicated AEs (N=22). For this reason, the data from the source tables for fatal AEs and adjudicated fatal AEs do not match.

In the primary efficacy studies, the respiratory category had the highest incidence of non-fatal serious adverse reports: 3% in the UMEC/VI 62.5/25 mcg and UMEC 62.5 mcg groups, and 2% in the remaining treatment groups.

Table 131. Adjudicated Non-Fatal Serious Adverse Reports (DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Any serious adverse report	25 (5)	49 (6)	45 (5)	27 (6)	37 (6)	57 (6)	20 (5)
Cardiovascular – any type	2 (<1)	7 (<1)	8 (<1)	4 (<1)	11 (2)	13 (1)	2 (<1)
Myocardial infarction/ischemic heart disease	0	5 (<1)	3 (<1)	3 (<1)	4 (<1)	5 (<1)	0
Congestive heart failure	0	0	0	0	1 (<1)	1 (<1)	0
Stroke – any type	1 (<1)	0	0	0	1 (<1)	2 (<1)	0
Thromboembolic	1 (<1)	0	0	0	0	1 (<1)	0
Indeterminate	0	0	0	0	1 (<1)	1 (<1)	0
Other cardiovascular cause	1 (<1)	2 (<1)	5 (<1)	1 (<1)	5 (<1)	5 (<1)	2 (<1)
Respiratory – any type	13 (2)	27 (3)	20 (2)	13 (3)	10 (2)	22 (2)	9 (2)
COPD exacerbation with evidence of pneumonia	3 (<1)	1 (<1)	2 (<1)	1 (<1)	3 (<1)	1 (<1)	2 (<1)
COPD exacerbation without evidence of pneumonia	9 (2)	21 (2)	13 (2)	12 (3)	4 (<1)	15 (1)	3 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	4 (<1)	2 (<1)	0	1 (<1)	4 (<1)	3 (<1)
Pulmonary embolism	0	0	0	0	1 (<1)	1 (<1)	0
Other respiratory cause	2 (<1)	1 (<1)	3 (<1)	0	1 (<1)	1 (<1)	1 (<1)
Other – any type	10 (2)	16 (2)	20 (2)	12 (3)	16 (3)	22 (2)	9 (2)
Unknown – any type	1 (<1)	0	1 (<1)	0	0	1 (<1)	0
Inadequate information	0	0	1 (<1)	0	0	0	0
Indeterminate	1 (<1)	0	0	0	0	1 (<1)	0

Data Source: Table 2.138
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Long-term study (DB2113359)

A total of 5 on-treatment or post-treatment fatal AEs were reported among 5 subjects in study DB2113359 (see table below) and adjudicated. The incidence of any fatal AE was 2% in the UMEC 125 mcg treatment group and <1% in the placebo treatment group. There were no fatal AEs in the UMEC/VI 125/25 treatment group. None of the fatal AEs were considered related to study drug by the investigator.

Table 132. Adjudicated Fatal Serious Adverse Reports (DB2113359 ITT Population)

Fatal Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any type	1 (<1)	0	4 (2)
Cardiovascular – any type	1 (<1)	0	1 (<1)
Myocardial infarction/ischemic heart disease	1 (<1)	0	0
Congestive heart failure	0	0	1 (<1)
Respiratory – any type	0	0	1 (<1)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)
Cancer – any type	0	0	3 (1)
Unknown primary	0	0	3 (1)
Other – any type	0	0	0
Unknown – any type	0	0	0

Data Source: Table 2.136
Abbreviations: AE=adverse event; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

In the long-term study, 'other causes' had the highest incidence of non-fatal serious adverse reports: 3% in the UMEC/VI 125/25 and UMEC 125 groups and 2% in the placebo group as shown in the table below. Non-fatal 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/VI 125/25 mcg (2% and 1%, respectively) and UMEC 125 mcg groups (2% and 1%, respectively).

Table 133. Adjudicated Non-Fatal Serious Adverse reports (DB2113359 ITT Population)

Serious Adverse Report Category – Subcategory (Where Applicable)	Number (%) of Subjects		
	Placebo N=109	UMEC/VI 125/25 N=226	UMEC 125 N=227
Any serious adverse report	7 (6)	14 (6)	15 (7)
Cardiovascular – any type	2 (2)	3 (1)	3 (1)
Myocardial infarction/ischemic heart disease	1 (<1)	2 (<1)	2 (<1)
Congestive heart failure	1 (<1)	0	0
Other cardiovascular cause	1 (<1)	1 (<1)	1 (<1)
Respiratory – any type	3 (3)	4 (2)	5 (2)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)
COPD exacerbation without evidence of pneumonia	3 (3)	2 (<1)	2 (<1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	1 (<1)	1 (<1)
Other respiratory cause	0	1 (<1)	1 (<1)
Other – any type	2 (2)	7 (3)	7 (3)
Unknown – any type	1 (<1)	0	0
Indeterminate	1 (<1)	0	0

Data Source: Table 2.140
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

Exercise studies (DB2114417 and DB2114418)

A total of 3 on-treatment or post-treatment fatal AEs were reported for 2 subjects: 2 fatal AEs in 1 subject (<1%) on UMEC/VI 62.5/25 mcg and 1 fatal AE in 1 subject on UMEC 125 mcg (see table below). None of the fatal AEs were considered by the investigator to be related to treatment. 1 subject in the UMEC 125 mcg group had a fatal serious adverse report adjudicated as unknown due to inadequate information. Another fatal SAE in the UMEC/VI 62.5/25 mcg group with a PT of "lung neoplasm malignant". This case was adjudicated as associated with cancer.

Table 134. Summary of On-Treatment or Post-Treatment Fatal Adverse Events (DB2114417 and DB2114418 ITT Population)

	Number (%) of Subjects					
Preferred Term	Placebo (N=321)	UMEC/VI 62.5/25 (N=282)	UMEC/VI 125/25 (N=272)	UMEC 62.5 (N=89)	UMEC 125 (N=91)	VI 25 (N=140)
Any event	**0**	**1 (<1)**	**0**	**0**	**1 (1)**	**0**
Death	0	0	0	0	1 (1)	0
Lung neoplasm malignant	0	1 (<1)	0	0	0	0
Metastases to central nervous system	0	1 (<1)	0	0	0	0

Data Source: Table 2.54
Abbreviations: ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

In the exercise studies as well, the 'other causes' category had the highest incidence of non-fatal serious adverse reports: 6% in the VI 25mcg group, 3% in the UMEC 125 mcg group, 2% in the placebo and both UMEC/VI groups, and no reports categorized as "other" in the UMEC 62.5 mcg group as shown in the table below. Non-fatal serious adverse reports were assigned to respiratory causes in 2% of the VI 25 mcg group and ≤1% in the other groups. Less than 1% of subjects in each treatment group had a serious adverse report categorized as cardiovascular in nature: UMEC/VI 125/25 mcg had no reports in this category.

Table 135. Adjudicated Non-Fatal Serious Adverse reports (DB2114417 and DB2114418 ITT Population)

	Number (%) of Subjects					
Serious Adverse Report Category – Subcategory (Where Applicable)	Placebo N=321	UMEC/VI 62.5/25 N=282	UMEC/VI 125/25 N=272	UMEC 62.5 N=89	UMEC 125 N=91	VI 25 N=140
Any serious adverse report	11 (3)	9 (3)	10 (4)	1 (1)	3 (3)	12 (9)
Cardiovascular – any type	3 (<1)	1 (<1)	0	0	0	1 (<1)
Myocardial infarction/ischemic heart disease	0	1 (<1)	0	0	0	1 (<1)
Stroke – any type	1 (<1)	0	0	0	0	0
Haemorrhagic	1 (<1)	0	0	0	0	0
Other cardiovascular cause	2 (<1)	0	0	0	0	0
Respiratory – any type	4 (1)	1 (<1)	4 (1)	1 (1)	0	3 (2)
COPD exacerbation with evidence of pneumonia	0	0	1 (<1)	0	0	0
COPD exacerbation without evidence of pneumonia	4 (1)	0	3 (1)	0	0	2 (1)
Pneumonia/respiratory tract infection without COPD exacerbation	0	0	0	0	0	1 (<1)
Pulmonary embolism	0	0	0	1 (1)	0	0
Other respiratory cause	0	1 (<1)	0	0	0	0
Other – any type	5 (2)	7 (2)	6 (2)	0	3 (3)	8 (6)
Unknown – any type	0	0	0	0	0	0

Data Source: Table 2.139
Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; UMEC=umeclidinium bromide; VI=vilanterol

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Seven subjects died during the study. Two subjects in the UMEC/VI treatment group (cardiac failure and death from unknown reason) and 5 subjects in the TIO group (sudden death, pancreatic

carcinoma, respiratory failure, pulmonary embolism, cardiac failure acute) had on treatment or post-treatment fatal AEs. None of the deaths were judged to be related to the study drug by the reporting investigator.

None of the SAEs reported during the treatment or post-treatment periods were assessed by the investigator as possibly related to the study treatment.

