14 September 2017
EMA/25056/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Elebrato Ellipta

International non-proprietary name: fluticasone furoate / umeclidinium / vilanterol

Procedure No. EMEA/H/C/004781/0000

Note

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

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Administrative information

Name of the medicinal product:	Elebrato Ellipta
Applicant:	GlaxoSmithKline Trading Services Currabinny Carrigaline County Cork IRELAND
Active substance:	FLUTICASONE FUROATE / UMECLIDINIUM BROMIDE / VILANTEROL TRIFENATATE
International Non-proprietary Name/Common Name:	fluticasone furoate / umeclidinium / vilanterol
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication(s):	Elebrato Ellipta is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist (for effects on symptom control see section 5.1).
Pharmaceutical form(s):	Inhalation powder, pre-dispensed
Strength(s):	92 µg / 55 µg / 22 µg
Route(s) of administration:	Inhalation use
Packaging:	Blister (alu)
Package size(s):	1 inhaler (14 doses), 1 inhaler (30 doses) and 3 inhalers (3 x 30 doses) (multipack)

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List of abbreviations

ADME	absorption, distribution, metabolism, and excretion
ADR	Adverse Drug Reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
APSD	aerodynamic particle size distribution
AST	aspartate aminotransferase
ATS	American Thoracic Society
BMI	body mass index
BUD	budesonide
CAT	COPD Assessment Test
CDLM	Capacity of Daily Living during the Morning
CEC	Clinical Endpoint Committee
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Database
CRF/eCRF	case report form/electronic case report form
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
ECG	electrocardiogram
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERS	European Respiratory Society
EXACT-RS	Exacerbations of Chronic Pulmonary Disease Tool
EXT	Extension (Population)
FDA	Food and Drug Administration
FEV_1	forced expiratory volume in one second
FF	fluticasone furoate
FOR	formoterol
FP	fluticasone propionate
FVC	forced vital capacity
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GSK	GlaxoSmithKline
HPA	hypothalamic-pituitary-adrenal
HR	hazard ratio
HRQoL	health-related quality of life
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroid
IND	Investigational New Drug
ITT	Intent-to-Treat (Population)
LABA	long-acting $beta_2$ receptor agonist
LAMA	long-acting muscarinic receptor antagonist
LRTI	lower respiratory tract infection
LS	least square
MACE	Major Adverse Cardiac Event
MCID	minimum clinically important difference

MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
mMRC	modified Medical Research Council
NHANES	National Health and Nutrition Examination Survey
PD	pharmacodynamic
PK	pharmacokinetic
PRAC	Pharmacovigilance Risk Assessment Committee
PRO	patient-reported outcomes
PT	Preferred Term
QTc(F)	corrected QT interval using Friedicia's formula
RAP	Reporting and Analysis Plan
RMP	Risk Management Plan
SAE	serious adverse event
SALM	salmeterol
SAR	serious adverse report
SD	standard deviation
SDAP	Summary Document Analysis Plan
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
SGRQ-C	St. George's Respiratory Questionnaire for COPD
SMQs	Standardised MedDRA Queries
SS	Serial Spirometry (Population)
TDI	Transitional Dyspnoea Index
TDI-SAC	Transitional Dysponea Index-self administered computerised version
TIO	tiotropium
UMEC	umeclidinium bromide
URTI	upper respiratory tract infection
VI	vilanterol
WM	weighted mean

1. Background information on the procedure

1.1. Submission of the dossier

The applicant GlaxoSmithKline Trading Services submitted on 2 December 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Elebrato Ellipta, 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 17 December 2015.

The applicant applied for the following indication:

Elebrato Ellipta is indicated as a maintenance treatment to prevent and relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for fixed combination products.

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).

Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advice from the CHMP on 21 March 2013 and 24 October 2013. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: David Lyons Co-Rapporteur: Harald Enzmann

- The application was received by the EMA on 2 December 2016.
- The procedure started on 23 December 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 March 2017. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 March 2017. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 24 March 2017.

- During the meeting on 21 April 2017, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 18 May 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 28 June 2017.
- During the PRAC meeting on 9 July 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 22 July 2017, the CHMP agreed on a list of outstanding issues to be sent to the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 11 August 2017
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 30 August 2017.
- During the meeting on 14 September 2017, 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 Elebrato Ellipta on 14 September 2017.

2. Scientific discussion

2.1.1. Disease or condition

Elebrato Ellipta is indicated as maintenance treatment to prevent and relieve symptoms associated with chronic obstructive pulmonary disease (COPD).

2.1.1. Epidemiology

COPD is strongly linked to tobacco smoking, particularly cigarette smoking and is a male predominant condition, in COPD clinical trials in developed countries generally about two thirds of included patients are male and for both males and females the average age tends to be in the early sixties. In poor countries the male predominance is not as marked as women may develop COPD as a result of cooking over open fires. The prevalence is quite variable on a local basis with higher prevalence linked to lower affluence and social status. Screening would be possible by mass measurement of lung function which is cheap, easy, and non-invasive, but is not done in practice. There have been no substantial trials of the value of screening for COPD. Tobacco smoking cessation or non/never smoking is an effective measure and societal efforts have been made in that direction rather than into screening programmes.

2.1.2. Biologic features

COPD is characterised by cough, excess sputum production, airways narrowing leading to air trapping and hyperinflation of the chest, and loss of lung tissue (emphysema). In its more advanced stages it causes strain and eventually failure, of the cardiac right ventricle.

2.1.3. Clinical presentation, diagnosis and stage / prognosis

Clinical presentation tends to be as cough and breathlessness in a heavy cigarette smoker and is unusual before approximately the age of forty.

Exacerbations in COPD are driven by episodes of acute inflammation, usually following a viral or bacterial infection. While current maintenance therapies prevent exacerbations in many COPD patients, exacerbation events in others remain poorly controlled, resulting in frequent use of oral corticosteroids and antibiotics and, in many cases, recurrent hospital admissions. This is particularly exemplified in a sub-population of patients termed frequent exacerbators. Despite treatment, some patients do not regain their baseline lung function following an exacerbation and repeated events can lead to an accelerated decline in lung function, resulting in a worsening overall quality of life for patients and a significant burden on healthcare resources.

The prognosis in terms of morbidity and mortality is directly linked to the extent of lung damage.

2.1.4. Management

Management is through smoking cessation, pharmacological intervention with bronchodilators and anti-inflammatory agents and, when necessary treatment of respiratory infections, physical rehabilitation is aimed primarily at muscle strengthening, and in advanced cases long term domiciliary oxygen administration is helpful and has a proven benefit on lung function. Some patients are suitable for lung volume reduction surgery to reduce non-gas exchanging thoracic space. Once developed the condition is only partly reversible so more treatment options are always welcome.

About the product

Fluticasone furoate (FF)/umeclidinium bromide (UMEC)/vilanterol (VI) Inhalation Powder (hereafter referred to as FF/UMEC/VI) is a triple combination of an inhaled corticosteroid, a long-acting muscarinic receptor antagonist, and a long- acting beta$_2$-adrenergic receptor agonist. The product is a fixed dose combination of 100 mcg FF, 74.2 mcg UMEC, and 25 mcg VI for oral inhalation administered via a single inhaler (ELLIPTA). These doses are the same as used in the dual combinations of FF/VI and UMEC/VI and UMEC monotherapy, all administered once-daily via the ELLIPTA inhaler, which have already been licensed for the treatment of chronic obstructive pulmonary disease (COPD in the European Union (EU).

Type of Application and aspects on development

The Applicant has received Scientific Advice from EMA/CHMP on three occasions and has conducted the clinical development in accordance with the advice received.

- Legal basis

Fixed dose combination according to Article 10b of Directive 2001/83/EC.

Optional scope of the Centralised Procedure according to Article 3(2)(a) (new active substance) of Regulation (EC) No 726/2004.

2.2. Quality aspects

2.2.1. Introduction

The finished product, Elebrato Ellipta, is presented as a pre-dispensed dry powder inhaler containing fluticasone furoate, umeclidinium bromide and vilanterol trifenetate as active substances.

Other ingredients are: lactose monohydrate and magnesium stearate.

Each single inhalation provides a delivered dose (the dose leaving the mouthpiece) of 92 micrograms fluticasone furoate, 65 micrograms umeclidinium bromide equivalent to 55 micrograms umeclidinium and 22 micrograms vilanterol (as trifenatate). This corresponds to a pre-dispensed dose of 100 micrograms fluticasone furoate, 74.2 micrograms umeclidinium bromide equivalent to 62.5 micrograms umeclidinium and 25 micrograms vilanterol (as trifenatate).

The product is available in the Ellipta inhaler which consists of a light grey body, beige mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid. The inhaler is a multi-component device composed of polypropylene, high density polyethylene, polyoxymethylene, polybutylene terephthalate, acrylonitrile butadiene styrene, polycarbonate and stainless steel. The inhaler contains two aluminium foil laminate blister strips that deliver a total of 14 or 30 doses (14 or 30 day supply). Each blister of one strip contains fluticasone furoate, each blister of the other strip contains umeclidinium (as bromide) and vilanterol (as trifenatate).

2.2.2. Active Substance

The product contains three established active substances: fluticasone furoate, umeclidinium bromide and vilanterol trifenatate. In all cases, the information provided on the active substances in the current application is consistent with the information provided in earlier marketing authorisation applications for related products: Relvar Ellipta (fluticasone furoate); Anoro Ellipta, Laventair Ellipta and Incruse Ellipta (umeclidinium bromide); Relvar Ellipta, Laventair Ellipta and Anoro (vilanterol trifenatate).

Fluticasone furoate

General information

The chemical name of fluticasone furoate is (6α,11β,16α,17α)-6,9-difluoro-17-{[(fluoromethyl)thio]carbonyl}-11-hydroxy-16- methyl-3-oxoandrosta-1,4-dien-17-yl 2-furancarboxylate corresponding to the molecular formula $C_{27}H_{29}F_3O_6S$. It has a relative molecular mass of 538.58 g/mol and the following structure:

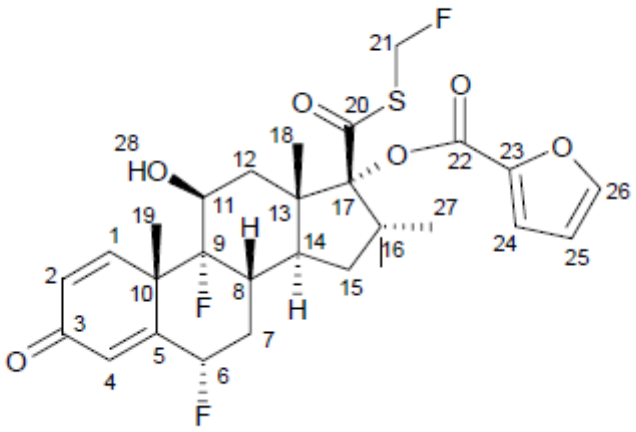


Figure 1 Fluticasone furoate structure

The chemical structure of fluticasone furoate was elucidated by elemental, infrared spectroscopy (IR), proton and carbon-13 nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS) of the primary reference standard, prepared using the proposed synthetic route described below. The solid state properties of the active substance were measured by X-ray powder diffraction (XRPD) and IR.

Manufacture, characterisation and process controls

Fluticasone furoate is synthesized in 6 main steps followed by micronisation, which is performed at a different site. The first step of the manufacturing process may be performed at an alternative site. The manufacturing process uses a commercially available well defined starting material with acceptable specifications.. The quality of the active substance used in the various phases of the development is considered to be comparable to that produced by the proposed commercial process.

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

Specification

The active substance specification includes tests for description, identification and solid state (IR), assay (HPLC) and impurities (drug-related impurities (HPLC), residual solvents (GC); water (KF), residue on ignition (Ph. Eur.) and particle size distribution (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for identity, assay and impurities testing has been presented.

Batch analysis data (n= 3 production-scale batches) of the active substance are provided. The results are within the specification and consistent from batch to batch.

Stability

Stability data from seven commercial scale batches of of both micronised and non-micronised active substance from the proposed manufacturers stored in the intended commercial packages for up to 60 months under long term conditions (25ºC/60% RH) and for up to 6 months under accelerated conditions (40 ºC/75% RH) according to the ICH guidelines were provided. No trends or out of specification results were observed for any of the stability-indicating parameters tested: fluticasone furoate content, drug-related impurities, water content, particle-size distribution and solid-state form.

Photostability testing following the ICH guideline Q1B was performed on six production scale batches. Stability data on four commercial scale batches (3 micronised and 1 non-micronised) under stress conditions for up to 3 months at 25 ºC /80% RH, 40 ºC /75% RH and 50 ºC /ambient humidity for micronised active substance and up to 3 months at 25 ºC /80% RH and 40 ºC /75% RH for non-micronised active substance have been provided. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months when stored in the proposed container at a temperature not exceeding 30 °C and protected from light.

Umeclidinium bromide

General information

The chemical name of umeclidinium bromide is 1-[2-(benzyloxy)ethyl]-4-(hydroxydiphenylmethyl)-1-azoniabicyclo[2.2.2]octane bromide corresponding to the molecular formula $C_{29}H_{34}NO_2 \cdot Br$. It has a relative molecular mass of 508.49 g/mol and the following structure:

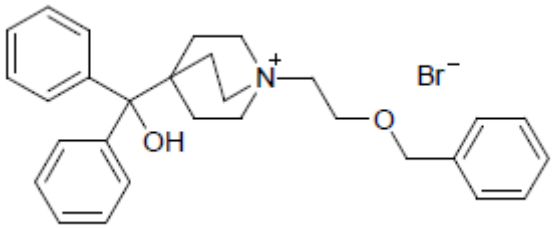


Figure 2 Umeclidinium bromide structure

The chemical structure of umeclidinium bromide was elucidated by elemental analysis, proton and carbon NMR, MS, and IR. The characterisation of the solid state properties of the active substance includes XRPD analysis PSD, specific surface area (SSA), surface texture, amorphous content by differential scanning calorimetry (DSC), melting point by DSC and particle shape. Physical characterisation has been undertaken on pivotal clinical, primary stability and representative production batches of micronised umeclidinium bromide.

Manufacture, characterisation and process controls

Figure 3 Umeclidinium bromide manufacturing process

A detailed description of the manufacturing process of umeclidinium bromide has been provided. The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by Design (QbD) such as risk assessment, design of experiment (DOE) studies, identification of potential critical process parameters (CPPs) that might have an impact on the critical quality attributes (CQAs) of the active substance.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. Pivotal batches of umeclidinium bromide were produced using the proposed commercial process.

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 micronised umeclidinium bromide specification is part of the wider control strategy whereby CQAs are appropriately controlled, by first intent, at their point of origin or where this has not been possible, by appropriate tests and acceptance criteria in the active substance specification. The active substance specification includes tests for the following CQAs: description (visual), identity and solid state form (IR), umeclidinium bromide content (HPLC), drug-related impurities (HPLC), particle size distribution (laser diffraction), residual solvents (GC), water content (KF), residue on ignition (sulphated ash).

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

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

Stability

Stability data from six commercial scale batches (three of 50 kg and three of 15 kg) of the micronised active substance from the proposed manufacturer stored in the intended commercial package for up to 60 months under intermediate conditions 40 ºC/75% RH were provided. Accelerated stability data on three commercial scale batches (50kg batch size) of micronised active substance from the proposed manufacturer stored under accelerated conditions at 40 ºC/75% RH were also submitted. No significant changes were observed for description, content, drug-related impurities, water content, particle size or solid state form by XRPD in batches stored for up to 60 months at 30 °C/65% RH or for up to 6 months at 40 °C/75% RH. All results complied with the specification.

Stress testing was performed on one commercial scale batch of micronised and on one commercial scale batch of non-micronised umeclidinium bromide under different storage conditions: 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. Photostability testing, following the ICH guideline Q1B was also performed

All stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period of 60 months from the date of manufacture of the non-micronised umeclidinium bromide when stored in the proposed container up to 30°C.