The most frequently occurring on-treatment SAEs in the UMEC/VI group were in the following categories: benign, malignant and unspecified neoplasms (5 subjects, 1%), respiratory, thoracic and mediastinal disorders (2 subjects, <1%), infections and infestations (3 subjects, <1%), hepatobiliary disorders (2 subjects, <1%) and cardiac disorders (1 subject, <1%). For subjects in the TIO group, the most frequently occurring on-treatment SAEs were in the following categories: neoplasms benign, malignant and unspecified (2 subjects, <1%), respiratory, thoracic and mediastinal disorders (4 subjects, <1%), infections and infestations (2 subjects, <1%), hepatobiliary disorders (2 subjects, <1%) and cardiac disorders (2 subjects, <1%).

Adverse events of special interest (AESI)

The main safety concerns with UMEC/VI relate to the known LAMA and LABA effects. Pharmacologic class effects of LAMA 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, cough. Pharmacologic class effects of LABAs include cardiovascular (increased heart rate, prolonged QT interval, cardiac rhythm abnormalities, palpitations, and myocardial ischemia), metabolic (low potassium and elevated glucose), and tremor effects. In addition, pneumonia and lower respiratory tract infections (LRTIs) are commonly reported in patients with COPD. These AESIs were proactively assessed (i.e., defined *a priori*) in the UMEC/VI COPD clinical development program through an evaluation of AESIs.

From the clinical pharmacology studies, the expected incidence is low and therefore only the integrated study results are discussed below.

Cardiovascular AESI and MACE analysis

The below table presents the incidence and exposure-adjusted frequencies of subjects with on treatment cardiovascular AESIs by special interest subgroup for the All COPD Clinical Studies Grouping. Cardiac arrhythmias were the most commonly experienced subgroup of cardiovascular AESIs, followed by hypertension and cardiac ischemia. The incidence of subjects with an event in the cardiac arrhythmias special interest subgroup ranged from 2% (UMEC/VI 62.5/25 mcg and TIO) to 6% (UMEC 125 mcg). Among exposure adjusted frequencies in the cardiac arrhythmias subgroup, placebo and UMEC 125 mcg had the highest frequencies at 131 and 134 subjects, respectively, with events per 1000 subject-years of exposure. Hypertension as a special interest subgroup was reported in 2% to 3% of subjects in each treatment group and cardiac ischemia as a special interest subgroup was reported in ≤2% of subjects in each treatment group. Overall, while differing incidences and exposure-adjusted frequencies of subjects with events were observed for some cardiovascular special interest subgroups across treatment groups, no dose- or treatment-related patterns were identified.

Table 136. Cardiovascular On-Treatment AESI Incidence and Exposure-Adjusted Frequency by Special Interest Subgroup (All COPD Clinical Studies ITT Population)

Cardiovascular AESI Subgroups	Placebo N=1637 SY=535	UMEC/VI 62.5/25 N=1124 SY=408	UMEC/VI 125/25 N=1330 SY=573	UMEC 62.5 N=576 SY=202	UMEC 125 N=1087 SY=454	VI 25 N=2501 SY=1271	TIO N=423 SY=173
Incidence	**Number (%) of Subjects**						
Acquired long QT	0	0	2 (<1)	1 (<1)	0	0	0
Cardiac arrhythmias	70 (4)	28 (2)	47 (4)	22 (4)	61 (6)	101 (4)	9 (2)
Cardiac failure	12 (<1)	11 (<1)	13 (<1)	8 (1)	11 (1)	56 (2)	5 (1)
Cardiac ischaemia	17 (1)	14 (1)	18 (1)	7 (1)	10 (<1)	39 (2)	4 (<1)
Hypertension	35 (2)	25 (2)	30 (2)	13 (2)	30 (3)	63 (3)	11 (3)
Sudden death	0	0	0	0	0	3 (<1)	0
Stroke	4 (<1)	1 (<1)	2 (<1)	1 (<1)	2 (<1)	12 (<1)	1 (<1)
Exposure-adjusted frequency	**Number of Subjects with Events per 1000 Subject-Years**						
Acquired long QT	0	0	3.5	4.9	0	0	0
Cardiac arrhythmias	130.9	68.6	82.1	108.7	134.3	79.4	52.0
Cardiac failure	22.4	27.0	22.7	39.5	24.2	44.1	28.9
Cardiac ischaemia	31.8	34.3	31.4	34.6	22.0	30.7	23.1
Hypertension	65.4	61.3	52.4	64.2	66.0	49.6	63.6
Sudden death	0	0	0	0	0	2.4	0
Stroke	7.5	2.5	3.5	4.9	4.4	9.4	5.8

Data Source: Table 2.112 and Table 2.115
Abbreviations: AE=adverse event; AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; SY=subject-years; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
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).

In the All COPD Clinical Studies Grouping, on-treatment SAEs in the cardiovascular special interest group were reported by ≤1% of subjects in any treatment group within each subgroup see table below. No dose- or treatment-related patterns were identified across treatment groups with respect to cardiovascular special interest SAEs by PT using incidence or exposure-adjusted frequencies.

Table 137. Cardiovascular On-Treatment Serious AESI Incidence by Special Interest Subgroup and Preferred Term (All COPD Clinical Studies ITT Population)

Cardiovascular AESI Group/ Subgroup	Preferred Term	Number (%) of Subjects						
		Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Cardiovascular	Any term	10 (<1)	9 (<1)	11 (<1)	7 (1)	15 (1)	44 (2)	3 (<1)
Acquired long QT	Any term	0	0	0	1 (<1)	0	0	0
	ECG QT prolonged	0	0	0	1 (<1)	0	0	0
Cardiac arrhythmias	Any term	0	1 (<1)	2 (<1)	4 (<1)	5 (<1)	16 (<1)	1 (<1)
	Arrhythmia	0	0	0	0	0	1 (<1)	0
	Atrial fibrillation	0	1 (<1)	0	1 (<1)	2 (<1)	3 (<1)	0
	Bradycardia	0	0	0	1 (<1)	0	0	0
	Bundle branch block left	0	0	0	0	0	1 (<1)	0
	Cardio-respiratory arrest	0	0	0	0	0	1 (<1)	0
	ECG QT prolonged	0	0	0	1 (<1)	0	0	0
	Rhythm idioventricular	0	0	0	0	1 (<1)	0	0
	Sudden cardiac death	0	0	0	0	0	1 (<1)	0
	Sudden death	0	0	0	0	0	1 (<1)	0
	Supraventricular extrasystoles	0	0	0	0	0	1 (<1)	0
	Supraventricular tachycardia	0	0	1 (<1)	0	0	4 (<1)	0
	Syncope	0	0	1 (<1)	1 (<1)	0	4 (<1)	1 (<1)
	Tachycardia	0	0	0	1 (<1)	0	0	0
	Ventricular extrasystoles	0	0	0	0	3 (<1)	0	0
Cardiac failure	Any term	1 (<1)	0	2 (<1)	0	2 (<1)	7 (<1)	0
	Cardiac failure	0	0	0	0	1 (<1)	2 (<1)	0
	Cardiac failure acute	0	0	0	0	0	1 (<1)	0
	Cardiac failure chronic	0	0	1 (<1)	0	0	0	0
	Cardiac failure congestive	1 (<1)	0	0	0	1 (<1)	3 (<1)	0
	Oedema peripheral	0	0	0	0	0	1 (<1)	0
	Pulmonary oedema	0	0	1 (<1)	0	0	0	0

Cardiovascular AESI Group/ Subgroup	Preferred Term	Number (%) of Subjects						
		Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Cardiac ischaemia	Any term	7 (<1)	7 (<1)	6 (<1)	4 (<1)	6 (<1)	15 (<1)	1 (<1)
	Acute coronary syndrome	0	0	1 (<1)	0	0	1 (<1)	0
	Acute myocardial infarction	0	0	1 (<1)	0	2 (<1)	4 (<1)	0
	Angina pectoris	2 (<1)	0	0	0	0	3 (<1)	0
	Angina unstable	0	1 (<1)	0	1 (<1)	2 (<1)	2 (<1)	0
	Cardiac enzymes increased	0	0	0	0	0	1 (<1)	0
	Coronary artery disease	1 (<1)	0	4 (<1)	2 (<1)	1 (<1)	1 (<1)	0
	Cardiac artery stenosis	0	0	0	0	1 (<1)	1 (<1)	0
	ECG T wave inversion	0	1 (<1)	0	0	0	0	0
	Myocardial infarction	3 (<1)	4 (<1)	1 (<1)	0	1 (<1)	2 (<1)	0
	Myocardial ischaemia	1 (<1)	1 (<1)	0	0	0	0	0
	Troponin increased	0	0	0	1 (<1)	0	0	0
	Vascular graft occlusion	0	0	0	0	0	0	1 (<1)
Hypertension	Any term	1 (<1)	0	1 (<1)	0	2 (<1)	2 (<1)	0
	Accelerated hypertension	0	0	0	0	1 (<1)	0	0
	Hypertension	1 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)	0
	Labile blood pressure	0	0	0	0	0	1 (<1)	0
Sudden death	Any term	0	0	0	0	0	3 (<1)	0
	Cardio-respiratory arrest	0	0	0	0	0	1 (<1)	0
	Sudden cardiac death	0	0	0	0	0	1 (<1)	0
	Sudden death	0	0	0	0	0	1 (<1)	0
Stroke	Any term	3 (<1)	1 (<1)	1 (<1)	0	2 (<1)	6 (<1)	1 (<1)
	Carotid artery stenosis	1 (<1)	0	0	0	0	0	0
	Cerebrovascular accident	2 (<1)	0	0	0	2 (<1)	4 (<1)	0
	Haemorrhagic stroke	0	1 (<1)	0	0	0	0	0
	Spinal epidural haemorrhage	0	0	1 (<1)	0	0	0	0
	Transient ischaemic attack	0	0	0	0	0	2 (<1)	1 (<1)

Data Source: Table 2.119
Abbreviations: AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; ECG=electrocardiogram; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

MACE (Major Adverse Cardiac Events)

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
- 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 "myocardial ischaemia" and "acute myocardial infarction"

In the broad-definition MACE analysis (i.e., including non-fatal cardiac ischaemia AESIs), the MACEs were low and similar across treatment groups (1% to 2%). From the narrow-definition MACE analysis, the incidences were low (<1%) in all treatment groups. In both there was a higher exposure-adjusted frequency in the placebo group as compared to the treatment groups.