Vilanterol trifenatate

General information

The chemical name of vilanterol trifenatate is: triphenylacetic acid - 4-{(1*R*)-2-[(6-{2-[(2,6-dichlorobenzyl)oxy]ethoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol corresponding to the molecular formula $C_{24}H_{33}Cl_2NO_5.\cdot C_{20}H_{16}O_2$. It has a relative molecular mass of 774.77 g/mol (vilanterol trifenatate) and the following structure:

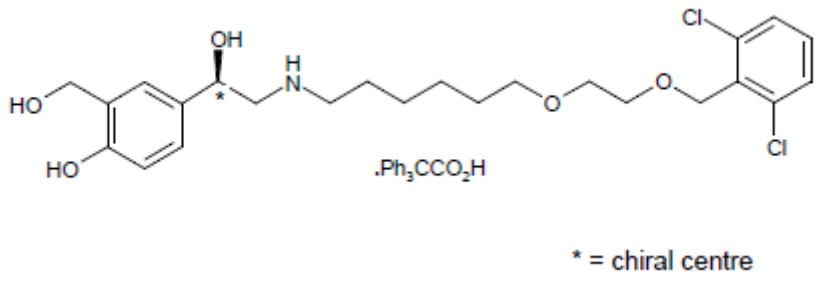


Figure 4 Vilanterol trifenatate structure

The chemical structure of vilanterol trifenatate was elucidated by spectroscopic analysis of the primary reference standard. The solid state properties of the active substance were measured by proton and carbon NMR, MS, IR, elemental analysis and X-ray crystallography.

Vilanterol trifenatate is size reduced prior to finished product manufacture.

Manufacture, characterisation and process controls

Pivotal batches of vilanterol trifenatate were produced using the proposed commercial process.

A detailed description of the manufacturing process has been provided. . The specifications and control methods for intermediate products, starting materials and reagents have been presented and are satisfactory.

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.

Specification

The active substance specification includes tests for the following CQAs: description (visual), identity (IR), vilanterol trifenatate content (HPLC), drug-related impurities (HPLC), , particle size distribution (laser diffraction) together with additional tests for enantiomer content (chiral HPLC), residual solvents (GC), water content (KF), and residue on ignition.

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

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data have been provided for 12 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 from 6 commercial scale batches of micronised vilanterol and two commercial scale batches of non-micronised vilanterol from the proposed manufacturers stored in a container closure system representative of that intended for the market for up to 60 months under long term conditions (25 ºC/60% RH) and for up to 6 months under accelerated conditions (40 ºC/75% RH) according to the ICH guidelines were provided. The following parameters were tested: description, vilanterol trifenatate content, impurities, enantiomer content (GSK907117C), water content, particle size distribution of the micronised and non-micronised active substance (laser diffraction), SSA of the non-micronised active substance and of the micronised vilanterol trifenatate (nitrogen gas adsorption), solid state form (XRPD) and melting point/amorphous content (DSC). Overall, no significant changes on stability were observed in any of the parameters tested.

Data on one commercial scale batch of micronised and one commercial scale batch of non-micronised vilanterol trifenatate under stress conditions (50°C/ambient humidity; freeze/thaw, photostability testing)

have been provided. Furthermore, additional stress testing studies were conducted in the solid state (14 days at 80 ºC under ambient and 75% relative humidities) 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 of 60 months for micronised vilanterol trifenatate when stored up to 25°C protected from light, in the proposed container.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Elebrato Ellipta is a pre-dispensed inhalation powder which is supplied in the Ellipta inhaler. The inhaler contains two foil-laminate blister strips: one strip contains pre-dispensed doses of 100 µg fluticasone furoate; the second strip contains pre-dispensed doses of 62.5 µg umeclidinium (as bromide) and 25 µg vilanterol (as trifenetate).

On actuation, the inhaler releases the contents of the two blisters, on each of the blister strips. This provides a delivered dose to the patient of 92 µg of fluticasone furoate, 55 µg of umeclidinium (as bromide) and 22 µg of vilanterol (as trifenatate) in each inhalation.

All excipients are well known pharmaceutical ingredients and routinely used for this pharmaceutical form; their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

The qualitative and quantitative composition of Elebrato Ellipta is presented in Table 4 below.

Table 1 composition of finished product

Component	Quantity (per 12.5mg blister)	Delivered Dose (per inhalation)	Function	Reference to Standard
Fluticasone Furoate Blister Strip[4]				
Fluticasone furoate micronised	100 mcg[5]	92 mcg	Active	GlaxoSmithKline[1]
Lactose monohydrate	to 12.5 mg	Note 9	Diluent/Carrier	JP, Ph. Eur and USP/NF[8]
Umeclidinium / Vilanterol Blister Strip[4]				
Umeclidinium bromide micronised	74.2 mcg[6]	55 mcg	Active	GlaxoSmithKline[2]
Vilanterol trifenatate micronised	40 mcg[7]	22 mcg	Active	GlaxoSmithKline[3]
Magnesium stearate	75 mcg	Note 9	Stabiliser	JP, Ph. Eur and USP/NF[8]
Lactose monohydrate	to 12.5 mg	Note 9	Diluent/Carrier	JP, Ph. Eur and USP/NF[8]

Notes:
mcg: microgram
1. Details of the specification of the drug substance are provided in S.4.1. Specification_Fluticasone Furoate
2. Details of the specification of the drug substance are provided in S.4.1. Specification_Umeclidinium Bromide
3. Details of the specification of the drug substance are provided in S.4.1. Specification_Vilanterol Trifenatate
4. A manufacturing overage of up to 8% of the fluticasone furoate powder blend and up to 8% umeclidinium/vilanterol powder blend, may be included in the blister strip.
5. The quantity of fluticasone furoate added may be adjusted to reflect the assigned purity of the input drug substance.
6. 74.2 micrograms of umeclidinium bromide is equivalent to 62.5 micrograms of umeclidinium (free cation). The quantity of umeclidinium bromide may be adjusted based on the assigned purity of the input drug substance.
7. 40 micrograms of vilanterol trifenatate is equivalent to 25 micrograms of vilanterol (free base). The quantity of vilanterol trifenatate may be adjusted based on the assigned purity of the input drug substance.
8. Excipients comply with JP, Ph. Eur and USP/NF and additional tests to ensure the quality for inhaled use. Details of the specification are provided in P.4. 1 Control of Excipients.
9. This component is an excipient, therefore no Delivered Dose is declared.

The formulation used during clinical studies is the same as that intended for marketing.

The pharmaceutical development of the finished product contains QbD elements and reference to quality risk management, as described in ICH Q8, Q9, Q10.

Extensive prior knowledge gained from the development of similar inhaled dry powder Ellipta products containing the same active substances at the same dose was used to inform the development of the formulation and its manufacturing process. Based on the experience gained with the Ellipta products platform, the applicant decided to formulate the active substances in two separate powders for inhalation within a single inhaler. One strip contains a blend of micronised fluticasone furoate and lactose monohydrate and has the same composition as the marketed product, Relvar Ellipta. The second strip contains a blend of micronised umeclidinium bromide, micronised vilanterol trifenatate, magnesium stearate and lactose monohydrate. The umeclidinium/vilanterol blister strip formulation is based on those established for the individual umeclidinium and vilanterol blister strips used within approved Ellipta products.

A comprehensive series of product characterisation studies has been conducted in accordance with the EU 'Guideline on the pharmaceutical quality of inhalation and nasal finished products' (EMEA/CHMP/QWP/49313/2005 Corr). The Ellipta inhaler consists of a light grey body, beige mouthpiece cover and a dose counter, packed into a foil laminate tray containing a desiccant sachet. The tray is sealed with a peelable foil lid. The inhaler is a multi-component device composed of polypropylene, high density polyethylene, polyoxymethylene, polybutylene terephthalate, acrylonitrile butadiene styrene, polycarbonate and stainless steel.

The inhaler contains two aluminium foil laminate blister strips that deliver a total of 14 or 30 doses (14 or 30 day supply). Each blister in one strip contains fluticasone furoate, each blister in the other strip contains umeclidinium (as bromide) and vilanterol (as trifenatate).

The secondary pack for Elebrato Ellipta is identical to the secondary pack currently used with the authorised products Relvar Ellipta and Anoro Ellita. The secondary pack has been shown to be capable of maintaining satisfactory storage conditions for the product; it is sufficiently robust to withstand the stresses likely to be encountered during transport of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps: manufacture of the fluticasone furoate blister strip (fluticasone furoate blending and filling), manufacture of the umeclidinium/vilanterol blister strip (umeclidinium bromide/vilanterol trifenatate blending and filling), assembly of the inhaler, and packing.

As part of the QbD approach used in the development of Elebrato Ellipta, the attributes of intermediates and the process parameters that could potentially affect finished product CQAs were investigated. CPPs, in-process controls and on-line tests have been identified. The in-process controls are adequate for the manufacturing of a pre-dispensed inhalation powder.

Product specification

The finished product release specifications include appropriate tests for this type of dosage form: description, identification of fluticasone furoate, umeclidinium, and vilanterol (UV); mean content of fluticasone furoate, umeclidinium, and vilanterol (HPLC); uniformity of delivered dose (for fluticasone furoate, umeclidinium, and vilanterol) (HPLC); fine-particle mass of fluticasone furoate, umeclidinium, and vilanterol (NGI); microbiological quality (by control of water activity or by enumeration/identification of microbial colonies).

Batch analysis results are provided for eight production-scale batches of Elebrato Ellipta, comprising four batches of the 30-dose and four batches of the 14-dose pack sizes. All of these batches were manufactured using the commercial process at the intended site of manufacture. All eight batches complied fully with the proposed release specification, confirming the consistency of the manufacturing process and its ability to manufacture according to the intended product specification.

Stability of the product

Stability data from three commercial batches of finished product stored for up to 18 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The registration stability batches have blister strips that are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The inhaler used in all the stability studies is representative of the commercial product, the only difference being the colour of the mouthpiece cover, and this is accepted.

Instead of the standard intermediate storage condition of 30 °C / 65 % RH, as defined in ICH Q1A (R2), a more challenging condition of 30 °C / 75 % RH was used. No significant changes were observed in three commercial scale batches in relation to the following tests at the 12-month time point:

In-use stability studies were conducted on three commercial batches following removal of the secondary packaging (foil laminate tray, lid and desiccant) at the initial time point and following storage under long-term conditions When the secondary packaging was removed, the unprotected inhalers were stored at 25 °C/75 % RH for 3 months.

The applicant has provided additional stability data under stress storage conditions. On one commercial batch stored at 50 °C and ambient relative humidity for three months, One commercial batch was subjected to a freeze/thaw cycle consisting of 6 hours storage at -5 °C followed by 6 hours storage at 40 °C for one month.

In conclusion, the physical and chemical changes observed at the different storage conditions were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SmPC.

Based on available stability data, the proposed shelf-life of 24 months and 6 weeks after opening the tray at the following condition ‘Do not store above 30 °C’ as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

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.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided on Elebrato Ellipta reflects the requirements of the applicable EU directives and guidelines.

All three active substances (fluticasone furoate, umeclidinium bromide and vilanterol trifenatate) have previously been approved for use with the Ellipta inhaler and the information submitted on their synthesis, specifications and stability in this application is consistent with the information provided in earlier marketing authorisation applications for related Ellipta products. This provides good assurance that active substances

of satisfactory quality can be consistently produced. The primary and secondary container closure (including the inhaler) are also identical to those used for currently authorised Ellipta products, except that the colour of the mouthpiece cover is product-specific.

Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. 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 clinical use.

The information provided on the finished product indicates that the formulation, method of manufacture, and specifications are adequate to ensure that a product of satisfactory quality will be consistently produced.

Adequate data has been provided in support of the stability of the product at the proposed shelf life.

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. Data has been presented to give reassurance on viral/TSE safety.

2.2.6. Recommendation(s) for future quality development

Not applicable

2.3. Non-clinical aspects

The non-clinical package contains literature data.

2.3.1. Introduction

The present MAA is a fixed dose combination of 100 μg fluticasone furoate (FF), 62.5 μg umeclidinium bromide (UMEC) and 25 μg of vilanterol (VI) in accordance with Article 10(b) of Directive 2001/83/EC as amended.

Fluticasone Furoate/Umeclidinium bromide/Vilanterol, Inhalation Powder (FF/UMEC/VI) combines an inhaled corticosteroid (ICS) (GW685698) with a long acting muscarinic antagonist (LAMA) (GSK573719) and a novel long-acting β2 agonist (LABA) (GW642444).

2.3.2. Pharmacology

The application composed of non-clinical data based on bibliographic literature substituting/supporting certain tests or studies.

Primary pharmacodynamic studies

Fluticasone furoate (GW685698)

Fluticasone furoate (GW685698) is a synthetic corticosteroid with potent anti-inflammatory action. It targets the human glucocorticoid receptor (GR), a ligand-activated transcription factor that regulates an extensive network of gene products which profoundly regulate pro-inflammatory cytokines in airway inflammatory cells.

Glucocorticoid receptor binding

In vitro, GW685698 bound with high affinity to the human glucocorticoid receptor (GR) and with significantly greater affinity than fluticasone propionate, budesonide and dexamethasone and dissociates very slowly from the receptor. X-ray crystal analysis of the GR ligand binding domain revealed that in the GW685698 structure, the furoate substituent fully occupied a 17α pocket making a number of hydrophobic packing interactions with the side chains lining the pocket which was more significant than that seen with the fluticasone propionate structure (Report RR2006/00018/00). The difference in receptor affinity between GW685698 versus fluticasone propionate may be due to increased hydrophobic packing interactions in the 17α pocket.

Glucocorticoid receptor functional assays

Activated GR affects a number of downstream pathways via a transrepressive mechanism - inhibiting the function of certain transcription factors such as Nuclear Factor κB (NFκB) and Activated Protein-1 (AP-1), or through a transactivation mechanism where the GR binds directly to DNA to cause an increase in the transcription of certain gene products [Barnes, 1998]. The influence of GW685698, the primary metabolite of GW685698 - GW694301X (M10), and a number of other clinically used steroids on these downstream signalling pathways was assessed in a variety of in vitro cellular assays.

The transrepressive effects of GW685698, its major metabolite GW694301X (M10) and a number of clinically used steroids were investigated in NFκB and AP-1 assays. In the NFκB assay, the ability of the test compounds to inhibit tumour necrosis factor-α (TNF-α)-induced NFκB function was assessed in human A549 (caucasian lung carcinoma) cells transfected with a vector containing the secreted alkaline phosphatase (SPAP) gene driven by a fragment of the ELAM promoter containing binding sites for NFκB. In the AP-1 assay, the ability of the test compound to inhibit epidermal growth factor (EGF)-induced AP-1-dependent increases in luminescence was assessed in human A549 cells transfected with a vector containing the firefly luciferase gene driven by the minimal interleukin (IL)-2 promoter containing AP-1 binding sites.

GW685698 was found to potently inhibit TNFα-induced NFκB function and an EGF-induced AP-1-dependent increase in luminescence, with comparable potency to fluticasone propionate and mometasone furoate. The metabolite GW694301X (M10) showed only very weak activity in functional assays (>6000-fold weaker than GW685698) and will therefore contribute negligible glucocorticoid activity in vivo.

In the NFκB inhibition assay, GR694301X was found to be a less potent agonist (pEC50 6.5 ± 0.2; n=10) than other steroids tested and between 1000- to 10000-fold weaker than GW685698 depending on assay dilution conditions, therefore, the metabolite is unlikely to contribute to steroidal activity at therapeutic doses.

The effect of GW685698 and a number of clinically used steroids on the pro-inflammatory NFkB transcription factor pathway was further examined in the human lung A549 epithelial cell line using an improved steroid dilution methodology which avoided loss of test compound through precipitation. A549 cells expressing SPAP were incubated with test compound and TNFα for 15 hours, and the activation of the NFκB transcription pathway was measured spectrophotometrically as previously performed.

TNFα-induced NFκB function was inhibited by GW685698 with comparable potency to fluticasone propionate and mometasone furoate. GW685698 also produced a maximal inhibitory response similar to that seen with fluticasone propionate and mometasone furoate. Budesonide, another clinically used glucocorticoid, had a substantially weaker potency for the inhibition of TNFα-induced NFκB function than GW685698. GW694301X (M10) showed only very weak activity in this assay (>10000-fold weaker than GW685698).

The differences observed in the NFκB EC50 inhibition values between the studies amounts to the new methodology employed in the various reports where precipitation of the compound is prevented thus prohibiting a loss of compound and an overestimation of the test compound's concentration and therefore an underestimation of potency.

Transactivation effects of GW685698, GW694301X (M10) and several clinically used glucocorticoids were investigated in human lung epithelial cell lines using 2 different glucocorticoid response element (GRE) transactivation assays. In addition, a rat liver cell assay was used to examine transactivation activity of the test compounds in an endogenous GRE system using the classical GRE-driven gene product tyrosine aminotransferase (TAT) assay.