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AEs in the cardiovascular category were reported in 9 subjects (2%) subjects in the UMEC/VI group and in 7 subjects (2%) in the TIO group. AEs in the pneumonia and lower respiratory tract infection category were reported for 4 subjects (<1%) in the UMEC/VI group and for 6 subjects (1%) in the TIO group. All individual AEs in the AE of special interest were reported in <1% of subjects in both the UMEC/VI and the TIO treatment groups.

Effects on Potassium AESIs

In the All COPD Clinical Studies Grouping, the incidence of events in the effects on potassium AESI group was <1% in all treatment groups including placebo and included the PTs "hypokalaemia" and "hyperkalaemia." The highest exposure-adjusted frequencies of this AESI group and of the 2 PTs included therein (hyperkalemia and hypokalemia) were in subjects treated with placebo.

Effects on Glucose AESIs

In all study groupings, the incidence of post-treatment effects on glucose AESIs was <1% for each treatment. No dose- or treatment-related patterns were identified in either incidence or exposure-adjusted frequencies of subjects with on-treatment effects on glucose AESIs by PT.

Tremor AESIs:

In the All COPD Clinical Studies Grouping, the incidence was <2% in all treatment groups including placebo and the events were described by the PTs "essential tremor" and "tremor. While differences in incidence and exposure-adjusted frequencies of subjects with events were observed for some tremor special interest events across treatment groups, no dose or treatment-related patterns were identified

Urinary Retention AESIs

In the all COPD clinical studies grouping, the incidence of urinary retention AESIs was <1% in all treatment groups including placebo. While there were no events reported in the placebo group, UMEC/VI 125/25 and UMEC 62.5, there were 2, 2 and 3 events respectively in the UMEC/VI 62.5/25, UMEC 125 and VI groups.

Ocular effects AESIs

In all study groupings, the incidence of on-treatment ocular effects AESIs was ≤1% in any treatment group. The exposure-adjusted frequency of these events was highest (24.2 events per 1000 subject years) in the UMEC 125 group, however the exposure-adjusted frequency in the UMEC/VI 125/25 group was lower than in placebo. No dose- or treatment-related patterns were identified in either incidence or exposure-adjusted frequencies of on-treatment AEs in the ocular effects special interest group by PT.

Gall bladder disorders AESIs

In all study groupings, the incidence of on-treatment events in the gallbladder disorders special interest group was ≤1% in any treatment group. No on-treatment gallbladder disorder AESIs were

reported in the UMEC/VI 125/25 mcg or TIO groups. No dose- or treatment-related patterns were identified in either incidence or exposure-adjusted frequencies of on-treatment AEs in this AESI group.

Intestinal obstruction AESIs

In all study groupings, the incidence of on-treatment events in the intestinal obstruction effects special interest group was <1% in any treatment group. No intestinal obstruction on-treatment AESIs were reported in the UMEC/VI 125/25 mcg group, either UMEC dose group or the TIO group. No dose- or treatment-related patterns were identified in either incidence or exposure-adjusted frequencies of subjects with on-treatment AEs in this special interest group.

Anticholinergic effects AESIs

Pharmacologic class effects of LAMAs include anticholinergic effects. The anticholinergic syndrome SMQ was used to search for these events since it contained the most pertinent PTs for a broad evaluation of anticholinergic effects, although the search was not aimed at looking for anticholinergic syndrome, which is an acute effect in the elderly. For this reason, the AESI category has been renamed "anticholinergic effects."

In the All COPD Clinical Studies Grouping, the incidence of on-treatment anticholinergic effects AESIs was 3% to 4% across all groups and the exposure-adjusted frequencies were similar in all groups including placebo and VI.

Table 138. Anticholinergic Effects On-Treatment AESIs by Preferred Term (All COPD Clinical Studies ITT Population)

Anticholinergic Effects AESI	Number (%) of Subjects						
Preferred Term	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423
Any term	47 (3)	30 (3)	51 (4)	18 (3)	39 (4)	100 (4)	15 (4)
Agitation	0	0	0	1 (<1)	0	1 (<1)	0
Ataxia	1 (<1)	0	0	0	0	0	0
Balance disorder	0	1 (<1)	0	0	0	0	0
Confusional state	0	0	1 (<1)	0	0	0	0
Delirium	0	0	0	0	1 (<1)	1 (<1)	0
Dizziness	14 (<1)	11 (<1)	14 (1)	3 (<1)	9 (<1)	35 (1)	2 (<1)
Dry eye	0	0	2 (<1)	0	0	0	1 (<1)
Dry mouth	6 (<1)	5 (<1)	15 (1)	3 (<1)	9 (<1)	9 (<1)	7 (2)
Dysphagia	3 (<1)	1 (<1)	0	0	0	2 (<1)	0
Hallucination, visual	1 (<1)	0	0	0	0	0	0
Loss of consciousness	0	0	0	1 (<1)	2 (<1)	2 (<1)	1 (<1)
Presyncope	0	0	0	1 (<1)	0	5 (<1)	0
Pyrexia	11 (<1)	5 (<1)	16 (1)	3 (<1)	9 (<1)	30 (1)	2 (<1)
Restlessness	1 (<1)	1 (<1)	0	0	1 (<1)	1 (<1)	0
Somnolence	1 (<1)	0	2 (<1)	0	1 (<1)	0	0
Tachycardia	5 (<1)	2 (<1)	4 (<1)	5 (<1)	2 (<1)	11 (<1)	1 (<1)
Thirst	0	0	0	0	0	1 (<1)	0
Urinary retention	0	2 (<1)	0	0	2 (<1)	2 (<1)	1 (<1)
Vision blurred	5 (<1)	1 (<1)	2 (<1)	1 (<1)	4 (<1)	6 (<1)	0
Visual acuity reduced	0	2 (<1)	0	0	1 (<1)	0	0

Data Source: Table 2.112

Abbreviations: AESI=adverse event of special interest; COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

LRTI and Pneumonia AESIs

In the All COPD Clinical Studies Grouping, the highest incidence and exposure-adjusted frequency of LRTI and pneumonia AESIs were among subjects treated with VI 25 mcg (5%, 95 subjects with an event per 1000 subject-years of exposure, respectively) and TIO (4%, 98 subjects with an event per 1000 subject-years of exposure), respectively. Notably, the incidence of these AESIs was the same in the combination UMEC/VI treatment groups and placebo (2%) and the exposure-adjusted frequency were similar as well (54-66 subjects with an event per 1000 subject-years of exposure).

In a subgroup analysis in the primary efficacy studies, based on ICS users at screening, the UMEC/VI 125/25 mcg, UMEC 125 mcg, and TIO treatment groups (2% of subjects in each treatment) reported a higher incidence of the AE term of "pneumonia" compared with placebo (<1%) whereas in the ICS non- users subgroup, the incidence of "pneumonia" was <1% across all treatment groups including placebo and TIO.

QTc interval

No definite dose-related signals were detected from the analysis of ECG and holter monitoring data in the phase III studies.

Withdrawal effects and rebound

In the clinical development programs reported in this application, subjects may have resumed their original maintenance therapy following participation in the studies. Unless other appropriate medications are prescribed upon discontinuation of treatment, the expected effect of withdrawal of study medication is an increase in signs and symptoms of COPD.

The clinical trials in the UMEC/VI development program were designed with a post-treatment follow-up period to evaluate AEs following discontinuation of study treatment and to assess any withdrawal effects. From the available data, there was no indication of withdrawal effects or rebound following discontinuation of UMEC/VI based on evaluation of post-treatment AE reports. However, subjects may have been prescribed alternate COPD medication, which makes interpretation of post treatment AE data difficult.

Laboratory findings

Glucose and potassium

Hypokalaemia and hyperglycaemia are recognised effects with some $beta_2$-agonists and are generally related to systemic exposure. In the primary efficacy studies, pre-dose non-fasting glucose and potassium were collected as part of the clinical laboratory tests at screening, Month 3, and Month 6 and additionally at Month 9 and Month 12 in the UMEC/VI long-term study as well as at the end of each 12-week treatment period in the Exercise Studies. There was no indication from the routine laboratory evaluations in the COPD program of a clinically remarkable treatment-related or dose-related effect on glucose or potassium in the studies with UMEC/VI, UMEC, or VI.