Overall, GW685698 potently increased transactivation in the human GRE, MMTV-GRE and endogenous TAT assays, with comparable potency to fluticasone propionate and mometasone furoate. GW694301X (M10) showed only very weak activity in the MMTV-GRE and endogenous TAT tests, i.e., 8000- to 11000-fold weaker than GW685698, consistent with the NFκB data.

GW685698 was found to potently inhibit the TNFα-induced release of IL-8 from the bronchial cells (IC50 = 3.5 pM) with comparable potency to fluticasone propionate (IC50 = 7.25 pM) and mometasone furoate (IC50 = 5 pM). Flunisolide and budesonide had far higher IC50 values of 590 and 48 pM, respectively, demonstrating their weaker GR activity.

GW685698 has the greatest inhibitory potency for TNF release from LPS-activated human primary peripheral mononuclear cells in vitro compared to clinically used inhaled glucocorticoids fluticasone propionate, budesonide, ciclesonide active principle (CAP) and prednisolone. pIC50 values are as follows: GW685698, 9.93; fluticasone propionate, 9.63; budesonide, 8.41; CAP, 8.5; prednisolone, 7.23.

In a series of in vitro functional assays examining the duration and rate of action of GW685698 compared to fluticasone propionate, sustained inhibition of cytokine synthesis (IL-6, IL-8 and GM-CSF) was achieved with GW658698 and was also accompanied by a longer duration of action compared to other clinically used steroids.

In monolayer of human lung epithelial (16HBE14o-) cells, GW685698 had a greater tissue retention compared to fluticasone propionate as well as a greater level of binding to a suspension of sliced human lung tissue.

In examining the protective effects of steroids on airway epithelial barrier, GW685698 demonstrated a highly efficacious cellular protection from protease induced damage with a potency greater than that seen with fluticasone propionate, mometasone furoate and other clinically used steroids. Furthermore, GW685698 was more potent in inducing a decrease in epithelial permeability.

The selectivity of GW685698 for the GR over a number of other steroid receptor subtypes was examined in vitro. GW685698 was highly selective for the human GR over other human steroid hormone receptor subtypes. Selectivity ranged from approximately 32- to >300000-fold, and was similar to that seen with fluticasone propionate and substantially better than that seen with mometasone furoate and ciclesonide active principle. W694301X (M10) had no affinity at the AR, ERα or ERβ receptors and displayed no activity in the MR antagonist assay up to a concentration of 1 mcM. GW694301X (M10) displayed low but measurable affinity for the PR receptor. However, this was at least 100-fold less than GW685698 and was therefore considered unlikely to contribute to any significant activity at this receptor.

In vivo Studies – Anti-inflammatory activity

The effect of GW685698 in the delayed type hypersensitivity model of ear inflammation was investigated in female BALB/c mice and male Lewis rats (Report SH2002/00044/00). GW685698 dose-dependently inhibited ear swelling induced by oxazolone sensitisation in mice and rats. When compared to fluticasone propionate, GW685698 exhibited comparable or superior anti-inflammatory activity in these models.

The effect of GW685698 was further evaluated in a Brown Norway lung eosinophilia model which measures an allergic inflammation of the lung by systemic sensitisation with 1 mg ovalbumin and inhaled challenge with 100 ng/ml ovalbumin aerosol characterised by a profound eosinophilia. GW685698 was associated with a dose-dependent inhibition of lung eosinophilia in this model (n=4 rats/group). Significant inhibition of

eosinophilia was achieved after a single dose of 30 mcg and the response was significantly greater (p=0.016) than that seen with an equivalent dose of fluticasone propionate (75% inhibition with GW685698 vs 50% inhibition with fluticasone propionate). A long anti-inflammatory duration of action was also observed in this model, with intratracheal administration of 100 mcg of GW685698 demonstrating 68% inhibition of inflammation when given 14 hours prior to ovalbumin challenge.

Finally, the inhibitory effects of GW685698 on antigen-induced nasal symptoms (sneezing and nasal rubbing) was compared to that of fluticasone propionate following intranasal administration to actively sensitised male Wistar rats. GW685698 showed a significant and dose-related inhibitory effect on antigen induced nasal symptoms (sneezing and nasal rubbing) of comparable potency to fluticasone propionate but with a longer duration.

Umeclidinium (GSK573719)

Umeclidinium (GSK573719) is a long-acting muscarinic antagonist (LAMA). Muscarinic antagonists competitively inhibit the binding of acetylcholine with M3 muscarinic cholinergic receptors on airway smooth muscle with consequent bronchodilation. M3 receptor antagonism in sub-mucosal glands results in reduction in airway obstruction.

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

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

Vilanterol (GW642444)

Vilanterol (GW642444) is a novel long-acting β2 agonist which targets the human beta adrenergic receptor. The human beta adrenergic receptor is coupled to Gs proteins which activate adenylate cyclise to form cyclic AMP from ATP. This cAMP produces relaxation of airway smooth muscle through modification of muscle regulatory proteins and changes in intracellular calcium concentration and is independent of the contracting agent. Selective β2-agonists stimulate the β2-adrenoceptors on the airway smooth muscle, resulting in bronchodilation.

In vitro studies

Radioligand binding studies were performed to investigate the binding kinetics of ^{3}H-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 ^{3}H-GW642444. The pKi values determined were in good agreement with literature values generated against antagonist radioligands. 3H-GW642444M

demonstrates a fast koff from the low affinity receptor state and a moderately slow k_{off} from the high affinity receptor state at ambient temperature.

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.

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 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.

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.

No pharmacodynamic studies were performed on the fixed dose combination fluticasone furoate/umeclidinium/vilanterol as there is sufficient data available for each compound which was considered acceptable.

Secondary pharmacodynamic studies

Fluticasone Furoate/Umeclidinium/Vilanterol

No secondary pharmacodynamic studies were performed on the fixed dose combination fluticasone furoate/umeclidinium/vilanterol as there is sufficient data available for each compound which was considered acceptable.

Fluticasone furoate (GW685698)

The secondary pharmacodynamic effects of GW685698 were investigated in male CD rats intratracheally dosed with vehicle, GW685698 (10 and 100 mcg) or fluticasone propionate (10 and 100 mcg) once daily for 3 days, since thymus involution is a documented index of systemic side effects of glucocorticoids. Thymus showed a weight reduction of 21.6 and 20.4% with GW685698 and fluticasone propionate at 10 mcg, respectively. At 100 mcg, the reduction was of 67% with GW685698 and of 78% with fluticasone propionate, respectively.

Umeclidinium (GSK573719)

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

As UMEC is a pan-active mAChR antagonist there is a potential for UMEC to have activity at extra-pulmonary muscarinic receptors (e.g., cardiac mAChR-2). However, based on local delivery to the lungs, the proposed low dose and the poor oral bioavailability of UMEC, the Applicant's conclusion that activity will likely be restricted to the airway is plausible. Available in vivo data support this as no effect on ACh-induced

bradycardia was seen following intratracheal dosing of UMEC (0.25 or 2.5 mcg) in guinea pigs suggesting that there was little or no systemic exposure to M2 receptors on the myocardium of the heart. Based on these data the Applicant calculated that UMEC had a therapeutic window of at least 10 fold between the desired bronchodilatory effect (mAChR-3) and adverse cardiovascular effects (mAChR-2) such as bradycardia.

Vilanterol (GW642444)

In in vitro studies the selectivity of GW642444A (1 mcM) for 7-transmembrane (7TM) receptors, ion channels and transporters was assessed in radioligand binding assays. An in vivo secondary pharmacology study has been performed to assess the effect of inhaled doses of GW642444A and salmeterol on cardiovascular parameters in conscious guinea pigs.

Safety pharmacology

Fluticasone Furoate/Umeclidinium/Vilanterol

FF, UMEC and VI alone, and UMEC/VI in combination, have undergone evaluation in safety pharmacology studies. When administered as a single agent FF did not affect any cardiovascular, respiratory or CNS parameters. Effects on the cardiovascular system were seen with the use of UMEC and VI separately, however, when used in double combinations there was no exacerbation of effects compared to the individual components. Safety pharmacology studies have not been conducted with the FF/UMEC/VI triple combination. The Applicant argues that the safety pharmacological profile of FF is separate and distinct from UMEC/VI and that therefore no (adverse) interaction between FF, UMEC and VI is anticipated. This argumentation is, however, not in line with the available literature which provides evidence for (potentiating) pharmacodynamic interactions between ICS and LABA. However, since the non-clinical safety profile of the FF/UMEC/VI triple combination has been evaluated in a 13-week inhalation repeat dose toxicity study in dogs (see Section 3.2.3 of this AR) and taking into account the clinical safety data available for the FF/UMEC/VI triple combination, the lack of safety pharmacology studies with the triple combination is acceptable.

Fluticasone furoate (GW685698)

Several safety pharmacology studies were performed to evaluate the effects of GW685698 on central nervous, cardiovascular and respiratory systems.

In vivo studies

Conscious male Wistar Han rats were administered with single dose of vehicle or GW685698 subcutaneously. Effect on central nervous system (locomotor coordination, skeletal muscle tone and reflexes), autononomic nervous system (pupil size, lacrimation, salivation, overt cardiovascular endpoints and urination), as well as on respiration rate and gastrointestinal tract, were evaluated for the first 30 minutes after dosing and at 1, 2, 4, 24 and 48 hours after drug administration.

CNS

Table 2 Safety pharmacology studies performed to evaluate the effects of GW685698 on CNS

Study N / GLP Compliance	Species / N / Sex / Group	Route / Dose (mcg/kg)	Noteworthy findings
WD2001/00889/00 (R23287) / Yes	Rat (Wistar Han) / 12 / Male / 3	Subcutaneous / 0, 4000, 10000	No overt effects. At 4000 mcg/kg: 1 rat displayed moderate handling-induced vocalisation during the first 30

			minutes after dosing
WD2002/00077/00 (D23351) / Yes	Dog (beagle) / 6 / Male / 3	Subcutaneous / 0, 4000, 10000	No overt effects noted over a 48 hour monitoring period. Delayed treatment-related findings as polyuria (2 to 4 weeks after dosing) and muscle wasting (4 to 5 weeks after dosing) were observed. Four treatment related macroscopic findings were observed in the liver. Pallor and enlargement were observed in all treated animals. Linear red capsular streaks and subcapsular haemorrhages were observed in high dose animals. The temporal and masseter muscles were observed to be wasted in all treated animals and this is considered to be related to treatment. Treatment related microscopic findings were observed in the adrenals, skin (injection and standard site), liver, popliteal and mesenteric lymph nodes, skeletal muscle, sternum, stomach and thymus. The majority of these changes are well established responses of the dog to high doses of exogenous corticosteroids. These were considered to be due to the prolonged release of GW685698 from the subcutaneous depot

In vivo studies

Rats: Conscious male Wistar Han rats were administered with single dose of vehicle or GW685698 subcutaneously. Effect on central nervous system (locomotor coordination, skeletal muscle tone and reflexes), autononomic nervous system (pupil size, lacrimation, salivation, overt cardiovascular endpoints and urination), as well as on respiration rate and gastrointestinal tract, were evaluated for the first 30 minutes after dosing and at 1, 2, 4, 24 and 48 hours after drug administration.

Dogs: Male beagle dogs were single subcutaneous administered with vehicle or GW685698. Effects on gastrointestinal tract autonomic nervous system (pupil size, lacrimation, salivation and urination) and central nervous system (behaviour, locomotor co-ordination, skeletal muscle tone and reflexes) for up to 48 hours after dosing were examined. Also, heart rate, body temperature and respiratory rate were recorded at approximately 24 hours and 1 hour before dosing and immediately following the 1, 2, 4, 6 and 24 hour observations.

Cardiovascular System

Table 3 Safety pharmacology studies performed to evaluate the effects of GW685698 on CVS.

Study N / GLP Compliance	Species / N / Sex / Group	Route / Dose (mcg/kg)	Noteworthy findings
WD2001/01020/00 (V23207) / Yes	Isolated dog Purkinje fibre/ NA / NA / NA	In vitro / 0.417, 1.240, 2.200 ng/mL	There was no effect on any action potential parameters in fibres treated with GW685698 at concentrations up to 2200 pg/mL. DL-sotalol hydrochloride (positive control) caused a prolongation of the action potential duration that was inverse frequency dependent, an effect consistent with its known activity as a blocker of repolarising K^+ channels.
FD2002/00033/00 (G01646) / Yes	Rat (Sprague Dawley) / 4 / Male / 2	Subcutaneous / 0, 4000	Mild though sustained increase in blood pressure and an associated reduction in heart rate, body temperature and spontaneous locomotor activity. Delayed

			treatment-related effects were observed several weeks later. These were considered to be due to the prolonged release of GW685698 from the subcutaneous depot
FD2002/00019/00 (I01702) / Yes	Dog (beagle) / 2 / Female / 2	Intravenous / 0, 100	No treatment-related effects were noted
FD2002/00011/01 (G01668) / Yes	Dog (beagle) / 6 / Male-Female / 3	Intravenous / 0, 30, 100	No treatment-related effects were noted

In vitro studies

Effect on QT interval. Purkinje fibre assay:

The effects of up to 2200 pg/mL of GW685698 on cardiac action potential, including action potential duration at 60 and 90% (ADP60 and ADP90), resting membrane potential, maximum rate of depolarisation and upstroke amplitude, were studied using isolated dog Purkinje fibres.

In vivo studies

Rat: The effect of a single subcutaneous dose of GW685698 on cardiovascular function was studied in conscious rats implanted with telemetry transmitters, measuring the mean arterial pressure, heart rate, body temperature and spontaneous locomotor activity from approximately 2 hours prior to dosing to at least 14 days post dose.

Dog: A study was performed to evaluate the effects of the intravenous administration of GW685698 on cardiovascular function in the conscious dogs and to select a suitable dose for the second study. Systolic, diastolic and mean arterial blood pressure, pulse pressure, heart rate and Lead II electrocardiogram were monitored.

In the second study, vehicle or GW685698 were administered on separate days using a crossover design to 2 male and 2 female beagle dogs. Also in this study, systolic, diastolic and mean arterial blood pressure, pulse pressure, heart rate and Lead II electrocardiogram were monitored.

Respiratory System

Table 4 Safety pharmacology study to assess the effects of GW685698 on respiratory system

Study N / GLP Compliance	Species / N / Sex / Group	Route / Dose (mcg/kg)	Noteworthy findings
FD2001/00004/00 (G01654) / Yes	Rat (Sprague Dawley) / 32 / Male / 4	Subcutaneous / 0, 4000, 10000	No effects on respiratory function

The effects of GW685698 on respiratory function were assessed in conscious male Sprague Dawley rats subcutaneously dose with vehicle, 1000 mcg/kg carbamylcholine chloride (positive control) and GW685698 at a dose of 4000 or 10000 mcg/kg. Respiratory rate, peak inspiratory and expiratory flows, inspiration and expiration times, minute volume and tidal volume were measured continuously for 4 hours post dose and for 1 hour periods between 23 and 24 hours and 47 and 48 hours post dose.

Umeclidinium (GSK573719)

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

ventilatory parameters with UMEC are observed in clinical trials in COPD patients and are regarded as beneficial.

Umeclidinium inhibited hERG channel tail current in vitro and, as expected from the pharmacology of muscarinic antagonists, caused a number of cardiovascular effects (increases in heart rate, prolongation of PR together with transient second degree AV block of Mobitz Type I followed by a decrease of RR interval). In the general toxicology studies, treatment with Umeclidinium caused tachycardia in dogs.

Vilanterol (GW642444)

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

CNS

Table 5 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 6 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) / 16 / 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) / 16 / 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 642444H 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 their 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 was also evaluated the effects of GW642444M in the cardiovascular function and ECG parameters. 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 7 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.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted for the combination fluticasone furoate/umeclidinium/vilanterol based on the data available for each compound which is considered acceptable.

2.3.3. Pharmacokinetics

Validated methods of analysis were employed to quantify FF, UMEC and VI in dog plasma using HPLC-MS/MS.