For most patients (≥83%) in the primary efficacy studies, glucose levels remained unchanged or shifted to normal compared with baseline at any time point post-baseline. Over the UMEC/VI, UMEC, and VI treatment groups, shifts to high glucose were reported for 12% to 15% of patients respectively; compared with placebo (14%) and TIO (13%).

The percentage of patients with shifts from baseline to low potassium at any time point post-baseline was <1% to 1% and similar across the UMEC/VI and component treatment groups compared with placebo (2%) and TIO (<1%).

Liver events

Liver chemistry [trial/treatment] stopping and follow up criteria were established a priori as defined below for alanine transaminase (ALT) and bilirubin using the upper limit of normal (ULN) and/or the international normalised ratio (INR):

- ALT ≥3xULN and bilirubin ≥2xULN (>35% direct bilirubin) (or ALT ≥3xULN and INR>1.5, if INR measured)
- ALT ≥8xULN
- ALT ≥5xULN but <8xULN persists for ≥2 weeks
- ALT ≥3xULN if associated with the appearance or worsening of symptoms of hepatitis or hypersensitivity such as fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia
- ALT ≥5xULN but <8xULN and cannot be monitored weekly for >2 weeks.

Any events of possible drug-induced liver injury with hyperbilirubinemia (defined as ALT 3xULN plus bilirubin 2xULN and/or INR>1.5) or Hy's Law events, required immediate study drug cessation and reporting as an SAE.

Three patients, one each in the UMEC 62.5 mcg group, the UMEC 125 mcg group, and the TIO group, were reported by the investigator as having liver events that exceeded the a priori stopping criteria; all were withdrawn from the study. Brief descriptions of these events are provided below. The two patients on UMEC treatments had significant co-existing biliary disease.

Table 139. Summary of AE Abnormal Liver Chemistry by Treatment Group (DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

	Number (%) of Subjects						
Preferred Term	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Alanine aminotransferase increased	1 (<1)	0	1 (<1)	0	1 (<1)	1 (<1)	2 (<1)
Alanine aminotransferase	0	0	0	0	0	1 (<1)	0
Aspartate aminotransferase increased	1 (<1)	0	0	0	0	1 (<1)	1 (<1)
Aspartate aminotransferase	0	0	0	0	0	1 (<1)	0
Bilirubin conjugated increased	0	0	0	1 (<1)	0	0	0
Gamma-glutamyltransferase increased	2 (<1)	4 (<1)	3 (<1)	3 (<1)	2 (<1)	2 (<1)	3 (<1)
Gamma-glutamyltransferase	0	0	0	0	0	1 (<1)	0
Hepatic enzyme increased	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)	2 (<1)	1 (<1)
Liver function test abnormal	0	1 (<1)	1 (<1)	0	0	0	0

Data Source: Table 2.02
Abbreviations: ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Haematology

At any time post-baseline, the majority of patients (≥84%) had hematology values within the normal range or had no change from baseline with respect to the normal range. Analytes for patients with the highest incidence of shifts to high or low relative to the normal range at any time point post-baseline were eosinophils (to low) , lymphocytes (to low), and segmented neutrophils (to high). However, the percentages of patients with abnormal values were generally low (≤13%) and similar across all treatment groups. There were no apparent treatment-related differences in the percentage of patients with shifts between baseline and any time post-baseline relative to the normal range for hematology.

Vital signs

Maximum or minimum post-baseline mean changes from baseline in vital signs were small and similar across all treatment groups (see table below).

Table 140. Maximum or Minimum Post-baseline Change from Baseline in Vital Signs (DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
Maximum Post-baseline[a] Change from Baseline in Systolic BP (mmHg)							
n	555	842	832	418	629	1034	423
Mean (SD)	13.2 (11.80)	13.4 (11.71)	12.8 (11.83)	13.2 (12.86)	14.0 (12.82)	13.0 (12.24)	12.5 (11.64)
Minimum Post-baseline[a] Change from Baseline in Diastolic BP (mmHg)							
n	555	842	832	418	629	1034	423
Mean (SD)	-9.5 (8.21)	-9.1 (8.16)	-9.2 (7.77)	-9.2 (7.97)	-9.7 (8.33)	-9.4 (8.10)	-8.9 (7.58)
Maximum Post-baseline[a] Change from Baseline in Pulse Rate (beats per minute)							

n	555	842	832	418	629	1034	423
Mean (SD)	9.9 (9.22)	9.3 (8.47)	9.8 (9.07)	10.1 (9.21)	9.9 (9.38)	9.6 (8.88)	9.9 (8.71)

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/VI or its individual components (UMEC and VI) on the occurrence of laboratory values outside the normal range. This included serum glucose and potassium and hepatic tests. Except for liver chemistry, the laboratory data were not integrated for the 'all COPD clinical studies grouping'. Overall, no UMEC/VI or VI associated changes in liver function tests of potential clinical concern were observed in the COPD clinical development program. The few episodes of liver abnormalities were generally transient or confounded by concurrent medical problems or concomitant medications.

Safety in special populations

There were no remarkable differences in the pattern of incidence of on-treatment AE, drug-related AEs, SAEs, or AEs leading to permanent discontinuation of study drug or withdrawal across treatments for subjects ≤64 years of age, 65 to 74 years of age, or 75 to 84 years of age compared with the ITT population. However the number of subjects ≥85 years of age was small (n=14 total) and therefore it is difficult to make conclusions on these data.

To ensure that the development and evaluation of UMEC/VI takes into account specific safety aspects related to aging, in accordance with current guidelines [ICH E7, 2012], the incidence of AEs of special concern for the elderly, including CNS (confusion/extrapyramidal) AEs, events related to falling, cardiovascular events, cerebrovascular events and infections were categorized based on age in a post hoc summary (see table below).

There were no remarkable differences in the pattern of incidence of on-treatment AEs related to CNS, falling, cardiovascular, cerebrovascular, or infections across treatments for subjects ≤64 years of age, 65 to 74 years of age, or 75 to 84 years of age compared with the ITT population.

Table 141. Incidence of On-Treatment Adverse Events Categories by Age (DB2113361, DB2113373, DB2113360, DB2113374 ITT Population)

Age subgroup (years)	Number (%) of Subjects						
	Placebo N=555	UMEC/VI 62.5/25 N=842	UMEC/VI 125/25 N=832	UMEC 62.5 N=418	UMEC 125 N=629	VI 25 N=1034	TIO N=423
CNS (confusion/extrapyramidal) AEs							
≤64	0	0	0	0	0	1 (<1)	0
65-74	0	0	0	0	0	0	0
75-84	0	0	1 (1)	0	1 (2)	0	0
≥85	0	0	0	0	0	0	0
AEs Related to Falling							
≤64	7 (2)	6 (1)	10 (2)	10 (5)	10 (3)	15 (3)	9 (4)
65-74	6 (4)	3 (1)	6 (2)	7 (5)	3 (1)	6 (2)	1 (<1)
75-84	0	4 (5)	1 (1)	3 (6)	3 (5)	3 (3)	1 (2)
≥85	0	0	0	0	0	1 (33)	0
Cardiovascular AEs							
≤64	28 (8)	33 (7)	31 (7)	19 (9)	24 (7)	58 (10)	14 (7)
65-74	8 (5)	30 (10)	19 (6)	15 (10)	18 (8)	33 (10)	11 (7)
75-84	4 (8)	7 (8)	5 (6)	7 (14)	10 (16)	4 (4)	2 (4)
≥85	0	0	0	0	0	0	0
Cerebrovascular AEs							
≤64	1 (<1)	0	1 (<1)	0	1 (<1)	2 (<1)	0
65-74	0	0	0	1 (<1)	0	1 (<1)	1 (<1)
75-84	1 (2)	1 (1)	0	0	0	0	0
≥85	0	0	0	0	0	0	0
Infection AEs							
≤64	74 (22)	95 (21)	97 (22)	49 (23)	68 (20)	132 (22)	59 (28)
65-74	35 (21)	75 (25)	75 (24)	36 (24)	57 (25)	90 (26)	41 (26)
75-84	12 (24)	24 (28)	16 (21)	15 (30)	13 (21)	22 (24)	13 (27)
≥85	0	2 (50)	0	1 (33)	1 (100)	0	1 (50)

Data Source: Table 2.151
Abbreviations: AE=adverse event; CNS=central nervous system; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol
Note: Percentages are based on the number of subjects within each subgroup (see Table 1.21).

Safety related to drug-drug interactions and other interactions

UMEC and UMEC/VI were generally well tolerated when coadministered with verapamil, a P-gp inhibitor and moderate CYP450 inhibitor, and VI was well tolerated when coadministered with oral ketoconazole 400 mg, a potent CYP450 inhibitor, as monotherapy and as FF/VI. There were no clinically significant findings with respect to the AE profile, safety laboratory results, vital signs assessments, or 12-lead ECG measures in these studies. There were no effects of ketoconazole on any pharmacodynamic endpoints relative to VI compared with placebo. UMEC was also well tolerated in both healthy and CYP2D6 poor metabolizer populations. No dose adjustment is warranted for UMEC/VI with the use of P-gp inhibitors or inhibitors of CYP2D6. Caution should be exercised when considering the co-administration of UMEC/VI with ketoconazole and other known strong CYP3A4 inhibitors as there is potential for increased cardiovascular adverse effects.