A range of nonclinical pharmacokinetic studies has been performed in order to support administration of FF, UMEC and VI, separately or in combination, for the treatment of patients with COPD and/or asthma. These studies have been also reviewed as part of the approved marketing authorisation applications (MAAs) for RELVAR (FF/VI), ANORO (UMEC/VI) and/or INCRUSE (UMEC) ELLIPTA products. A summary of the pharmacokinetics for FF, UMEC and VI was provided.

The applicant has performed a toxicokinetics study as part of the repeat dose toxicity studies in which the triple combination (FF/UMEC/VI) was administered to dogs once daily for 13 weeks via oropharyngeal tube inhalation and systemic exposures were compared to each of the individual components administered alone.

Absorption

Fluticasone furoate/umeclidinium/vilanterol

The pharmacokinetics of FF, UMEC and VI in combination were assessed in a repeat dose toxicity study (Study 2013N169979) conducted in beagle dogs for 13 weeks. FF, UMEC and VI alone or in combination as a powder aerosol formulation at a ratio of 4:5:1, respectively, was administered by inhalation. In general, there was no consistent difference in systemic exposure (AUC0-t or Cmax) to any test article on any of the sampling occasions across the duration of the study. For FF or VI, when co-administered with the other test articles, systemic exposure (AUC0-t and Cmax) increased approximately proportionally with dose. For UMEC co-administered with FF and VI, Cmax increased approximately proportionally with dose. The AUC0-t for UMEC was variable between the sampling occasions, however, the AUC0-t consistently increased with an increase in dose. Generally across the study there was no consistent difference in systemic exposure between the sexes; however, systemic exposure to UMEC was consistently higher in males than in females.

The pharmacological properties of each single mono-component described in the literature have been described below for convenience.

Fluticasone furoate (GW685698)

Absorption of GW685698 from the lung following inhalation administration was moderately rapid in all non-clinical species (mouse, rat, rabbit, dog), Tmax being generally up to 1.5 hours after the end of the inhalation period or sooner. GW685698 was well absorbed in the rat and dog following oral administration with oral absorption estimated as at least 30 and 19% respectively, based on the recovery of drug related material (DRM) in bile and urine in bile-duct cannulated (BDC) animals. In the rat, rabbit and dog, however, oral systemic exposure to GW685698 was limited by its negligible oral bioavailability - approximately 1% or lower when dosed as a suspension. The low oral absolute bioavailability of GW685698 is most likely due to extensive first pass metabolism. Oral absorption of GW685698 in human, as in animals, was good with at least 30% of the administered dose absorbed following oral administration of 14C-GW685698 in solution based on a comparison of radioactivity AUC0-t values following oral and intravenous administrations. Corresponding human oral bioavailability, as in animals, was low (approximately 1%), mediated, as in animals, by extensive first pass metabolism of orally absorbed drug.

In single i.v. dose pharmacokinetic (PK) studies, PK profiles were comparable in both genders among all species examined (rat, rabbit, dog and human). High clearance and large volume of distribution was achieved indicating extensive distribution to all tissues.

Following a single subcutaneous administration in rat and dog, GW685698 had a long apparent plasma half-life (approximately 25 and 160 hours in rat and dog, respectively) suggesting absorption rate limited elimination. This is consistent with formation of a depot which provided sustained release of GW685698 into the systemic circulation over a long period of time. Animals dosed by subcutaneous administration may have prolonged exposure compared to animals or humans dosed by inhalation administration and are thought to explain the delayed effects observed in the safety pharmacology study.

In repeat dose inhalation studies in mouse, rat, rabbit and dog for up to 39 weeks, 58 weeks, 2 weeks and 39 weeks, respectively, Inter-animal and inter-study variability of systemic exposure to GW685698 was high as is typical following inhalation administration. The mean data, however, consistently showed the same trends between studies.

Systemic exposure to GW685698 following inhalation administration to mice, rats, rabbits, dogs and human increased with increasing dose, in either a proportional or less than dose-proportional manner. Overall,

there was little evidence of accumulation of GW685698 in animals on repeated administration with less than 2-fold change in systemic exposure reported following repeated administration on the majority of studies. Small increases were occasionally reported in the rat and dog. Accumulation of GW685698 following repeated inhalation administration to human was also less than 2-fold. Systemic exposure was typically similar in males and females in the mouse, rat, rabbit, dog and human. Tmax usually occurred immediately following the end of the dosing period (nominally 1 hour in duration) in all species. The addition of magnesium stearate as an excipient in rat and dog vehicle formulations did not influence the toxicokinetics of GW685698.

Umeclidinium (GSK573719)

Absorption of GSK573719 from the lung following inhalation administration was rapid in all non-clinical species. Systemic exposure to UMEC following inhalation administration to mice, rats, rabbits, dogs and humans increased with increasing dose in an approximately proportional manner. Cmax was usually detected immediately after the administration in all species, indicating rapid absorption across the lung.

Vilanterol (GW64244)

Absorption of GW642444 from the lung following inhalation administration was rapid in all nonclinical 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, see table below) 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. A comparison of the systemic exposure to GW642444 achieved in pivotal toxicity studies and in humans following its administration at the proposed commercial dose is seen in the table below. 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. Mouse, rat and dog 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 nonclinical 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.

Distribution

Fluticasone furoate/umeclidinium/vilanterol

The binding of FF, UMEC and VI to human liver microsomal protein was investigated in vitro, approximately 72%, 47% and 40% respectively was bound to protein following equilibration.

The substrate potential of FF and VI in vitro was assessed by measuring the time dependent transport of [^{14}C]-labelled FF or VI in BCRP, OATP1B1 and OATP1B3 expressing vesicles or cells. The substrate potential of UMEC in vitro was assessed by measuring the time-dependent transport of [^{14}C]-labelled UMEC in BCRP, BSEP, OATP1B1, OATP1B3, OAT1 and/or OAT3 expressing vesicles or cells. Solute carrier (SLC) transporter expressing cells (S2 and HEK293 cells), as well as ATP binding cassette (ABC) transporter expressing vesicles or cells (LLC-PK1 cells), were utilized.

Data from previous submissions where FF was demonstrated to inhibit the OATP1B1 transporter, UMEC was demonstrated to be an in vivo substrate for the human organic cation transporters OCT1 and OCT2, but not OCT3, OCTN1 or OCTN2. VI was shown not to be an in vitro substrate for the transporters OCT1, OCT3, OCTN1 or OCTN2.

FF (weak substrate only), UMEC and VI are in vitro substrates for the human transporter protein P-glycoprotein (P-gp) which is consistent with the limited or lack of distribution of drug-related material into the central nervous system (CNS) observed in the quantitative whole body autoradiography (QWBA) studies.

The PK properties relating to each monocomponent are provided below based on literature data.

Fluticasone furoate (GW685698)

Protein Binding:

The plasma protein binding characteristics of 3H-GW685698 were determined using an ultrafiltration method. The mean binding of 3H-GW685698 was found to be high (>99.5 in dog, rabbit, mouse and human; >97% in rat) and showed no concentration-dependence across the range of 0.2 to 5 ng/mL. Plasma protein binding at the lowest concentration investigated (0.2 ng/mL) was 96.4, 99.6, 99.6, >99.5 and >99.6% in rat, dog, rabbit, mouse and human, respectively.

In a second study, plasma protein binding characteristics of 3H-GW685698 was determined using ultracentrifugation. In all species tested, the binding of 3H-GW685698 to plasma proteins was moderate (75 to 93%) and similar across the 3H-GW685698 concentration range used (0.2 to 5 ng/mL). No apparent sex-related differences were observed in the plasma protein binding of 3H-GW685698 in humans.

In a study examining the binding properties of 14C-GW685698 (20 to 250 ng) in selected human plasma proteins, fresh human plasma and protein solutions, binding was comparable to that seen in the ultrafiltration method. The extent of binding in albumin solution and α1-acid glycoprotein solution was high being 96% and 90%, respectively. The extent of binding to γ-globulin was low at 33%. There was no evidence of any concentration-dependent binding of 14C-GW685698 across the concentration range employed.

Whole blood distribution:

Blood samples collected from male mice, rats, rabbits, dogs and humans were utilised in a study of the distribution of 3H-GW685698 in whole blood. The blood to plasma concentration ratios were similar for each species and no concentration-dependent blood cell association was observed across the concentration range of 0.2 to 5 ng/mL. In all species investigated, 3H-GW685698 had a higher association for plasma than for blood cells. Percentage associated with cellular fraction ranged from 6 to 23%. As the concentration in blood is lower than the corresponding plasma concentration, the clearance in vivo from the blood will be higher than that from plasma. No apparent sex related differences were observed in the blood distribution of 3H-GW685698 in humans.

Whole blood distribution of radioactive 14C-GW685698 was also examined in dogs. 14C-GW685698 was administered intravenously (infusion over 30 minutes) to male beagle dogs (n=3) at a dose of 100 mcg/kg, as a 0.1 mg/mL solution in PEG 400: 8% w/v 2-hydroxypropyl β-cyclodextrin solution (aqueous) (1:3). Radioactivity was assessed in the excreta and also in plasma and whole blood taken from each dog at various time points up to 96 hours after dosing. Whole blood concentrations of total radioactivity were lower than those observed in the corresponding plasma samples at all time points investigated. Mean whole blood:plasma radioactivity concentration ratios ranged from 0.64 to 0.74. These data indicated that circulating radioactivity was predominantly associated with the plasma fraction.

Membrane transporter inhibition studies:

GW685698 and GW694301X (M10) inhibited human OATP1B1 in a stably transfected CHO-OATP1B with cell line with calculated IC50 values of 0.2 and 2.6 mcM (0.11 and 1.4 mcg/mL), respectively. In contrast, GW685698 and GW694301X (M10) did not inhibit transport of digoxin by human P-gp by polarized Madin-Darby canine kidney MDCKII-MDR1 cells transfected with the human MDR1 gene (produces the P-gp protein) at concentrations up to 30 and 100 mcM (16 and 54 mcg/mL), respectively. Finally in an effort to determine if GW685698 was a substrate for human P-gp, the potential for P-gp to transport GW685698 was investigated using stable transfected MDCKII-MDR1 cells cultured as monolayers plus or minus an inhibitor of human P-gp (GF120918). The apparent passive permeability of GW685698 was moderate [P7.4 of 80 ± 45 nm/s (mean ± SD)], indicating that it should diffuse across most membranes. The basal to apical efflux

ratio for GW685698 in the absence of GF120918 was 3 and this was reduced to 0.5 in the presence of the inhibitor, indicating that the compound was a substrate of P-gp.

In vivo distribution studies:

The tissue distribution of 3H-GW685698 has been assessed in the albino and pigmented rat using quantitative whole body autoradiography (QWBA) following iv and oral administration.

In the first of three tissue distribution studies performed using the intravenous route of drug administration, pigmented (Random Hooded) and albino (Wistar Han) male rats (n=5 and 15, respectively) received 3H-GW685698 as a single bolus dose of 133 mcg/kg. The vehicle used in this study comprised 10% Cremaphor in saline. Rats were killed (n=1 and 3 for pigmented and albino, respectively) at 0.5, 1, 4, 24 and 168 hours after dose administration, and QWBA performed. In general, radioactive drug-related material (DRM) was widely distributed throughout the tissues and most tissue radioactivity levels were higher than those found in the blood at 0.5 to 24 hours post dose. At 168 hours, tissue levels of radioactivity were only detectable (lower limit of quantification of 13 ng equi/g tissue), by QWBA, in the liver (40 ng equi/g of tissue) and kidney cortex (21 ng equi/g tissue in the region of proximal tubules). The highest levels of DRM were seen 0.5 hours after administration in the small intestine and small intestine wall, indicating extensive biliary clearance and secretion across the gastrointestinal tract wall. Levels in the lower large intestine rose later as might be expected from passage of gastrointestinal contents. Levels of DRM in the stomach and stomach wall were also high at the early time points. This may indicate transfer of a weakly acidic metabolite into the stomach. Tissue half-lives of radioactivity in liver, blood and kidney (cortex) as determined over 24 to 168 hours after intravenous administration ranged from 90 to 170 hours. DRM was not detectable (lower limit of quantification of 13 ng equi/g tissue) in the uveal tract of the pigmented rats, indicating no notable binding to melanin had occurred for the parent or metabolites. The tissue distribution of radioactivity was similar in albino (WH) and pigmented (RH) rats.

In the second intravenous whole body autoradiography study, 14C-GW685698 was administered as a bolus over approximately 30 seconds to 6 male pigmented rats (Lister Hooded) at a dose of 1000 mcg/kg. The vehicle used in this study comprised 40% polyethylene glycol 400 and 10% DMSO in saline. Single rats were killed at 1 and 4 hours, and 1, 3, 10 and 35 days post dose, and whole body autoradiography performed. Non-uniform levels of radioactivity were found in the liver, lung, spleen and bone marrow, particularly at 1 and 4 hours and 1 and 3 days post dose, consistent with microcrystalline deposits of either undissolved or precipitated test material building up in the capillaries of the vascular system within the aforementioned tissues. Consequently, no quantification of the autoradiograms was performed in this study. This pattern of radioactivity was attributed to the dosing method and vehicle employed since it was not observed in subsequent studies that utilised alternative vehicles and infusion dosing (up to 1 hour) and using similar doses.

Qualitative assessment of the autoradiograms revealed that DRM was widely distributed in the tissues at the first sampling time (1 hour); that the highest concentrations of radioactivity were found at this time; and that radioactivity concentrations declined such that by the final sampling time at 35 days, no tissues contained visible levels of radioactivity. Compared with other tissues, the brain and spinal cord only contained low levels of radioactivity at 1 and 4 hours post dose. Low levels of radioactivity were noted in the uveal tract/retina during the first 3 days post dose but radioactivity was no longer detectable at 10 days, suggesting no notable binding to melanin.

To overcome the precipitation of DRM observed in the previous study, the study was repeated with 14C-GW685698 given as an infusion over a 30 minute period to 6 male pigmented rats (Lister Hooded) at a dose of 1000 mcg/kg. The vehicle used in this study comprised 10% Cremaphor in saline. Single rats were killed at 1 and 4 hours, and 1, 3, 10 and 35 days post dose, and QWBA performed. Radioactivity was widely distributed at 1 hour after the start of the infusion (first time point). Highest levels of radioactivity at this time were measured in the following organs, presented in descending order of radioactivity: mucosa of the

small intestine, liver, Harderian gland, kidney cortex, preputial gland, adrenal cortex, exorbital lachrymal gland, brown fat, intra-orbital lachrymal gland, mucoas of the caecum, pancreas, white fat, aortic wall, epimysim and blood. The vast majority of tissues attained their highest observed concentrations at this time. Relatively low levels of radioactivity were associated with the brain, spinal cord and lens of the eye at 1 and 4 hours post dose. Thereafter, radioactivity was not measurable (lower limit of quantification of 3 to 5 ng equi/g tissue) in these tissues. By 10 days post dose, tissue concentrations of radioactivity had declined such that all values were either close to or below the limits of reliable quantification. At 35 days post dose, very low but quantifiable levels of radioactivity could be measured only in the spleen and blood.

In examining distribution after oral administration, pigmented (Random Hooded) and albino (Wistar Han) male rats (n=5 and 15, respectively) received a single oral administration of 3H-GW685698 at a nominal dose of 133 mcg/kg.

Rats were killed (n=1 and 3 for pigmented and albino, respectively) at 1, 4, 8, 24 and 168 hours post dose, and QWBA performed. There was limited distribution of radioactive drug-related material (DRM) into the tissues. The kidney, liver, spleen and gastrointestinal tract were the only tissues with higher levels than in the blood at 1 to 24 hours after dosing. This limited distribution contrasts with the findings after intravenous dosing and is probably due to relatively low absorption and rapid biliary clearance of the material that is absorbed. At 168 hours, radioactivity was only detectable, by QWBA, in the liver (17 ng equi/g tissue) and in the kidney cortex (18 ng equi/g tissue in the region of proximal tubules), as observed after intravenous dosing. The half-life of radioactivity in the liver, blood and kidney (cortex) of albino rats, measured over the period 24 to 168 hours post dose, ranged from between 70 to 110 hours. The levels of DRM in the blood were consistent with a half-life of <110 hours. No DRM was detectable (lower limit of quantification of 13 ng equi/g tissue) in the uveal tract of pigmented rats, indicating that no notable binding to melanin had occurred for the parent or metabolites. There was no apparent difference between DRM levels in albino and pigmented rats.

Umeclidinium (GSK573719)

The in vitro plasma protein binding of UMEC was moderate in animals and human. Protein binding data obtained using plasma from renally or hepatically impaired human subjects was slightly higher to that in plasma from healthy subjects. Blood cell association of UMEC was low in nonclinical species and human. Protein binding and blood cell association for UMEC were independent of concentration over the range investigated. In addition, UMEC was shown to be a substrate of human P-gp and of human organic cation transporter OCT1 and OCT2. These transporters are predominantly located in the liver and kidney, respectively. This data is contraindicative of distribution into tissues, and suggestive of the involvement of an active transport mechanism in the distribution of UMECStudies in rats showed that radioactivity was rapidly and widely distributed following intravenous administration. Tissue concentrations decreased with time and were generally below the limit of quantification by 10 days after dosing. Highest concentrations or radioactivity were observed in liver and kidneys, the organs associated with clearance of UMEC. Some accumulation in the uveal tract and retina was detected. In addition, retention of UMEC in the lungs of mice was demonstrated for up to 24 hours following a single intranasal administration.

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.

Metabolism

Fluticasone Furoate/Umeclidinium/Vilanterol

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

Fluticasone furoate (GW685698)

In vitro studies:

In vitro studies were performed using hepatic microsomes, hepatocytes and heterologiusly expressed cytochrome P450 (CYP) enzymes. The major route of metabolism observed in vitro, in all species, was hydrolysis of the S-fluoromethyl carbothioate function to form the carboxylic acid, GW694301X (M10).

There was no evidence of metabolism of GW685698 by human lung microsome or s9 preparations (WD2004/00004/00). GW685698 was metabolised in dog nasal s9 preparations but not metabolised in rat s9 nasal preparations or human CYP2A13 (a CYP450 isoenzyme known to be present in human nasal mucosa).

In vivo studies:

In all nonclinical species (mouse, rat, dog, rabbit and human), the principal route of metabolism was hydrolysis of the S-fluoromethyl carbothioate to form a range of metabolites including GW694301X (M10).

Umeclidinium (GSK573719)

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

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).

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 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.

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.

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 nonclinical species (mouse, rat, female rabbit and dog) investigated (78

to 94% of the total metabolism). In general, metabolic profiles in nonclinical and human hepatocytes were qualitatively similar. The extent of metabolism of 14C-GI179710 was high in all species investigated.

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.

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 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 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).

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).

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. Unchanged GW642444 was the only major component observed in dog plasma following intravenous dosing.

In humans, information on metabolism was obtained from human plasma on Day 7 following repeated inhalation dosing of GW642444 at 200 mcg/kg to asthmatic subjects.

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.

Excretion

Fluticasone Furoate/Umeclidinium/Vilanterol

No excretion PK studies were performed on the fixed dose combination fluticasone furoate/umeclidinium/vilanterol which was considered acceptable based on the data provided for the individual compounds.

Fluticasone furoate (GW685698)

Rat:

Following a single oral of 3H-GW685698, 100 mcg/kg (nominal) in male and female Wistar Han rats, the majority of the DRM was excreted in the faeces (90% to 92% of the dose) with the majority being excreted within the first 24 hours after dosing (77% to 87% of the dose). Very little of the dose (0.5 to 0.7%) was excreted in the urine.

Following a single intravenous dose of 3H-GW685698 as a bolus at 100 mcg/kg in male and female Wistar Han rats, most of DRM was again excreted in the faeces (90% to 97% of the dose), with the majority being excreted within the first 24 hours after dosing (79% to 89% of the dose). These data indicated that the majority of the DRM was eliminated via the bile into the gastrointestinal tract.

Dog:

Following a single oral of 3H-GW685698 (100 mcg/kg (nominal)) to beagle dogs, the majority of DRM was excreted mainly in the faeces via biliary excretion, with negligible renal excretion (the maximum urinary recovery of DRM was about 2%). The mean total recovery of DRM (including cage washes at less than 1% of dose) was 91% over 168 hours. The majority of DRM was excreted within 48 hours. No apparent sex-related differences were observed in the excretion of radioactive DRM.

Following intravenous dosing of 3H-GW685698 (100 mcg/kg) as a slow bolus to beagle dogs, excretion of the DRM occurred mainly in the faeces via biliary excretion, with negligible renal excretion (the maximum urinary recovery of DRM was about 2%).

Following intravenous infusion of 14C-GW685698 (100 mcg/mL) over a 30 minute period to beagle dogs, the majority of radioactivity was eliminated in the faeces, which accounted for a mean of 81.1% of the dose administered, consistent with biliary secretion of GW685698 DRM followed by faecal excretion. Urinary elimination was minor, accounting for a mean of 3.5% of dose. Elimination was initially rapid with a mean of approximately 80% of the dose being recovered by 48 hours post dose. Subcutaneous administration also showed comparable elimination routes in beagle dogs dosed with 100 mcg/mL 3H-GW685698 when compared with oral and iv, although at a slower rate.

Umeclidinium (GSK573719)

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

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

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 (see table below). Elimination of radioactivity was rapid with a mean of approximately 86% of the dose being eliminated during 0 to 24 hours post 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).

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.

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.

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) (500mcg/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. 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.

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 (see table below). 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.

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.

Pharmacokinetic drug interactions

Fluticasone furoate/umeclidinium/vilanterol

FF and VI are inhibitors and substrates for CYP3A4; and UMEC is a substrate for CYP2D6. Simulations were conducted using the SimCYP™ population based simulator, which predicts a 1.25-fold difference in mean AUC between PM and EM populations which is comparable to that observed in the clinic, where a 1.3-fold difference in AUC was observed between the populations. All three molecules are substrates but not inhibitors of P-gp. FF, UMEC and VI are not substrates of BCRP, OATP1B1 or OATP1B3 transporters, and FF inhibits OATP1B1. UMEC is also not a substrate for OAT1 and BSEP transporter, but is a weak poor substrate of OAT3 where time-dependent uptake of UMEC into cells expressing OAT3 was only 2-fold greater than control cells.

The limited in vitro inhibitory activity of FF, UMEC, and VI do not meet any of the thresholds of concern stipulated in regulatory guidance. These thresholds of concern are still not met even when taking into account the in vitro binding of FF, UMEC, and VI to human microsomal components. Based on this in vitro information, there should be minimal risk regarding an in vivo interaction should a potent inhibitor of one of these transporter systems be co-administered with FF, UMEC or FF. Therefore, the inhibition and induction potential of FF/UMEC/VI at low inhalation doses appears to be negligible.

Fluticasone furoate (GW685698)

Cytochrome P450 induction by GW685698 in animals

The potential for GW685698 to induce cytochrome P450 enzymes was investigated in rats. Portions of the liver were collected from groups of Wistar Han rats (n=6/sex) which had received a daily inhaled dosed of GW685698 at a target dose of 64 mcg/kg in a 4 week toxicology study.

Daily treatment of the rats with GW685698 at this dose for 4 weeks was not found to have any significant effects on hepatic microsomal protein or total cytochrome P450 (CYP) concentrations, or on the activities of the CYP1A, CYP3A, CYP2B, CYP2E or CYP4A enzymes.

No other nonclinical studies have been performed to specifically investigate the potential for GW685698 to undergo pharmacokinetic drug interactions when administered concomitantly with other drugs or foods.

Umeclidinium (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.

Vilanterol (GW64244)

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

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.

2.3.4. Toxicology

Following comparison of the pharmacological and toxicological profiles of FF, UMEC and VI, as well literature data, no causes for significant toxicological concern were identified for the triple combination, FF/UMEC/VI. However, since the triple combination had not been evaluated previously in nonclinical species, and in accordance with the ICH M3 (R2) guidance (2009), a 13 week inhaled toxicity study in dogs with the triple combination FF/UMEC/VI was conducted. This included toxicokinetic evaluations, and a weight of evidence review of the immunotoxicity potential of FF, UMEC and VI.

Single dose toxicity

Fluticasone Furoate/Umeclidinium/Vilanterol

No single dose toxicity studies were performed on the fixed dose combination Fluticasone Furoate/Umeclidinium/Vilanterol which was considered acceptable based on the data available for each compound. The data presented below summarises current knowledge on each mono-component.

Fluticasone furoate (GW685698)

Single dose toxicity studies have been performed in order to determine the inhalation toxicity of GW685698. In addition, single dose toxicities have been performed with GW685698 administered via the oral, SC and IV routes. Dose levels in the inhalation studies represented the highest technically achievable aerosol concentrations with a particle size distribution suitable for inhalation testing in rodents.

In one study, CD-1 mice were given vehicle alone (lactose) or GW685698 then killed on Day 3 or Day 15. It was observed marked body weight loss in the majority of males (mean 4.3%) and all females (mean 10.8%). Treatment-related microscopic findings are limited to atrophy in the thymus of all GW685698-treated animals and lymphoid depletion in the spleen of 4 animals. Reversibility of the microscopic findings and body weight was apparent.

Umeclidinium (GSK573719)

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

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.

Repeat dose toxicity

Fluticasone Furoate/Umeclidinium/Vilanterol

The objective of the 13 week study was to determine the toxicity and toxicokinetics of FF (GW685698), UMEC (GSK573719) and VI (GW642444) when given in combination to dogs via daily inhalation (oropharyngeal tube) administration for 10 minutes/day for 13 consecutive weeks at an anticipated clinical ratio of 4:1:5 for GW685698, GW642444 and GSK573719, respectively and to compare findings with each of the test articles administered alone.

The study was carried out by the inhaled route of administration as this is the proposed therapeutic route in humans. The beagle dog had been selected as the non-rodent species on the basis of similarities in the pharmacokinetic and metabolic handling of FF, UMEC and VI between the selected species and humans, and data obtained in previously submitted studies.

Test article-related findings consistent with expected class effects of corticosteroids, long acting beta2 adrenergic receptor agonists (LABAs) or long acting muscarinic acetylcholine receptor antagonists (LAMAs) were noted. No major exacerbations of these findings were evident for FF/UMEC/VI when administered in either high or low dose combinations at a ratio of 4:5:1.

FF/UMEC/VI was administered at a ratio of 4:5:1, consistent with the ratio in the combination originally investigated in the clinic. However, the product proposed for marketing in this application contains FF/UMEC/VI in a ratio of 4:2.5:1. Although the ratio investigated in dogs differs from that proposed for

marketing, since all findings are related to FF and there was no exacerbation with the triple combination which contained a higher ratio of UMEC compared to FF and VI, the study is considered to support FF/UMEC/VI commercial product at the proposed ratio.

Overall, sufficient safety margins are seen when principle toxicological findings are compared to that seen at the proposed human clinical dose.

Available information for each mono-component is provided below.

Fluticasone furoate (GW685698)

The repeated dose inhalation profile toxicity of GW685698 was appropriately assessed in mice, rats and dogs at doses up to 76.9, 20.3 and 59.6 mcg/kg/day for durations up to 13, 26 and 39 weeks, respectively. The high doses used in these studies were selected on the basis of maximum tolerated repeat dose, which were generally limited by decreased body weight gain. In dogs and rats, systemic exposures (AUC) achieved at these doses were less than 10-fold those achieved in humans at the proposed commercial dose of 100 mcg/day. Therefore, exposure multiples are not given for the effects observed. The obtained findings in these studies were typically associated with glucocorticoid excess and commonly reported for other marketed inhaled steroids including GW685698, therefore a NOAEL was not identified. The GW685698 related findings observed in these studies are described below.

Clinical observations included reductions in body weight or lower body weight gain in mice, rats and dogs at most dose levels; hair loss and/or skin thinning in mice, rats and dogs in most dose groups, and hair growth being predominantly in the telogen phase in rats dosed at ≥8.3 mcg/kg/day for 26 weeks and in dogs given GW685698 at ≥20.6 mcg/kg/day with or without GW642444 in the 13 week combination toxicity study.

Immunosuppression observations included buccal cavity papillomas (canine papilloma virus), exacerbation of minor respiratory tract lesions, chronic inflammation of the stomach and demodecosis in the 13 and 39 week studies in dog.

Lymphoid tissues showed the expected reversible lymphoid depletion in thymus (together with thymic atrophy and reduced thymus weight), spleen, larynx, tonsils, lymph nodes (mesenteric, mandibular, bronchial, cervical), NALT, GALT and / or laryngeal mucosal-associated lymphoid tissue in mice, rats and dogs in most studies.

Haematology observations included lymphocytopenia, eosinopenia and neutrophilia in mice, rats and dogs in most studies, together with increase in red blood cell parameters (haematocrit, haemoglobin concentration and/or erythrocyte count) in rats and decrease in dogs.

In the pituitary gland, it was observed reduction in ACTH-producing cells with the resulting increased prominence of other cellular types including the acidophilic cells in the 39 week study in dogs. The impact of this effect included cortical atrophy, a reduction in adrenal weight and lower or absent plasma levels of cortisol in all dog studies.

Metabolic effects included changes in clinical chemistry parameters in rats and dogs (plasma triglycerides, cholesterol, total protein, glucose, alkaline phosphatase and alanine aminotransferase activities, urinary volume and electrolytes). In addition, reversible hepatocellular vacuolation/increased rarefaction was seen in most dog studies.

In the lungs, it was observed increase of minimal eosinophilic inclusions in a very small proportion of Clara cells of the bronchial epithelium at all dose levels in rat studies for ≥ 3 months. This effect did not exceed levels of severity seen in background data, did not progress with longer durations of dosing since it was not seen in the carcinogenicity study, and is a normal physiological response to the deposition of particulate material in the rat.

In the kidney, it was observed slight increase of the naturally occurring hyaline droplets in the renal cortical tubules of male rats in some rat studies up to 13 weeks duration with GW685698 alone or in combination with GW642444. This effect was of mild severity, and similar to those normally expected in healthy control rats so it is considered not to indicate a direct nephrotoxic effect.

In the mammary glands of female rats given GW685698 alone and in combination with GW642444 in the 4 and 13 week combination toxicity studies, an increased secretory activity was observed. This effect has been reported with other marketed corticosteroids, therefore it is considered to have little relevance to the therapeutic use.

In the rat teeth, it was observed pallor of incisor teeth associated with vacuolation, degeneration and disorganisation of the ameloblast layer (≥52 mcg/kg/day) and/or disorganisation of the odontoblast layer at all doses (≥7.85 mcg/kg/day) in animals exposed to GW685698 alone and in combination with GW642444 in the 13 week study. These effects were not seen in the dog, mouse or rabbit. This is a known effect of corticosteroids and it is possible that paediatric patients may be susceptible to these effects of inhaled corticosteroids, however, it is less likely to be of relevance for use in adults or adolescent patients.

In the stomach, minimal or slight inflammatory changes predominantly in the cardia region, were seen in the 39 week dog study at doses ≥30.1 mcg/kg/day. These changes were considered secondary to the immunosuppressant effects of treatment. This pathology is variable in both species, did not progress with longer treatment, and it is considered a class effect.

In addition, there was an increase of connective tissue hyalinisation in the pyloric mucosa of the stomach at all doses in the 2 year carcinogenicity study in the mouse. This alteration was not seen in rats or dogs, and it is considered to be a local effect on the mucosa since a high proportion of the inhaled dose is swallowed.

In the gall bladder, an increase of luminal mucin was seen in dogs which appear to be dog specific. A minor increase in lipid vacuolation in the bile duct and gall bladder epithelium, not associated with cellular degeneration or inflammatory changes, was also seen in some dog studies. Since this effect is of similar severity to that observed in untreated dogs, and is a dog-specific observation, it is considered not of concern for human safety.

In the skeletal muscle, it was observed pallor and/or minimal to slight myofibre atrophy in hindlimbs of dogs given GW685698 at ≥61.0 mcg/kg/day (achieving systemic exposures ≥4-fold those achieved at the proposed commercial dose) with or without GW642444 in the 13 week combination toxicology study. This is an effect sometimes seen with corticosteroids in the dog following long-term administration.

Umeclidinium (GSK573719)

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

According to the Applicant, the spectrum of microscopic changes observed in the upper respiratory tract of mice, rats and dogs are considered to be indicative of a local irritant effect to Umeclidinium, which could have been exacerbated by the drying of the mucosa associated with the antimuscarinic pharmacological action of UMEC. This justification is considered acceptable. In humans, local irritancy (e.g. cough, nasopharyngitis, oropharyngeal pain) were commonly reported during clinical trials across all treatment arms which included placebo. However, they were not associated with any sequelae.