Discontinuation due to adverse events

The subject disposition in the primary efficacy studies, long-term safety study and the exercise studies have been presented under the section of main studies. Given below is the subject disposition which gives information on the discontinuation due to AES from all COPD clinical studies.

A total of 8138 subjects were randomized and included in the ITT population for the All COPD Clinical Studies (see table below). The majority of subjects completed the study (74% to 82% across the UMEC/VI, UMEC, and VI treatment groups versus 74% for placebo and 83% for TIO). Overall, the most common primary reasons for withdrawal were lack of efficacy (4% to 7% across the UMEC/VI and component treatment groups versus. 10% for placebo and 5% for TIO) and AEs (6% to 7% across UMEC/VI and component treatment groups versus 6% for placebo and 5% for TIO). Lack of efficacy due to COPD exacerbation was reported by 4% to 6% of subjects across the UMEC/VI and component treatment groups compared with 7% for the placebo group and 4% for the TIO group.

Table 142. Overall Subject Disposition (All COPD Clinical Studies ITT Population)

	Number (%) of Subjects							
	Placebo N=1637	UMEC/VI 62.5/25 N=1124	UMEC/VI 125/25 N=1330	UMEC 62.5 N=576	UMEC 125 N=1087	VI 25 N=2501	TIO N=423	Total N=8138
Completion status, n (%)								
Completed [a]	1206 (74)	918 (82)	1043 (78)	466 (81)	807 (74)	1868 (75)	353 (83)	6121 (75)
Withdrawn	431 (26)	206 (18)	287 (22)	110 (19)	280 (26)	633 (25)	70 (17)	2017 (25)
Primary/subreason for withdrawal [b], n (%)								
Adverse event	91 (6)	65 (6)	75 (6)	38 (7)	69 (6)	154 (6)	20 (5)	512 (6)
Lack of efficacy	160 (10)	54 (5)	54 (4)	27 (5)	76 (7)	180 (7)	20 (5)	571 (7)
Exacerbation	122 (7)	47 (4)	47 (4)	25 (4)	58 (5)	138 (6)	16 (4)	453 (6)
Protocol deviation	29 (2)	13 (1)	22 (2)	7 (1)	12 (1)	48 (2)	1 (<1)	132 (2)
Subject reached protocol-defined stopping criteria	58 (4)	30 (3)	70 (5)	14 (2)	65 (6)	80 (3)	11 (3)	328 (4)
ECG abnormality	22 (1)	27 (2)	45 (3)	8 (1)	31 (3)	31 (1)	11 (3)	175 (2)
Laboratory abnormality	0	0	0	2 (<1)	1 (<1)	2 (<1)	0	5 (<1)
Holter monitoring abnormality	17 (1)	3 (<1)	28 (2)	4 (<1)	34 (3)	9 (<1)	0	95 (1)
Study closed/terminated	2 (<1)	0	4 (<1)	0	4 (<1)	3 (<1)	0	13 (<1)
Lost to follow-up	12 (<1)	5 (<1)	13 (<1)	0	11 (1)	26 (1)	3 (<1)	70 (<1)
Withdrew consent	65 (4)	39 (3)	49 (4)	24 (4)	43 (4)	119 (5)	15 (4)	354 (4)
Subject relocated	6 (<1)	5 (<1)	8 (<1)	2 (<1)	4 (<1)	6 (<1)	0	31 (<1)
Frequency of visits	6 (<1)	3 (<1)	7 (<1)	3 (<1)	2 (<1)	7 (<1)	2 (<1)	30 (<1)
Burden of procedures	9 (<1)	6 (<1)	7 (<1)	4 (<1)	8 (<1)	6 (<1)	5 (1)	45 (<1)
Other	17 (1)	23 (2)	25 (2)	12 (2)	27 (2)	17 (<1)	8 (2)	129 (2)

Data Source: Table 1.16

Abbreviations: COPD=chronic obstructive pulmonary disease; ITT=intent-to-treat; TIO=tiotropium; UMEC=umeclidinium bromide; VI=vilanterol

Note: In cross-over studies, subjects who completed both treatment periods were counted as a completer under each treatment received and the Total column.

Note: Subjects who withdrew prior to Period 2 were counted as a withdrawal in both their Period 1 treatment and the Total column. Subjects who withdrew during Period 2 were counted as a completer under their Period 1 treatment and as a withdrawal under their Period 2 treatment and the Total column.

Note: Reasons for withdrawal by period (including washout) are presented in Table 1.20.

a. Subjects were considered to have completed the treatment period if they attended the last clinic visit and did not withdraw at the visit.

b. Subjects only recorded 1 primary reason for withdrawal and were not required to indicate sub-reasons. However, subjects could have selected more than 1 sub-reason if appropriate.

However in the long-term safety study, a different trend was seen which may be of some concern.

Table 143. 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.

In the long-term study, a larger proportion of the patients in the treatment groups reached the protocol specified stopping criteria as compared to the placebo group. This is a trend only in the longer-term study. The withdrawals were due to ECG abnormalities or holter abnormalities.

Study ZEP117115

On-treatment AEs leading to permanent discontinuation of study drug or withdrawal were reported for 17 subjects (4%) in the UMEC/VI group and for 10 subjects (2%) in the TIO group.

The most frequently occurring AEs leading to permanent discontinuation of study drug or withdrawal in the UMEC/VI group were in the following categories; neoplasms benign, malignant and unspecified (6 subjects, 1%) and respiratory, thoracic and mediastinal disorders (3 subjects, <1%). For subjects in the TIO group, the most frequently occurring AEs leading to permanent discontinuation of study drug or withdrawal were categorized as respiratory, thoracic and mediastinal disorders (4 subjects, <1%).

In the analyses of change from baseline in vital signs, there were occasional statistically significant comparisons between the UMEC/VI and TIO; however, LS mean changes from baseline were small at all time points, similar across treatment groups, and not considered to be clinically relevant.

2.6.1. Discussion on clinical safety

Overall, the safety profile of UMEC/VI FDC is based on 6,855 patients with COPD. This includes 2,908 patients who received UMEC/VI once daily in the phase III clinical studies, of whom 1,578 patients received the recommended dose of 62.5/25 mcg in 24 week studies (studies DB2113373, DB2113360, DB2113374 and ZEP117115) 1,104 patients received a higher dose of UMEC/VI 125/25 mcg (UMEC at twice the recommended dose and VI at the recommended dose) in the 24 week studies (studies DB2113361, DB2113360, DB2113374) and 226 patients received 125/25 mcg in one 52 week study (study DB2113359).

The overall safety profile of UMEC/VI is in line with the safety profile of other approved LAMAs and LABAs. The common adverse events with an incidence of at least 1% in the UMEC/VI group and a greater incidence (by at least 1%) as compared to placebo or with a plausible causative link to the treatment included cough, pharyngitis, URTI, nasopharyngitis, sinusitis, oropharyngeal pain, dry mouth, UTI, headhache and constipation. Adverse events with incidence less than 1% but with a greater incidence in the UMEC/VI group as compared to placebo include atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles and rash.

The incidence of drug related serious adverse events were low and were comparable across treatment groups. No particular dose-related or treatment related trends were seen for any of the adverse events of special interests. A distinct difference in safety profile between the lower dose and the higher dose of UMEC/VI was not observed from these studies. Similarly no distinctive difference in safety profile between the combination (UMEC/VI) and the monocomponents (UMEC and VI alone) were observed from these studies.

In the overall COPD patient population safety analysis, it was noted that the death rate for VI 25 mcg was 17.3/1,000 patient years, the highest of any treatment group. Most of the fatal events were from studies HZC102871 and HZC102970, in which VI was given with fluticasone furoate (FF). The Applicant was requested during the evaluation to discuss the narratives of these events including whether treatment was with FF/VI or with VI alone. The Applicant clarified that only data from subjects that did not receive FF with VI were included from studies HZC102871 and HZC102970. Data from the VI only arms and/or placebo arms of five FF/VI studies were included in a pooled analysis with 9 studies from the UMEC/VI program (all COPD studies grouping). In this analysis, the death rate in the VI arm was slightly higher at 17.3/1,000 patient years. Studies HZC102871 and HZC102970 from the FF/VI programme were 52 week exacerbation studies. It should be noted that these studies included subjects with more severe COPD which may have contributed to the higher death rate. When VI data from FF/VI studies are removed from the All COPD grouping, the percentage of deaths is similar for each treatment group. Clinical narratives for deaths in the VI 25mcg treatment arm were provided by the Applicant as requested by the CHMP. Listings for all fatal events by treatment groups from the 'All COPD studies' grouping were also provided. From the narratives, the majority of the reported events were those that commonly occur in an older population of subjects or that are frequently seen in subjects with COPD, and were mostly associated with the Cardiac Disorders and Respiratory, Thoracic, and Mediastinal Disorders system organ classes. Smoking-related disease also confounds these cases. All fatal cases apart from one were considered unrelated by the investigator. The Applicant's clarifications were considered acceptable by the CHMP.

The adequacy of the overall evidence on long-term safety for the mono-components and the UMEC/VI FDC especially due to the potential 'safety signals (cardiovascular safety & pneumonia/LRTI) was questioned during the evaluation.