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

Granuloma formation in the lung was observed in one dog study and was considered to be secondary to excessive antimuscarinic pharmacology. Gall bladder distension and myofibre degeneration detected in one

14-day dog study was not observed in pivotal studies in dogs, and available clinical data indicate no increased risk for gall bladder distension or clinical symptoms. Therefore, all these findings are considered of less importance and without clinical significance which is acceptable.

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. 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. 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. 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 ratand 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. 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. 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). This effect in only the high dose combination and is considered of no clinical relevance since at these doses, systemic exposures were 77-fold (GW642444) and 6-fold (GW685698) greater than those in patients at the proposed commercial doses.

In the skeletal muscle, minor microscopic changes were seen in male rats in all groups given GW642444 at ≥6.29 mcg/kg/day (expected AUC0-t is similar to AUC0-t at the human commercial dose) alone or in combination with GW685698 in the 4 week combination toxicity study. These changes were not seen in the other performed studies with GW642444 at doses achieving AUC0-t >2500-fold greater than that at the proposed commercial dose.

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.

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 male 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. As 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.

Genotoxicity

Fluticasone Furoate/Umeclidinium/Vilanterol

In accordance with ICH guidance ICH M3 (R2), no genotoxicity studies with the FF/UMEC/VI combination were carried out. Previous in vitro or in vivo genotoxicity studies with either FF, UMEC or VI indicate that none of the components of the combination product represents a genotoxic hazard to humans.

Fluticasone furoate (GW685698)

GW685698 was not mutagenic in a battery of in vitro studies (bacterial mutagenicity test or chromosomal damage in a mammalian) and in vivo micronucleus tests in rats. Concentrations used in the in vitro tests were limited by precipitation or cytotoxicity and intravenous doses up to the maximum tolerated were used in vivo, which achieved up to 500000-fold C_{max} obtained following inhaled administration at the proposed commercial dose of 100 mcg/day.

Umeclidinium (GSK573719)

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

Vilanterol (GW642444)

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.

Carcinogenicity

Fluticasone Furoate/Umeclidinium/Vilanterol

In accordance with ICH guidance ICH M3 (R2), carcinogenicity studies were not performed with FF/UMEC/VI combination. The carcinogenic potential of FF, UMEC and VI was thoroughly assessed for the single mono-components. There were no treatment-related increases in tumour incidence following lifetime administration of FF or UMEC by the inhalation route. In the inhaled carcinogenicity studies with VI, proliferative changes were seen in the female reproductive tract of rats and mice, and pituitary gland of rats. Non-clinical carcinogenicity findings with VI were similar to other beta-2 agonists. All proliferative effects seen at high systemic exposures in rats and mice have been observed following administration of other beta-2 agonists, and are considered not to be clinically relevant.

Fluticasone furoate (GW685698)

Mouse carcinogenicity study

The carcinogenic potential of GW685698 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), 2.2, 6.1, 18.8 mcg/kg/day in lactose once daily, for 1 hour/day.

There was no evidence of an effect of treatment on mortality rates. Unscheduled deaths were comparable across all groups at weak 78 and at week 104 the percentage survival was greater than or equal to 30% across all groups.

A treatment related increased incidence of hairloss, chiefly on the head/nasal region, was recorded for animals at all doses. Microscopically in the skin there was an increased incidence of inflammatory changes (epidermal ulceration/hyperplasia, dermal fibrosis and scabs) at all doses. Reduced body weight gain was seen at 6.09 and 18.8 mcg/kg/day, and minor changes in haematology (reduced lymphocytes in males (all doses) and increased platelets in females (18.8 mcg/kg/day) and clinical chemistry parameters (lower urea and higher total protein levels) were observed in week 104. Microscopic pathological findings in the lymphoid tissues and stomach together with inflammatory changes in the respiratory tract were seen at all doses. In the lungs there was a reduction in the amount of BALT in males and females in all treated groups. The severity of the change showed a clear relationship to dose. There was also a reduced incidence of epithelial eosinophilic inclusions in the nasal cavity in males and females from all treated groups. In the stomach there was dose-related increase in the incidence and severity of connective tissue hyalinisation in the stomach of males and females at all doses. These findings are considered to be related to the pharmacological action of this class of compound.

Treatment with GW685698 did not increase the incidence of any neoplastic finding. There was a slight increase in the incidence of bronchioloalveolar epithelial hyperplasia, and of bronchioloalveolar adenoma in the lungs of males receiving 6.1 mcg/kg/day, compared with concurrent controls. However the increased incidence of bronchioloalveolar adenoma was considered to be fortuitous given that the incidence of the adenomas was not dose dependent (i.e. absent on the high dose group), a low incident was seen in females at the same dose and a comparable incidence was observed in historical controls for this tumour type.

Toxicokinetic analysis revealed systemic exposure to GW685698 was demonstrated in each of the dosed groups.

Rat carcinogenicity study

The carcinogenic potential of GW685698 was assessed in a 2 year inhalation repeat dose study in which groups of rats (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).

Survival in male rats was unaffected by treatment with GW685698X. However, in females there was a treatment-related reduction in survival at 3.19 and 8.61 mcg/kg/day during the final 13 weeks of the study although there were no associated histopathological changes. A treatment related degree of hairloss, chiefly located on the head/nasal region, was recorded for intermediate and high dose animals. Minor changes in haematology (significantly reduced total white cells, lymphocytes, eosinophils, basophils and monocytes) and clinical chemistry parameters (higher potassium levels in males and bilirubin levels in females) occurred at 8.61 mcg/kg/day.

Treatment with GW685698 did not increase the incidence of any neoplastic finding for any group of animals. However, there were decreased incidences of haemangioma and lymphangioma in the mesenteric lymph node and of thymoma (lymphoid) in animals receiving 8.6 mcg/kg/day. The incidence of focal endothelial hyperplasia in the mesenteric lymph node was also reduced in this group.

Microscopic pathological findings in the lymphoid tissues together with changes in inflammatory responses in the respiratory tract were seen at all doses. In the nasal turbinates a decreased cellularity of the NALT was accompanied by a decreased incidence and/or degree of eosinophilic inclusions in the olfactory

epithelium at all doses. However, in the lungs, decreased cellularity of the BALT was accompanied by a minimal increase in the incidence of eosinophilic inclusions in the bronchiolar epithelium at all doses. This latter finding was consistent with similar observations after 13 and 26 weeks treatment demonstrating a lack of progression despite lifetime administration; the content of the inclusions was identified as Surfactant Protein-D. Furthermore, the incidence of inflammatory cells or inflammation was reduced at all doses in the lamina propria of the respiratory epithelium of the nasal cavity, the nasopharynx, trachea, tracheal bifurcation at the point of bifurcation and in the adjacent trachea and bronchi at 3.2 and 8.6 mcg/kg/day, and in the nasal turbinates, lungs and lamina propria of the larynx at 8.6 mcg/kg/day. Other changes included an increased incidence of pigmented macrophages in the lamina propria of the larynx at all doses, alveolar pigmented macrophages (females only) and perivascular/peribronchiolar pigmented macrophages in the lung, and decreased incidence of foamy macrophages in the lung at 3.2 and 8.6 mcg/kg/day. At all doses there was an increased incidence of dilated vaginations from the ventral pouch of the larynx and an increased incidence of mastocytosis in the mesenteric lymph node. At 8.6 mcg/kg/day there was an increased incidence of dilated glands in the trachea (males only). The lung changes were associated with a decreased incidence of pale lungs observed macroscopically at the terminal kill.

GW685698 was only quantificable at the highest dose level (8.6 mcg/kg/day). Systemic exposure to GW685698 (as assessed by AUC0-t and Cmax) was similar in both Weeks 45 and 58 and in males and females. At 8.16 mcg/kg/day overall AUC0-t was 0.320 ng.h/mL and Cmax was 0.122 ng/mL (data combined for males and females at Weeks 45 and 58).

Umeclidinium (GSK573719)

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

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

Vilanterol (GW642444)

Mouse carcinogenicity study

The carcinogenic potential of GW642444 was assessed in a 2 year inhalation repeat dose study in which groups of mice (84/sex/group) were administered estimated achieved doses of 0, 6.4, 62, 615, 6150 or 29500 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).

Reproductive and Developmental toxicity

Fluticasone Furoate/Umeclidinium/Vilanterol

No reproductive and developmental toxicity studies were carried out as agreed with CHMP, Scientific Advice EMEA/H/SA/2498/2/2013/I, and in accordance with ICH guidance ICH M3 (R2). Previous findings in reproductive toxicity studies with FF were typical of those seen following systemic exposure to potent corticosteroids. In the rat there was no effect on male fertility, and only a slight increased incidence of prolonged oestrus cycles in females. There was also no effect on offspring in the pre- and post-natal study. Although corticosteroids are generally teratogenic in animal species, FF was not teratogenic. There was however, evidence of delayed/incomplete ossification of sternebrae in rat fetuses and abortion of rabbit fetuses, though each at doses associated with maternal toxicity. UMEC had no effects on male or female mating performance or fertility, nor any effects on embryofetal survival and development in either the rat or rabbit. VI did not affect male or female rat fertility nor did it produce any adverse effects on the developing rat fetus. However, in the rabbit, inhaled doses of VI caused a number of class-related but inconsistent findings such as cleft palate, open eyelids, sternebral fusion and abnormal frontal bone ossification. Co-administration of FF and VI in a rat embryofetal development study did not reveal any new effects.

Fluticasone furoate (GW685698)

Male fertility

GW685698 or vehicle (lactose) was administered by inhalation once a day for 1 hour to groups of 25 male Wistar Han rats at estimated achieved doses of 6.6, 12.9 and 29.4 mcg/kg/day for 28 days prior to cohabitation with females, during cohabitation, and through to necropsy on Day 69 to 73.

A dose-dependent reduction in body weight progression and food intake was observed at all doses. No other clinical signs or macroscopic pathological findings were observed. There were no effects on fertility of the males or early embryonic development of the offspring of untreated females with which they were mated. The No Observed Adverse Effect Level (NOAEL) for reproduction and fertility of male rats of the F0 generation and on the early in utero development of the F1 generation was 29.4 mcg/kg/day.

Female fertility, early embryonic and embryofetal development

GW685698 or vehicle (lactose) was administered by inhalation, once a day for 1 hour, to groups of 22 female Wistar Han rats at estimated achieved doses of 0, 11, 23 and 91 mcg/kg/day from 2 weeks prior to mating until gestation Day 17.

Animals receiving 91 mcg/kg/day showed overall body weight loss during the first week of dosing followed by a period of lower body weight gain persisting into the first half of the gestation period. This was coupled with slightly reduced food consumption.

There were no clinical signs, macroscopic findings, adverse effects upon mating performance, pre-coital interval or fertility related to treatment with GW685698. A slightly higher incidence of longer oestrus cycles (4 or 5 days) was observed in animals at 91 mcg/kg/day. No major skeletal or visceral abnormalities were noted in the foetuses from females at any dose. However, lower fetal weight (5%) and related increased incidence of fetuses with incompletely ossified sternebrae were noted in females exposed to 91 mcg/kg/day. Owing to these effects, the NOAEL for fertility, early embryonic and embryofoetal development in the rat was considered to be 23 mcg/kg/day.

Embryo-foetal development

A preliminary study was conducted to evaluate the toxicity of GW685698 when administered by inhalation to pregnant New Zealand white rabbits. This provided sufficient information to select doses for a subsequent definitive embryofoetal development study in the rabbit. In the preliminary study, groups of 6 female New Zealand white rabbits were treated, from gestation day 8 to 20, with vehicle (lactose) or GW685698. Animals were exposed once a day for 1 hour at estimated achieved doses of 9.7, 46.6 and 85.1 mcg/kg/day.

Dose-related reductions in maternal body weight gain were evident at all dose levels together with a reduction in food consumption at 9.7 and 46.6 mcg/kg/day. There were no clinical signs related to treatment with GW685698. All rabbits at 85.1 mcg/kg/day and 2 of 6 females at 46.6 mcg/kg/day were terminated between gestation day 19 and 23 following abortion of their fetuses. Post-implantation losses were increased and litter weights reduced in all GW685698 treated groups. Mean foetal weights were also lower in animals treated at 46.6 mcg/kg/day. Due to the effects on maternal and fetal body weight, a targeted high dose of 10 mcg/kg/day was considered suitable for a subsequent definitive study.

In the definitive study, GW685698 or vehicle (lactose) was administered (1 hour/day) by inhalation to groups of 22 female New Zealand white rabbits from gestation Day 8 to 20 at estimated achieved doses of 1.8, 3.2 and 8.1 mcg/kg/day.

A transient loss in body weight was noted in all GW685698 treated groups over the first 4 days of treatment, thereafter, weight gain was comparable to controls. There were no treatment related effects on food consumption or clinical signs.

There were also no treatment related effects on corpora lutea, implantation count, placental or foetal weight. An increased incidence of incompletely ossified sternebrae and metacarpals/phalages was seen in foetuses from animals treated at 3.2 or 8.1 mcg/kg/day. However, since there was a greater incidence at 3.2 mcg/kg/day than 8.1 mcg/kg/day and there was no associated effect on fetal weight, this finding is considered to be unrelated to treatment. A NOAEL of 8.1 mcg/kg/day was ascribed for embryofoetal development in the rabbit.

Pre- and post-natal development study

To investigate potential effects on pregnancy, parturition and lactation, and on pre- and post-natal survival, growth, development, and reproductive performance of offspring, GW685698 or vehicle (lactose) was administered by inhalation to groups of 22 or 23 female Wistar Han rats from gestation day 6 to 20 and Days 2 to at least Day 21 post partum. Animals were exposed once daily for 1 hour at estimated achieved doses of 0, 5.5, 15.7 and 27.2 mcg/kg/day. The female F0 generation were allowed to deliver naturally. At 84 days post partum, the F1 generation males and females were cohabited in a ratio of 1 to 1 for up to 14 days. Mated F1 females were allowed to deliver naturally and they and their litters (F2 generation) were evaluated on Day 7 post partum.

In the F0 generation, dose dependent reductions in body weight gain were observed in pregnant dams given 15.7 or 27.2 mcg/kg/day, resulting in lower body weights compared to controls. At 15.7 and 27.2 mcg/kg/day, lower food consumption was also evident. The gestation index, length of gestation, numbers of live and dead pups, sex ratio, and live birth index were unaffected by treatment with GW685698.

For the F1 generation pups, viability, survival and lactation indices, clinical condition, pup weights and gross pathology were unaffected by treatment of the F0 Dams. Development of these pups to adulthood was similarly unaffected (including preputial separation and vaginal opening). Behavioural performance (assessed by motor activity, auditory startle habituation and water maze) was comparable to controls.

Following mating of the F1 generation, all measured parameters, including mating index, fertility index and conception rate, gestation index and gestation length, sex ratio, and numbers of live, dead and malformed pups were comparable to controls. Pup viability and survival indices, clinical condition, pup body weights and terminal examinations were also undisturbed in the F2 generation compared to controls.

The NOAEL for developmental (F1/F2) effects was considered to be 27.2 mcg/kg/day.

Umeclidinium (GSK573719)

Fertility

In reproductive and developmental toxicity studies in the rat and rabbit, UMEC had no effects on male or female mating performance or fertility at inhaled doses of up to 180 and 294 mcg/kg/day, respectively. The male fertility study and the pre-and post-natal study in rats were conducted by subcutaneous administration; however, considering the high exposure observed by this route of administration, this is not considered an issue. Systemic exposure at the NOAEL in maternal rats was approximately 80 times the exposure in humans at the proposed commercial dose of 62.4 µg/kg/day.

Embryo-foetal development

No effects on embryofetal survival and development were seen in either the rat or rabbit following inhaled doses up to 278 and 306 mcg/kg/day, respectively or in the rabbit following subcutaneous doses up to 180 mcg/kg/day.

Pre- and post-natal development study

In a rat pre-and post-natal study, slightly decreased pre-weaning pup body weights in litters was related to a decreased maternal body weight gain and food consumption. There were no other effects on pre-natal or post-natal development.

Vilanterol (GW642444)

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.

Embryo-foetal development

GW642444 (as the triphenylacetate salt, GW642444M) was administered as a dry powder formulation to mated females 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.

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.

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.

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 water maze evaluations. F1 offspring assigned to Subset 2 were euthanized after behaviour 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.

Immunotoxicity

Fluticasone Furoate/Umeclidinium/Vilanterol

A weight of evidence review for potential immunotoxicity was carried out. Overall immune-related findings attributed to FF in preclinical toxicity studies were typical of those previously reported for systemic exposure to glucocorticoids, immunosuppression and worsening of existing infections, and were largely reversible on withdrawal of treatment. Further, despite the immunosuppressive effects common to drugs of this class, tumour immunosurveillance did not appear to be affected. There were no findings in general toxicology studies that indicated a direct effect of UMEC on the immune system. Immune-related findings in general toxicology studies included hyperplasia, metaplasia and inflammatory cell infiltration in the upper respiratory tract of mice, rats and dogs, and interstitial, bronchoalveolar and granulomatous inflammation in lung of dogs, and were considered secondary to irritancy or foreign body reactions, respectively. It is likely that these changes are a secondary reaction to inhaled exogenous material in animals where the mucus defence mechanism has been compromised by administration of supra-pharmacological doses of anti-muscarinics and are not directly related to test article. VI alone produced findings generally consistent with the expected class effects of inhaled beta2-agonists, respiratory tract irritancy, and there was no consistent evidence of unintended immunomodulation in general toxicology studies. In combination toxicity studies test article related finding consistent with the expected class effects of administration of either a corticosteroid or long-acting muscarinic acetylcholine receptor antagonist were noted. There were no new toxicities in animals exposed to two or all three test compounds in combination relative to either test article alone that indicated immunotoxicity.

Fluticasone furoate (GW685698)

The tolerability of an aerosol formulation of GW685698 during daily 1 hour inhalation exposures for 5 days, and the sensitisation potential of GW685698 when inhaled for 1 hour for 5 consecutive days, followed by a 17 day off-drug period and a single 1 hour inhalation challenge exposure, was investigated in the guinea pig. In the tolerability arm of this study, groups of 5 male guinea pigs were given 0 (air only) and an estimated achieved dose of 70.6 mcg/kg/day) GW685698 once daily for 5 days by nose only inhalation. The daily doses of GW685698 were well tolerated.

To assess the sensitisation potential of GW685698, groups of 10 male guinea pigs were given GW685698X (0, 67.1, 71.2 mcg/kg/day) via inhalation for 60 minutes for 5 consecutive days, followed by a 17 day off-drug period and a single 60 minute inhalation challenge exposure (ovalbumin or saline).

There was no evidence of respiratory hypersensitivity reactions in guinea pigs exposed to 5 daily doses of GW685698 followed by a single inhalation challenge exposure 17 days later. The positive control (ovalbumin) did elicit an acute anaphylactic reaction.

2.3.5. Ecotoxicity / environmental risk assessment

The provided ERA demonstrated that fluticasone furoate, umeclidinium bromide and vilanterol trifenatate PEC surfacewater values are below the action limit of 0.01 µg/L and are not PBT substances as log Kow does not exceed 4.5. Results from chronic aquatic toxicity tests revealed that both umeclidinium bromide and vilanterol trifenatate are very toxic to alga. Umeclidinium bromide was also toxic to daphnia in chronic studies but toxicity was not exhibited in the chronic fish study. Likewise, vilanterol trifenatate was harmful to daphnia in chronic aquatic studies and toxicity was exhibited in the chronic fish study. However, test concentrations associated with these effects are orders of magnitude in excess of the PEC in surface water and therefore umeclidinium bromide and vilanterol trifenatate are unlikely to represent a risk at the aquatic environment. Because fluticasone furoate is a glucocorticoid and as such could be considered as a potential endocrine disruptor, the applicant investigated the potential endocrine activity of this compound. Accordingly, a fish early life-stage test was conducted, as a range-finder to set concentrations for an extended early life-stage test. The study concluded that no statistically significant effects were observed between the controls and any of the test concentrations in terms of hatching success, post-hatch survival, growth or spawning ability. Consequently, fluticasone furoate, umeclidinium bromide and vilanterol trifenatate are not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

The applicant has performed a13-week repeat dose toxicity with the triple fixed dose combination of FF/UMEC/VI study in Beagle dogs with appropriate toxicokinetics sampling. This study used a 4:5:1 fixed combination of FF:UMEC:VI which differs from the proposed clinical combination of 4:2.5:1, however, since this difference involves a reduced level of UMEC the combination used for the non-clinical studies is considered acceptable.

In this bridging study observed toxic effects are primarily considered to be known corticosteroid, muscarinic antagonist or beta2 agonist class effects associated with their primary pharmacology and indicative of local irritant effects of the compounds.

A weight of evidence review for potential immunotoxicity was carried out. Overall immune-related findings attributed to FF in preclinical toxicity studies were typical of those previously reported for systemic exposure to glucocorticoids. There were no findings in general toxicology studies that indicated a direct effect of UMEC on the immune system. VI alone produced findings generally consistent with the expected class effects of inhaled beta2-agonists.

Based on the studies presented and the proposed clinical dose, the FDC (fluticasone furoate, umeclidinium bromide and vilanterol trifenatate Inhalation Powder -– Trelegy Ellipta and Elebrato Ellipta) would not be considered to represent a potential for toxicity than those already known for each monocomponent of the pharmacological classes. The findings do not raise any new significant safety concerns for the clinical use of Trelegy Ellipta and Elebrato Ellipta as an inhalation powder at the proposed human therapeutic dose of 100/62.5/25 mcg/day (fluticasone furoate, umeclidinium bromide and vilanterol trifenatate).

The pharmacodynamic, pharmacokinetic and toxicological effects of fluticasone furoate, umeclidinium bromide and vilanterol trifenatate alone and in combination are considered to have been well characterised in non-clinical studies considering also the available data related to each monocomponent.

2.3.7. Conclusion on non-clinical aspects

Overall, the non-clinical data are appropriate to support the use of Trelegy Ellipta and Elebrato Ellipta in the clinical setting.

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.

Certain Quality Control issues were identified by the applicant regarding appropriate document version control and the detection of minor programming errors relating to some of the efficacy analyses in the clinical trials presented to support the application. The applicant has identified the probable cause of these errors, and has adequately described measures to resolve these.

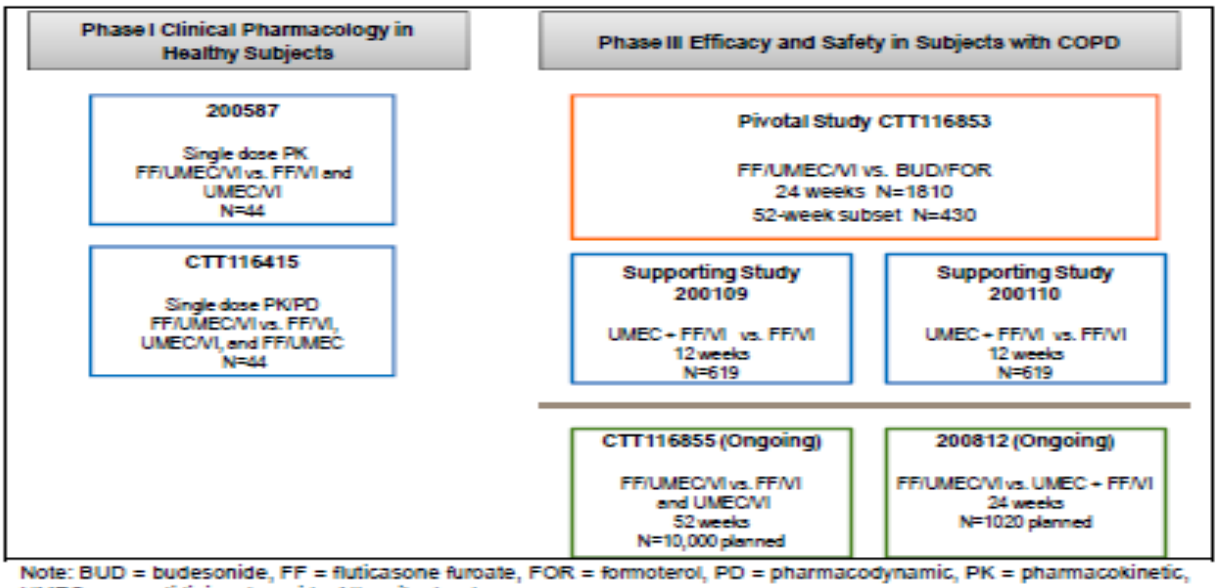
Tabular overview of clinical studies

Table 8

Study ID	Study format
200587	Single dose PK FF/UMECVI vs. FF/VI and UMEC/VI in healthy volunteers n = 44
CTT116415	Single dose PK/PD FF/UMECVI vs. FF/VI, UMEC/VI and FF/UMEC in healthy volunteers n = 44
CTT116853	Safety and efficacy of FF/UMEC/VI vs BUD/FOR in patients with COPD n = 1810 for 24 weeks and n = 430 for 52 weeks
200109	Safety and efficacy of UMEC + FF/VI vs. FF/VI on patients with COPD n = 619 for 12 weeks
200110	Safety and efficacy of UMEC + FF/VI vs. FF/VI on patients with COPD n = 619 for 12 weeks (replicate of 200109)

The clinical programme is described in the figure below.

Clinical Programme in Support of FF/UMEC/VI



Note: BUD = budesonide, FF = fluticasone furoate, FOR = formoterol, PD = pharmacodynamic, PK = pharmacokinetic, UMEC = umeclidinium bromide, VI = vilanterol

Figure 5

During Scientific Advice (EMEA/H/SA/2498/1/FU/1/2013/II), the CHMP agreed that a single Phase III study of FF/UMEC/VI versus an approved ICS/LABA (CTT116853) and two supporting studies with UMEC + FF/VI (200109 and 200110) could form the basis of an initial MAA thus the focus of this Clinical Overview is on the results of these studies.

2.4.2. Pharmacokinetics

Two randomised, single-dose, 4-period crossover clinical pharmacology studies have been performed with FF/UMEC/VI in healthy adult subjects (CTT116415 and 200587). They investigated the systemic exposure and systemic PD (CTT116415 only) of the triple combination product FF/UMEC/VI, compared with the dual therapies FF/VI and UMEC/VI. Total systemic exposure was similar for FF, UMEC, and VI when administered as a triple therapy compared with FF/VI and UMEC/VI.

Study 200587 was a Phase 1, open-label, randomised, single-dose (4 inhalations), 4-period, 4-sequence crossover study in healthy subjects.

The study was conducted at a single investigative centre, Parexel International, Harbor Hospital Centre, 7th floor, 3001 S. Hanover Street, Baltimore, Maryland, United States 21225, from July to September 2013.

The aim of the study was to compare the systemic PK of the components of FF/UMEC/VI triple combination at two dose strengths of UMEC (62.5 and 125 mcg). The high dose strength of UMEC (125 mcg) was investigated as the study was conducted prior to the decision of utilising only the lower dose of UMEC (62.5 mcg) in clinical development.

In addition, the FF/VI (100/25 mcg) and UMEC/VI (62.5/25 mcg) dual combination arm was included to compare the individual components in the triple versus dual combination. In order to adequately characterise the systemic PK profile for each component, subjects received a supra-therapeutic (4-fold multiple) dose of the fixed-dose combination (FF/UMEC/VI 100/62.5/25 and 100/125/25 mcg, and FF/VI 100/25 mcg and UMEC/VI 62.5/25 mcg). Study drug was administered as four inhalations by dry powder inhaler (DPI) at each dosing session.

Study CTT116415 was a Phase I, randomised, double-blind, single-centre, single-dose (4 inhalations), 4-period, 4-sequence crossover study in healthy subjects. The aim of the study was to assess the PK and PD of FF, UMEC, and VI and to compare the systemic PK of the components of FF/UMEC/VI triple combination at the high dose strength of UMEC (125 mcg) versus each dual combination FF/VI (100/25 mcg) and FF/UMEC (100/125 mcg). The high dose strength of UMEC (125 mcg) was investigated in CTT116415 because the study was conducted prior to the decision of utilising only the lower dose of UMEC (62.5 mcg) through clinical development. In order to adequately characterise the systemic PK profile for each component, the healthy volunteer subjects received a supra-therapeutic (4-fold multiple) dose of the triple fixed-dose combination (FF /UMEC/VI (100/62.5/25 mcg), FF/VI (100/25 mcg), and FF/UMEC (100/125mcg). Study drug was therefore administered as four inhalations via a DPI at each dosing session. In addition to plasma, urine was collected to provide complementary PK data for UMEC. It is important to note that although FF/UMEC was used as a treatment arm in CTT116415, no data from FF/UMEC has been used to support comparability of PK or PD properties in the current submission.

Table 13 provides an overview of the PK results for individual parameters for FF, UMEC, and VI from the two studies.

Table 9 Summary of Statistical Pharmacokinetic Parameters CTT116415 and 200587

Parameter	Treatment Comparison (Test vs. Ref)	Ratio (SE loge)	90% CI for ratio	CVw%a
		FF		
AUC(0-8) (pg.h/mL)	FF/UMEC/VI 400/500/100 vs FF/VI 400/100	1.173 (0.029)	1.118, 1.230	13.2
	FF/UMEC/VI 400/500/100 vs FF/UMEC 400/500	1.053 (0.029)	1.004, 1.104	
Cmax (pg/mL)	FF/UMEC/VI 400/500/100 vs FF/VI 400/100	1.233 (0.045)	1.144, 1.328	20.7
	FF/UMEC/VI 400/500/100 vs FF/UMEC 400/500	1.007 (0.045)	0.935, 1.085	
	UMEC			

AUC(0-2) (pg.h/mL)	FF/UMEC/VI 400/500/100 vs FF/UMEC/VI 400/250/100	1.044 (0.031)	0.991, 1.100	14.6
	FF/UMEC/VI 400/250/100 vs UMEC/VI 250/100	1.004 (0.031)	0.953, 1.058	
Cmax (pg/mL)	FF/UMEC/VI 400/500/100 vs FF/UMEC/VI 400/250/100	1.040 (0.048)	0.960, 1.127	22.7
	FF/UMEC/VI 400/250/100 vs UMEC/VI 250/100	0.983 (0.048)	0.908, 1.066	
	VI			
AUC(0-6) (pg.h/mL)	FF/UMEC/VI 400/500/100 vs FF/UMEC/VI 400/250/100	1.051 (0.024)	1.010, 1.094	11.2
	FF/UMEC/VI 400/250/100 vs FF/VI 400/100	0.988 (0.024)	0.949, 1.028	
	FF/UMEC/VI 400/250/100 vs UMEC/VI 250/100	1.086 (0.024)	1.043, 1.130	
Cmax (pg/mL)	FF/UMEC/VI 400/500/100 vs FF/UMEC/VI 400/250/100	1.095 (0.032)	1.038, 1.155	15.1
	FF/UMEC/VI 400/250/100 vs FF/VI 250/100	1.061 (0.032)	1.006, 1.120	
	FF/UMEC/VI 400/250/100 vs UMEC/VI 250/100	1.205 (0.032)	1.142, 1.271	

Table 10 *Special populations*

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials			
CTT116853	720/1810 (40%)	180/1810 (10%)	9/1810 (<1%)
200109	230/619 (37%)	67/619 (11%)	2/619(<1%)

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
200110	230/619(37%)	35/619 (6%)	4/619 (<1%)

2.4.3. Pharmacokinetics in the target population

The PK profile of the components of FF/UMEC/VI in subjects with COPD has been characterised using population PK in the pivotal Study CTT116853.

A subset of 152 randomised subjects from selected countries; 74 subjects on FF/UMEC/VI combination and 78 subjects on BUD/FOR provided blood samples at Weeks 12 and 24 for PK assessment. A population PK approach was employed in this study with samples collected from two subsets of COPD subjects (i.e., different subjects providing sparse and serial samples):

- PK Subset A (sparse PK samples): Approximately 130 subjects (to achieve approximately 64 subjects treated with FF/UMEC/VI) had two blood samples at each of two visits collected as follows:
    - Visit 5 (Week 12): Pre-dose and in the window 5 to 15 minutes post-dose
    - Visit 6 (Week 24): In the windows 5 to 15 minutes and 45 to 90 minutes post-dose
- PK Subset B (serial PK samples): A subset of subjects provided 24-hour serial spirometry at Visit 6 (Week 24/Day 168). Approximately 20 subjects (to achieve approximately 10 subjects treated with FF/UMEC/VI) had 7 blood samples collected as follows:
    - Visit 6 (Week 24): Pre-dose and in the windows 5 to 15 minutes, 45 to 90 minutes, 2.5 to 4 hours, 6 to 8 hours, 10 to 12 hours, and 23 to 24 hours post-morning dose.