The Applicant clarified during the evaluation that there were no specific exclusion criteria regarding CV risk in the UMEC/VI phase 3 studies. In the primary efficacy studies and the long-term safety study, the majority of subjects (55 - 68% in each treatment group) reported at least one CV risk factor, 18 - 35% reported a current cardiac disorder and approximately half (49%) of the subjects were current smokers. In addition, patients with a past medical history of myocardial infarction (5-6%) and stroke (<1%-4%) were included in the primary efficacy studies and long-term safety study. The prevalence of these cardiovascular conditions were comparable to the estimates reported for COPD patients who were managed for their disease Therefore, patients with significant cardiovascular disease at screening were included in the UMEC/VI studies.

An assessment of UMEC/VI's and UMEC's safety profile according to the presence/absence of cardiovascular risk factors at screening was conducted for the ITT population in the primary efficacy studies and the long-term safety study. The results of this assessment showed that there were no remarkable differences in the overall pattern of adverse events across treatment groups based on the presence/absence of a cardiovascular risk factor at screening, compared with the ITT population in either the primary efficacy studies or the long-term safety study. Occasional differences in the incidence of subjects with CV AESIs across treatment groups were observed, but did not show an additive effect with the combination over individual components or a dose response in subjects with or without a cardiovascular risk factor at screening.

Although a higher number of patient withdrawals were noted in the long-term safety sudy (study DB2113359) due to Holter/ECG abnormalities in the active treatment groups compared with placebo, the majority of the ECG abnormalities leading to withdrawal were unlikely to have lead to more severe cardiovascular events. None of these ECG or Holter withdrawals was associated with any concurrent clinically relevant symptoms. Overall withdrawal rates were similar between the placebo group and active treatments. The results of the long-term safety study are considered applicable to the broad COPD patient population including those with severe cardiovascular disease.

The number of cardiovascular events occurring in the UMEC/VI studies were generally small and moreover do not show any consistent dose-related trends for the two doses of UMEC or UMEC/VI. The reported events have been included in section 4.4 of the SmPC and caution is advised when UMEC/VI is used in patients with severe cardiovascular disease. Cardiovascular and cerebrovascular disorders is included an important potential risk in the RMP. Further data will also be collected in study WWE117397 as described in the RMP. Finally the CHMP also requested the Applicant to conduct a post-authorisation safety study to further further investigate the risk of selected cardiovascular and cerebrovascular events with UMEC/VI compared with TIO in the treatment of COPD (as described in the RMP).

The number of cases of pneumonia and LRTI are comparable across different treatment arms and appears to be in line with the incidence expected in this population. There are no dose-related trends seen for either UMEC or UMEC/VI in this database.

No dose adjustment is warranted for UMEC/VI with the use of P-gp inhibitors or inhibitors of CYP2D6. Caution should be exercised when considering the co-administration of UMEC/VI with ketoconazole and other known strong CYP3A4 inhibitors as there is potential for increased cardiovascular adverse effects.

Only one study (study DB2113359) provided long-term safety data (52 weeks) for UMEC/VI 125/25. This study included 562 patients (ITT population). No long-term safety data on UMEC/VI 62.5/25 was presented. It was highlighted that the long-term safety data presented by the Applicant just about meets the requirements of ICH E1 "The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of non-life threatening conditions". During the evaluation, the Applicant presented additional data from a new long-term safety study (study DB2115362) in Japanese

patients. In this new study, which was open label, 112 subjects were treated during 52 weeks with UMEC/VI 125/25. No new safety concern has been identified in this new study.

The safety data from UMEC/VI 125/25 is only supportive of the long-term safety of UMEC/VI 62.5/25, the only strength pursued by the Applicant. The CHMP concluded that the overall exposure in the UMEC & VI treatment arms as well as the UMEC/VI treatment arms across the studies is in line with ICH E1 requirements. However, long-term safety will be further characterized as part of the post-authorisation safety study that the Applicant was requested to conduct.

In addition study DB2113359 did not include subjects with very severe airflow obstruction. Subjects with post-salbutmaol FEV1 ≥35% to < 80% only were included and moreover these subjects were not required to be symptomatic. In clinical practice, it is likely that the combination of UMEC/VI will be used in a generally more severe and symptomatic population than the population included in the long-term safety study. The Applicant was requested during the evaluation to comment on that. The Applicant acknowledged that the long-term safety study did not include the very severe COPD cases and that the patients included did not need to be symptomatic. However, despite this, a broad range of patients including severe COPD patients have been included in study DB2113359 as seen from the baseline GOLD staging, ICS use and hospitalisation data. The CHMP concluded that the safety data presented does not give rise to any significant safety concerns. It is acknowledged that the long-term study DB2113359 did not include very severe patients of COPD. However it is accepted by the CHMP that this was to ensure safety of the study population in a placebo controlled study. This exclusion of very severe COPD patients is not uncommon in long-term placebo controlled studies. Long-term safety is included as missing information in the RMP and will be further characterized as part of the post-authorisation safety study that the Applicant was requested to conduct.

2.6.2. Conclusions on the clinical safety

The overall safety profile of UMEC/VI is in line with the safety profile of other LAMAs and LABAs.

The incidence of drug related serious adverse events were low and were comparable across treatment groups. No particular dose-related or treatment related trends were seen for any of the adverse events of special interests. A distinct difference in safety profile between the lower dose and the higher dose of UMEC/VI was not observed from these studies. Similarly no distinctive difference in safety profile between the combination (UMEC/VI) and the monocomponents (UMEC and VI alone) were observed from these studies.

Although a higher number of patient withdrawals were noted in the long-term safety sudy due to Holter/ECG abnormalities in the active treatment groups compared with placebo, the majority of the ECG abnormalities leading to withdrawal were unlikely to have lead to more severe cardiovascular events. None of these ECG or Holter withdrawals was associated with any concurrent clinically relevant symptoms. Overall withdrawal rates were similar between the placebo group and active treatments.

The number of cardiovascular events occurring in the UMEC/VI studies were generally small and moreover do not show any consistent dose-related trends for the two doses of UMEC or UMEC/VI. Cardiovascular and cerebrovascular disorders is included an important potential risk in the RMP and a caution statement has been included in the SmPC. Further data will also be collected in study WWE117397 and in the PASS as described in the RMP.

Only one study provided long-term safety data (52 weeks) for UMEC/VI 125/25. No long-term safety data on UMEC/VI 62.5/25 was presented. Long-term safety is included as missing information in RMP and will be further characterized as part of the PASS (as described in the RMP).

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 Laventair 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

Based on the PRAC review of the Risk Management Plan version 4.0, the PRAC considers by consensus that the risk management system for umeclidinium bromide/vilanterol (Laventair) for the maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD) 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**

Table 144. Summary of safety concerns

Summary of safety concerns	
Important identified risks	None identified
Important potential risks	Cardio- and Cerebrovascular Disorders
	Asthma-related intubations and deaths
	Paradoxical bronchospasm (which may be life threatening)
	Narrow angle glaucoma
	Bladder outflow obstruction and urinary retention
Missing information	Safety in pregnancy and lactation
	Off-label use in Asthma (including paediatric use)
	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 VI as a substrate of OATP1B1 and 1B3 c) provide data for UMEC as a substrate for BCRP and BSEP d) provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers e) provide data for UMEC as a substrate of OATP1B1 and 1B3

- **Pharmacovigilance plan**

Table 145. 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)
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 cardiovascular and cerebrovascular events of interest after the start of exposure to UMEC/VI 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: Q1 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 or new users of UMEC compared to COPD patients initiating long-acting bronchodilators. *Secondary:* Quantify the disease burden of COPD and estimate the incidence of cardiovascular 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 Off-label use	Planned	Final report: Q4 2019
Regulatory review of the UMEC/VI 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/Ki in the gut based on free drug concentrations b) providing data for VI as a substrate of OATP1B1 and 1B3 c) providing data for UMEC as a substrate for BCRP and BSEP d) providing further	A series of post authorisation *in vitro* studies will determine the potential for drug-drug interactions.	Planned	Final report: Q1 2015

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)
	clarification for the lack of effect of UMEC in CYP 2D6 poor metaboliser, possibly through studies in microsomes and hepatocytes e) provide data for UMEC as a substrate of OATP1B1 and 1B3			

- **Risk minimisation measures**

Table 146. 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 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 and sympathomimetics, including umeclidinium/vilanterol. Therefore, umeclidinium/vilanterol should be used with caution in patients with severe cardiovascular disease."* 4.8 Undesirable Effects Atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, supraventricular extrasystoles and tachycardia are included in the table of adverse reactions. A patient appropriate equivalent message will also be included in the user tested patient information leaflet.	Not applicable
Asthma-related intubations and death	Prescription-only medication. Proposed text in SmPC: "*4.4 Special warnings and precautions for use* *Asthma* *Umeclidinium/vilanterol should not be used in patients with asthma since it has not been studied in this patient population."*	Not applicable
Paradoxical bronchospasm (which may be life-threatening)	Prescription-only medication. Proposed text in SmPC: "*4.4 Special warnings and precautions for use* *Paradoxical bronchospasm* *As with other inhalation therapies, administration of umeclidinium/vilanterol may produce paradoxical bronchospasm that may be life-threatening. Treatment with umeclidinium/vilanterol should be discontinued immediately if paradoxical bronchospasm occurs and alternative therapy instituted if necessary."*	Not applicable
Narrow angle glaucoma	Prescription-only medication.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Proposed text in SmPC: "*4.4 Special warnings and precautions for use* *Antimuscarinic activity* *Consistent with its antimuscarinic activity, umeclidinium/vilanterol should be used with caution in patients with urinary retention or with narrow-angle glaucoma."*	
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/vilanterol should be used with caution in patients with urinary retention or with narrow-angle glaucoma."*	Not applicable
Safety in Pregnancy and lactation	Prescription-only medication. Proposed text in SmPC: "*4.6 Fertility, pregnancy and lactation* *Pregnancy* *There are no data from the use of umeclidinium/vilanterol in pregnant women. Studies in animals have shown reproductive toxicity at exposures which are not clinically relevant after administration of vilanterol. Umeclidinium/vilanterol 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 or vilanterol are excreted in human milk. However, other beta2-adrenergic agonists are detected in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue umeclidinium/vilanterol therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman."*	Not applicable
Off-label use in	Prescription-only medication.	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Asthma	Proposed text in SmPC: "*4.4 Special warnings and precautions for use* *Asthma* *Umeclidinium bromide/vilanterol should not be used in patients with asthma since it has not been studied in this patient population.*"	
Safety in long-term use	Prescription-only medication.	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. The use of ANORO/LAVENTAIR has not been studied in patients with severe hepatic impairment and should be used with caution.* *5.2 Pharmacokinetic properties* *Hepatic impairment* *Patients with moderate hepatic impairment showed no evidence of an increase in systemic exposure to either umeclidinium or vilanterol (C_{max} and AUC) following administration of umeclidinium/vilanterol with umeclidinium at twice the recommended dose and vilanterol at the recommended dose and no evidence of altered protein binding between patients with moderate hepatic impairment and healthy volunteers. Umeclidinium/vilanterol has not been evaluated in patients with severe hepatic impairment.*"	Not applicable

Following the PRAC advice, the Applicant submitted a revised version 5.0 of the RMP addressing some outstanding points regarding the post-authorisation safety study to quantify the incidence of selected cardiovascular and cerebrovascular events in COPD patients using inhaled UMEC/VI or inhaled UMEC (study 201038).

This included the following updated tables for the Pharmacovigilance 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)

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)
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 cardiovascular and cerebrovascular events of interest after the start of exposure to UMEC/VI 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
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 or new users of UMEC compared to COPD patients initiating long-acting bronchodilators. *Secondary:* Quantify the disease burden of COPD and estimate the incidence of cardiovascular 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 Off-label use	Planned	Final report: Q4 2019
Regulatory review of the UMEC/VI submission has	Additional investigations to provide information to	A series of post authorisation *in vitro*	Planned	Final report:

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)
highlighted additional *in vitro* drug interaction investigations which should be completed. [Category 3]	address: a) binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations b) providing data for VI as a substrate of OATP1B1 and 1B3 c) providing data for UMEC as a substrate for BCRP and BSEP d) providing further clarification for the lack of effect of UMEC in CYP 2D6 poor metaboliser, possibly through studies in microsomes and hepatocytes e) provide data for UMEC as a substrate of OATP1B1 and 1B3	studies will determine the potential for drug-drug interactions.		Q1 2015

The RMP version 5.0 was considered acceptable.

The CHMP endorsed this advice without changes.

The CHMP, having considered the data submitted, was of the opinion that Pharmacovigilance activities in addition to the use of routine Pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
Submission of the final clinical study report for study WWE117397 (observational study to collect safety data reflecting the "real world" experience with UMEC/VI and UMEC alone based on new prescriptions from the distributed network of electronic medical records (EMR) databases	31 December 2019
Submission of the final study report for the following in vitro PK binding studies: • binding of UMEC to microsomes and recalculation of I/Ki in the gut based on free drug concentrations. • provide data for VI as a substrate of OATP1B1 and 1B3.	31 March 2015

Description	Due date
• provide data for UMEC as a substrate for BCRP and BSEP. • provide further clarification for the lack of effect of UMEC in CYP 2D6 poor metabolisers. • provide data for UMEC as a substrate of OATP1B1 and 1B3.	

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

A statistically significant and clinically relevant superiority of UMEC/VI FDC over placebo on both the lung function endpoint of trough FEV1 and the symptomatic endpoint of TDI was shown during the clinical development program. The combination of UMEC/VI has also consistently demonstrated a numerical superiority over the UMEC and VI mono-components alone or TIO alone) in both the primary endpoint of trough FEV1 and key secondary endpoint of TDI focal score.

On the lung function endpoint of trough FEV1, the improvement in UMEC/VI 62.5/25 over VI alone (contribution of UMEC) was 95 mL and 90 mL in studies DB2113373 and DB2113360. This is a clinically relevant and statistically significant improvement. Similarly for the comparison of UMEC/VI 62.5/25 over tiotropium, an improvement in trough FEV of 112 mL, 90 mL and 60ml in studies ZEP 117115, DB 2113360 and DB2113374 respectively were observed. The variability observed in improvements of trough FEV1 of UMEC/VI versus TIO is mainly due to the variability in improvement in trough FEV1 with TIO and overall it is accepted that the improvement in trough FEV observed with UMEC/VI are clinically relevant and significant.

For the comparison of UMEC/VI versus UMEC (contribution of VI), the observed improvements in trough FEV1 were 79 mL, 52 mL, 37 mL and 53 mL (studies DB2113361, DB2113373, DB2113374 and DB2113359 respectively). Taken together these improvements in lung function are considered an acceptable additional contribution that is clinically meaningful in the context of the UMEC/VI FDC as compared to UMEC, VI or TIO alone, which is the standard therapy currently established in clinical practice.

With regards to symptomatic endpoints, for the comparison of UMEC/VI (including both dose strengths) over UMEC alone, VI alone or TIO alone, there are three sets of data on TDI score (the primary symptomatic endpoint) and one set on SGRQ (the secondary symptomatic endpoint). Of the three sets of TDI score available, in one study (DB2113361) statistical significant results for UMEC/VI FDC over UMEC and VI alone was demonstrated. The magnitude of difference for the comparison UMEC/VI against UMEC or VI alone was 0.5 and 0.6 respectively. In a second study (DB2113373), the results for the combination over the mono-components were not statistically significant (these results cannot therefore be considered as conclusive). The numerical difference observed for the comparison

UMEC/VI FDC against UMEC or VI alone was 0.3 and 0.4 respectively. For the third comparison from the meta-analysis of the active controlled studies, none of the comparisons of UMEC/VI 62.25 over UMEC, VI or TIO alone was statistically significant. The difference were 0.4, 02 and 0.1 respectively, while for the comparisons of the higher dose UMEC/VI 125/25 over UMEC, VI or TIO alone, only the comparison over UMEC was statistically significant. The differences observed were 0.8, 0.6 and 0.4 respectively. In the recently submitted study ZEP117115 where UMEC/VI 62.5/25 was compared to TIO, a significant difference was shown for SGRQ (-2.1).

Overall, from 4 sets of symptomatic data, there were two sets that were significant and two that showed numerical superiority for UMEC/VI. Taking into consideration the difficulty to demonstrate a clinically important difference when compared to other active treatments, the Applicant has presented responder analysis for the symptomatic endpoint TDI which shows the clinical relevance of UMEC/VI over the mono-components alone and TIO, the current standard LAMA monotherapy.

Uncertainty in the knowledge about the beneficial effects.

For a new FDC like UMEC/VI, a clinically relevant and statistically significant superiority over the mono-components on both a lung function endpoint and a symptomatic endpoint should be demonstrated.

On the lung function endpoint of trough FEV1, the results observed were mixed, with some comparisons showing a clinically relevant and statistically significant superiority whereas others did not. Taking all the results together for the comparison of UMEC/VI versus UMEC alone (contribution of VI), the improvement in trough FEV1 was somewhere between 45 – 60 mL. In the integrated analysis of primary efficacy studies, the improvement in trough FEV1 for the comparison of UMEC/VI versus UMEC alone was 64 mLs pointed out by the Applicant, these comparisons of calculating the difference between the FDC and one mono-component (to infer on the contribution of the other mono-component), assume that the effect seen in the monotherapy arm will be fully seen in the combination arm, which is not true for combination of two bronchodilators. The effects of a combination of two bronchodilators seem to be less than the additive effects of the two components, which suggest there is a loss of effect of each component when they are used in combination. Therefore this method of estimation gives an under-estimate of the true contribution of VI alone. Also, it has been conclusively shown that UMEC/VI has a clinically relevant and significant benefit over TIO and that cross-study comparisons show that the effects of UMEC alone and TIO alone are comparable. Taking all these factors in to consideration, it can be accepted that the contribution of VI to the combination is significant and clinically relevant.

A distinct and clinically relevant improvement in lung function (trough FEV) between UMEC/VI 125/25 and UMEC/VI 62.5/25 was not observed in the four main efficacy studies. The comparison of both UMEC/VI 125/25 and UMEC/VI 62.5/25 over TIO in studies DB2113360 and DB2113374 also did not show a clinically relevant improvement in trough FEV1 at D169, although a consistent numerical improvement was shown. The lack of clinically significant and conclusive dose-response between the two doses of UMEC in the phase III studies does not support the need for two different doses of UMEC in the UMEC/VI FDC. The Applicant's decision to only pursue the UMEC/VI 62.5/25 lower dose was supported by the CHMP.

Risks

Unfavourable effects

The overall incidence of drug related adverse events in the primary efficacy studies was around 6-10% in all treatment groups. The incidence of drug related adverse events in the treatment groups as compared to the placebo groups was comparable or a small increase in the treatment groups was

noted. There were no drug related SAEs in the placebo group, TIO group and the UMEC/VI 125/25 groups and less than 1% incidence in the other treatment groups.

In the primary efficacy studies, the common adverse events with an incidence of at least 1% in the UMEC/VI group and a greater incidence (by at least 1%) as compared to placebo or with a plausible causative link to the treatment included cough, pharyngitis, URTI, nasopharyngitis, sinusitis, oropharyngeal pain, dry mouth, UTI, headhache and constipation. Adverse events with incidence less than 1% but with a greater incidence in the UMEC/VI group as compared to placebo include atrial fibrillation, supraventricular tachycardia, rhythm idioventricular, tachycardia, supraventricular extrasystoles and rash. All of these AEs which could potentially be related to either a LAMA or a LABA are included in the UMEC/VI SmPC.

In general the number of drug related adverse events was low and the reported events do not give rise to any major safety concerns. A definite dose-related signal was not detected for any significant adverse event in the safety database presented for UMEC/VI. There were numerical differences between treatment groups for many of the adverse events but a definite conclusive trend was not seen for any treatment group on any significant adverse event.

In the recently concluded 24-week active control study ZEP117115, the safety profile of UMEC/VI was comparable to that of TIO and the safety profile was consistent with that determined in earlier studies. There were no new safety signals that were reported from this study.

When the incidence of adverse events in the UMEC/VI was compared to the monocomponents (UMEC or VI) or TIO, there were no significant event that conclusively had a higher incidence in the combination as compared to the monocomponents or TIO. From the available data there is no indication that the safety concerns are higher with UMEC/VI FDC as compared to the mono-components UMEC or VI alone or TIO. But it must be remembered that the mono-components are not yet authorised and hence there is no safety experience with their use in clinical practice.

Uncertainty in the knowledge about the unfavourable effects

The overall available data on long-term safety (>48 weeks) is considered limited. The total long-term exposure (>48 weeks) for UMEC/VI, UMEC and VI are 148, 133 and 590 patients respectively. Given that the COPD population often have other co-morbidities, the potential for long-term significant adverse events is limited for UMEC and VI. In addition, neither UMEC nor VI is currently authrorised. Long-term safety is will be further characterized as part of the PASS (as described in the RMP).

Although a higher number of patient withdrawals were noted in the long-term safety sudy due to Holter/ECG abnormalities in the active treatment groups compared with placebo, the majority of the ECG abnormalities leading to withdrawal were unlikely to have lead to more severe cardiovascular events. None of these ECG or Holter withdrawals was associated with any concurrent clinically relevant symptoms. Overall withdrawal rates were similar between the placebo group and active treatments.

The number of cardiovascular events occurring in the UMEC/VI studies were generally small and moreover do not show any consistent dose-related trends for the two doses of UMEC or UMEC/VI. Cardiovascular and cerebrovascular disorders is included an important potential risk in the RMP and a caution statement has been included in the SmPC. Further data will also be collected in study WWE117397 and in the PASS as described in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

The benefits of UMEC/VI FDC on lung function endpoint (trough FEV1) and symptomatic endpoint (TDI score) have been shown to be consistently, numerically larger than the mono-component treatment arms and also than TIO (marginally on TDI). What level of increase in the lung function endpoint and symptomatic endpoint, over and above what is seen with the treatment of either LAMA or LABA alone, can be considered as clinically relevant, has not yet been establised. However it is important to demonstrate that the UMEC/VI FDC is superior to its mono-components in a convincing and compelling manner to offset the potential additional risk of adding another active substance to the long-term treatment of the patient, although no such increased risk has been seen in the UMEC/VI clinical development so far.

On the symptomatic endpoint, a statistically significant result on TDI was demonstrated for UMEC/VI over the mono-components UMEC or VI alone and in another study a statistically significant result on SGRQ was demonstrated for UMEC/VI over TIO. While in two other studies numerical superiority of the symptomatic endpoint of TDI was shown for UMEC/VI over monocomponents and TIO. Due to the lack of an agreed extent of clinical relevance for an additional effect of a FDC over active comparator, the Applicant has presented responder analysis data, which has consistently demonstrated that the proportion of responders were greater in the UMEC/VI arms as compared to the monotherapy arms. Taking all the above into consideration and the known difficulties with symptomatic endpoints (inconsistent results and not very sensitive to treatment changes), the overall superiority of UMEC/VI over monotherapies on the symptomatic endpoint can be considered as satisfactorily demonstrated.

Similarly for the trough FEV1 endpoint, a statistically significant improvement was generally demonstrated for UMEC/VI over the monocomponents or TIO (except in one study DB 2113374 where comparison against UMEC alone was not significant). For the comparison of FDC over monotherapy, there is no generally agreed extent of benefit on trough FEV1 which is considered clinically significant. However, based on published literature, for the recently approved LAMA/LABA FDC an improvement in trough FEV1 of around 70 - 90 mL was observed. For the UMEC/VI versus VI and UMEC/VI versus TIO comparisons, the improvement in trough FEV1 was generally above 70 mL, whereas for the UMEC/VI versus UMEC comparison (contribution of VI) it was of 79 mL, 52 mL, 37 mL and 53 mL from four different studies. The Applicant presented a justification which showed that this method of determining VI contribution is an under-estimate of the actual effects. Furthermore UMEC/VI has shown clear superiority over TIO on this endpoint and UMEC 62.5 appears to have similar effect size as TIO on this endpoint. Therefore the contribution of VI to the UMEC/VI FDC based on this endpoint can be accepted as clinically relevant.

Neither UMEC nor VI are currently authorised as mono-components. The available data shows that there are no significant safety concerns with the combination as compared to the monocomponents and the reported adverse events are in line with the safety profile of these classes of molecules (LAMAs and LABAs). Long-term safety data on the FDC is currently limited. Long-term safety is included as missing information in RMP and will be further characterized as part of the PASS (as described in the RMP).

Benefit-risk balance

The CHMP considers that the available data provides evidence of clinically relevant effects of the UMEC/VI FDC in the treatment of COPD without any significant increase in safety concerns. Therefore, the overall benefit/risk of Laventair is considered positive.

Discussion on the benefit-risk balance

UMEC/VI has shown a clinically and statistically significant effect on lung function (trough FEV1) and symptomatic endpoint (TDI) as compared to placebo.

The superiority of UMEC/VI over the monocomponents (UMEC or VI) has been demonstrated to an acceptable extent, both on lung function endpoint (trough FEV1) and symptomatic endpoint (TDI score). For the symptomatic endpoint, this is based on a responder analysis. The contribution of UMEC (comparison of UMEC/VI versus VI) to the combination is higher than the contribution of the VI (comparison of UMEC/VI versus UMEC) on trough FEV1 and TDI score.

As compared to TIO, the standard COPD licensed treatment, a clinically significant superior effect on lung function and symptomatic endpoint (TDI or SGRQ) was observed, the latter based on a responder analysis. In a recently concluded active control study (study ZEP117115), a significant and relevant effect of UMEC/VI over current standard LAMA monotherapy of TIO was more convincingly demonstrated.

The available safety data on the UMEC/VI FDC does not raise any particular significant safety concerns. However the overall long-term safety data is considered limited. Long-term safety will be further characterized as part of the PASS (as described in the RMP).

Taking the overall evidence of benefits and risks discussed above, the benefit-risk balance is considered to be positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Laventair in the 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 product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

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

- **Obligation to conduct post-authorisation measures**

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

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 Laventair compared with tiotropium (study 201038), according to a protocol agreed by the PRAC.	By Q3 2024

New Active Substance Status

Based on the review of data, the CHMP considers that the active substance umeclidinium bromide is qualified as a new active substance and acknowledges that the active substance vilanterol trifenatate contained in the medicinal product Laventair qualified as a new active substance at time of submission of this application. On 13 November 2013 a marketing authorisation valid throughout the European Union for Relvar Ellipta was issued, containing vilanterol as trifenatate.

The CHMP considered that Laventair is a new combination of two active substances.

Divergent Position

The undersigned members of CHMP did not agree with the CHMP's opinion recommending the granting of a Marketing Authorisation for Laventair for the following indication:

Laventair is indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The reasons for divergent opinion were as follows:

The totality of evidence available for this novel fixed dose combination is not conclusive. Consequently the benefit-risk is not considered to be favourable at present.

A clinically relevant effect on trough FEV1 has not been demonstrated when the combination is compared to UMEC alone, suggesting that the selected dose of VI may not be appropriate for the combination. Therefore, clinical relevance of adding vilanterol to the combination on pulmonary function is not justified.

Conflicting results have been obtained for symptomatic endpoints. Moreover, there is limited short-term information regarding the impact of the combination on the rate of exacerbations as no specific studies have been carried out by the Applicant.

The overall evidence on long-term safety for the combination is not sufficient, considering that neither of the mono-components are currently marketed.

London, 20 February 2014

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Daniela Melchiorri Concepcion Prieto Yerro