Analysis Methods:

FF, UMEC, and VI plasma data were used for population PK analyses using non-linear mixed effects modelling with NONMEM programme version 7.1.2.

Due to the availability of extensive clinical pharmacology data (including population PK) for FF, UMEC, and VI from the mono and dual programmes, along with the limited sample size in the study, there was no plan to undertake covariate analysis for assessing the influence of subject demographics and baseline characteristics on the PK of FF, UMEC, and VI. Two methodologies were used in analysing the sparse data in CTT116853. Monte Carlo simulations of previously reported population PK models for FF, UMEC, and VI in COPD subjects were undertaken. The time course of sparse observed PK data from study CTT116853 was overlaid on the 90% prediction intervals from the simulations. In addition, a model-based estimation approach was applied whereby the plasma data for FF, UMEC, and VI from CTT116853 were combined with the respective historical data used to develop population PK models for FF, UMEC, and VI. Model parameter estimates were compared following analysis of the combined dataset (historical data set and CTT116853) versus the original historical data (without CTT116853). The below the limit of quantification (BLQ) data were treated as censored data and analysed with the full likelihood approach.

Two population PK models in subjects with COPD for VI were available to support the UMEC/VI and FF/VI combination therapies. The systemic exposure of VI estimated from the VI population PK model in UMEC/VI programme was, on average, higher for Cmax and AUC at steady state compared with that obtained from the VI population PK model from the FF/VI programme. Thus, a decision was made to utilise the VI population PK model from the UMEC/VI programme to analyse the VI data in CTT116853 from a safety perspective. The adequacies of the population PK model were assessed through diagnostic plots and visual

predictive checks. The post-hoc individual parameter estimates from each model for FF, UMEC, and VI were utilised to estimate population exposure values. The geometric mean and the associated 95% CIs of AUC and Cmax at steady state are summarised for FF, UMEC, and VI from CTT116853 and compared with results from historical data from the previous models.

Results:

Post-hoc estimates of model parameters from CTT116853 were within the range observed from historical data with FF, UMEC, and VI. This was further confirmed using the model-based estimation approach where there were no marked changes in the PK parameter estimates of FF, UMEC, and VI using the combined dataset (CTT116853 and historical data) versus the historical data (without data from CTT116853).

Based on the post-hoc PK parameter estimates for FF, UMEC, and VI following the triple fixed-dose combination (FF/UMEC/VI), steady state systemic exposures were computed and are summarised in Table 14.

Table 11 Summary of Cmax and AUC Results for FF, UMEC, and VI from CTT116853 and Historical Data

Historical Data

Study	Treatment	Dose (mcg)	n	C_{max} (pg/mL) Geo Mean [95% CI]	AUC (pg.h/mL) Geo Mean [95% CI]
FF					
CTT116853	FF / UMEC / VI (triple)	100/62.5/25	74	13.2 [11.2, 15.1]	188 [160, 216]
HZC112206, HZC112207,HZC110946	FF/VI	100/25	391	11.9 [10.9, 12.9]	182 [170, 195]
HZC112206, HZC112207,HZC110946	FF	100	333	11.5 [10.5, 12.4]	181 [167, 196]
UMEC					
CTT116853	FF / UMEC / VI (triple)	100/62.5/25	74	55.7 [50.4, 60.9]	341 [301, 381]
DB2113373	UMEC / VI	62.5/25	410	68.5 [65.2, 71.9]	308 [293, 328]
DB2113373	UMEC	62.5	417	70.3 [67.0, 73.8]	318 [303, 334]
DB2113373	Mono and combo	62.5	827	69.3 [67.0, 71.6]	312 [302, 323]
VI					
CTT116853	FF / UMEC / VI (triple)	100/62.5/25	74	101.4 [91.1, 111.9]	666 [604, 728]
DB2113373	UMEC / VI	62.5/25	410	128.2 [122.1,134.6]	612 [589, 637]
DB2113373	VI	25	421	128.2 [122.0,134.6]	613 [589, 637]
DB2113361	UMEC / VI	125/25	402	128.4 [122.3, 135.0]	617 [592, 642]
DB2113361	VI	25	404	128.2 [122.0,134.9]	611 [587, 635]
DB2113361, DB2113373	All arms combined	25	1637	127.9 [124.9,131.0]	615 [603, 627]

Data Source: CSR CTT116853 Table 10; Table 32, Table 33, and Table 34

The steady state AUC over the dosing interval for FF, UMEC, and VI estimated from the population analysis in CTT116853 (with FF/UMEC/VI) is within the range of the historical data in subjects with COPD given mono or dual combination therapies. Although Cmax at steady state for FF following FF/UMEC/VI was also in the range of historical data, corresponding Cmax values for UMEC and VI were generally lower with FF/UMEC/VI compared with historical data with dual combinations. The lower Cmax values for UMEC and VI are not expected to be clinically relevant with respect to safety or efficacy following triple FF/UMEC/VI combination.

2.4.4. Pharmacodynamics

2.4.5. Discussion on clinical pharmacology

The supra-therapeutic dose of all components and particularly umeclidinium are not fully informative for the purpose of this application. However, given that all three active components are been authorised at the proposed doses, this could be acceptable. A PK/PD study, or studies performed with doses to be used in clinical practice would have been more informative.

2.4.6. Conclusions on clinical pharmacology

The three components of Elebrato have been approved and have been widely used singly and in fixed double combinations.

2.5. Clinical efficacy

2.5.1. Dose-response studies and main clinical studies

Study CTT116853 was a Phase III, 24 week, randomised, double blind, double dummy, parallel group comparison of the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI (100/62.5/25 mcg) administered once daily in the morning via a dry powder inhaler with budesonide/formoterol 400mcg/12mcg administered twice-daily subjects with chronic obstructive pulmonary disease. There was an extension to 52 weeks in a subset of subjects.

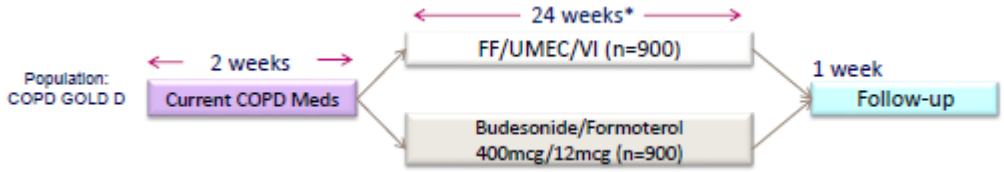
The study was conducted at 162 investigative centres in fifteen countries in Europe and Asia, from January 2015 to April 2016.

Objectives

The primary aim of the study was to evaluate the effects of FF/UMEC/VI on lung function and health related quality of life (HRQoL) compared with BUD/FOR after 24 weeks of treatment.

Secondary objectives were to evaluate the effect of FF/UMEC/VI compared with BUD/FOR on the annual rate of exacerbations and to evaluate the safety profile of FF/UMEC/VI compared with BUD/FOR over 24 weeks and 52 weeks of treatment.

The overall scheme for the 24 week part of the study is shown diagrammatically below.



Methods

Subjects who met the inclusion/exclusion criteria at screening entered a two week run-in period. During which they remained on their existing COPD medications and were provided with short-acting salbutamol to be used on an as-needed basis (rescue medication). Following the run-in period, eligible subjects were randomised (1:1) to one of the following double-blind treatment groups:

FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA OD in the morning and placebo via the Turbuhaler BID

BUD/FOR 400/12 mcg via the [Symbicort] Turbuhaler BID and placebo via the ELLIPTA OD in the morning

The randomisation was stratified based on smoking status.

Subjects discontinued all existing COPD medications at the start of the randomised treatment period but could continue their study-supplied rescue salbutamol as needed.

On-treatment clinic visits occurred after 2, 4, 12, and 24 weeks of treatment. The subset of subjects remaining on study treatment for up to 52 weeks had additional clinic visits at 36 weeks and 52 weeks.

Subjects completed a daily eDiary that captured symptoms of COPD, (EXACT-RS and other symptoms suggestive of potential exacerbation) activity limitation, and salbutamol use. Subjects with increasing respiratory symptoms were automatically notified through the eDiary to contact the investigator for further evaluation of their increasing symptoms. The eDiary device was also used at visits to collect responses to other questionnaires: SGRQ-C, BDI/TDI, COPD Assessment Test (CAT), Subject Global Rating of Activity

Limitation and Global Rating of Change in Activity Level, Subject Global Impression of COPD Severity and Global Rating of Change in Severity, EuroQol Questionnaire (EQ-5D-5L), and Inhaler Preference.

In addition, subjects at selected centres were asked to participate in one or more additional procedures at the time of study entry:

24-hour serial spirometry at screening and Week 24 (approximately 400 subjects)

24-hour Holter monitoring at screening and Week 24 (approximately 400 subjects)

Physical activity monitor (accelerometer) worn for 7 days from screening, for 7 days from randomisation, and for 7 days prior to Week 24 (up to approximately 350 subjects)

PK blood draws (approximately 150 subjects)

Study design

The CHMP Scientific Advice Working Party (SAWP) agreed with a proposal to compare

FF/UMEC/VI with an established ICS/LABA in a single study examining lung function and symptoms (St. George's Respiratory Questionnaire [SGRQ]) as co-primary endpoints in a study of 6 months duration (with an extension to 12 months in a subset of patients).

The SAWP agreed that the proposed comparator study (CTT116853) of FF/UMEC/VI versus BUD/FOR, together with the supporting UMEC + FF/VI studies (200109 and 200110) could form the basis of an initial MAA. The CHMP noted that since the initial clinical advice, there had been two important developments (CHMP positive Opinions for FF/VI and for UMEC/VI) which need to be taken into consideration when choosing the active comparator. The CHMP recommended that use of FF/VI as an active comparator would be more appropriate.

However, the CHMP acknowledged that an authorisation may be possible with superiority demonstrated only against one authorised fixed dose combination (ICS/LABA or LAMA/LABA), but for this the demonstrated superiority in efficacy must be compelling.

The SAWP also noted that it was not necessary to repeat studies in special populations or perform drug interaction studies.

The CHMP also agreed that the design of the 52-week exacerbation study (CTT116855) with regard to comparators, patient population, run-in, and co-primary endpoints is appropriate and acceptable and that a single large exacerbation study could be expected longer-term to provide sufficient evidence to support a claim for exacerbation benefit in the FF/UMEC/VI SmPC (EMEA/H/SA/2498/1FU/1/2013/II.

Main Inclusion Criteria

Male and non-pregnant female subjects at least 40 years of age who were current or former cigarette smokers (with at least 10 pack-years at screening) diagnosed with COPD as defined by the American Thoracic Society/European Respiratory Society (ATS/ERS) [Celli, 2004] were eligible. Subjects had to demonstrate at screening:

A score of ≥10 on the COPD Assessment Test (CAT – range of possible scores 0 to 40 with higher scores indicating more severe disease).

A post-bronchodilator FEV1 <50% predicted normal OR

A post-bronchodilator FEV1 <80% predicted normal and a documented history of≥2 moderate exacerbations or one severe (hospitalised) exacerbation in the previous 12 months

A post-salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70. Percent predicted values were calculated using the ERS Global Lung Function Initiative reference equations. Subjects must also have been receiving daily maintenance treatment for their COPD for at least three months prior to screening.

Main Exclusion Criteria

Subjects who had a current diagnosis or asthma, COPD caused by α1-antitrypsin deficiency, other respiratory disorders, lung resection within 12 months of screening, or other clinically significant diseases in the opinion of the investigator, were not eligible.

Subjects also could not have had pneumonia or a severe COPD exacerbation that had not resolved within 14 days of screening, a respiratory tract infection that had not resolved within 7 days of screening, an abnormal chest X-ray, or used prohibited medications within specific time intervals prior to screening.

The study was designed to be as inclusive as possible with regards to the inclusion of subjects with significant cardiovascular disease in order to allow an assessment of safety that was more representative of the targeted population ('real world') than often seen in clinical trials (e.g. subjects with a past history of previous myocardial infarction [>6 months prior to screening] and New York Heart Association Class 1–3 heart failure were eligible and QTc exclusion criteria were broadened).

Permitted Concomitant Medications

COPD Medications

Study supplied salbutamol (had to be withheld for at least 4 hours prior to spirometry testing)

Oral or injectable corticosteroids (short course ≤14 days) only for the short-term treatment of COPD exacerbations and/or pneumonia

Antibiotics (short course ≤14 days) for the short-term treatment of COPD exacerbations and/or pneumonia

Mucolytics such as acetylcysteine

Long-term oxygen therapy

Maintenance phase of pulmonary rehabilitation treatment (subjects were not allowed to initiate treatment during the study)

Any COPD medication deemed medically necessary for the short-term treatment of a moderate/severe COPD exacerbation or pneumonia Medications for rhinitis (e.g., intranasal corticosteroids, antihistamines, cromolyn, nedocromil, nasal decongestants)

Topical and ophthalmic corticosteroids

Localised corticosteroid injections (e.g., intra-articular and epidural)

Vaccinations (e.g., influenza, pneumonia, Shingles vaccines, etc)

Allergy immunotherapy

Antibiotics for short-term treatment (≤14 days) of acute infections

Smoking cessation treatments

Cough suppressants

Use of positive airway pressure for sleep apnoea

Systemic and ophthalmic beta-blockers

Tricyclic antidepressants and monoamine oxidase inhibitors (MAOIs)

Diuretics

Oral muscarinic antagonists for the treatment of overactive bladder

CYP3A4 inhibitors

Prohibited COPD medications.

Inhaled and systemic corticosteroids (except for the short term treatment of a COPD exacerbation or pneumonia)

Long- and short-acting muscarinic antagonists

Long- and short-acting beta2-agonists

PDE4 inhibitors (roflumilast)

Theophylline preparations

Cromoglycate and nedocromil inhalers

Zafirlukast, montelukast, zileuton

Acute phase of pulmonary rehabilitation (at any time during the study including run-in)

Long-term systemic antibiotic therapy (>14 days)

Outcomes/endpoints

Co-Primary Endpoints

The co-primary endpoints were; change from baseline in trough FEV1 at week 24 and change from baseline in SGRQ total score at week 24.

Secondary endpoints

Secondary endpoints were; annual rate of on-treatment moderate/severe COPD exacerbations, assessment of respiratory symptoms using the EXACT-RS score and sub-scale scores (breathlessness, cough and sputum, and chest symptoms). Transitional Dyspnoea Index (TDI) focal score at Week 24, Daily Activity Question - percentage of days with a score of 2.

Statistical methods

For the co-primary endpoints, the null hypothesis is no difference between treatment groups (H0: $\mu T - \mu S = 0$), with the alternative hypothesis that there is a difference between treatment groups (H1: $\mu T - \mu S \neq 0$), where μT is the mean change from baseline for FF/UMEC/VI and μS is the mean change from baseline for BUD/FOR.

The treatment comparisons of primary interest were FF/UMEC/VI once daily versus BUD/FOR twice daily for the co-primary endpoints. The primary analyses was performed using a mixed model repeated measures (MMRM) analysis based on a two-sided hypothesis testing approach, and used data for the ITT population collected while subjects were on study medication.

To account for multiplicity of the co-primary comparisons, the Hochberg method was used to control overall Type I error at $\alpha=0.05$. Both comparisons were to be declared statistically significant if the unadjusted p-value for both was significant at the 0.05 level. Should the largest unadjusted p-value for the two comparisons be above 0.05, the other comparison was to be declared statistically significant if the smaller unadjusted p-value was below 0.025; equivalent to declaring statistical significance if the adjusted p-value is below 0.05.

FF/UMEC/VI once daily and BUD/FOR twice daily was compared for secondary efficacy and other endpoints using the ITT population. If at least one of the co-primary endpoints was statistically significant, inferences were to be drawn from unadjusted p-values for the treatment comparisons on secondary and other endpoints and were declared statistically significant if below p = 0.05. If neither of the co-primary endpoints was statistically significant, testing on the secondary and other endpoints was to be performed and presented for descriptive purposes only. Secondary endpoints and other efficacy endpoints were not adjusted for multiplicity. Many centres enrolled a very small number of subjects and so rather than adjusting for centre in the statistical analyses, a geographical region was used, based on country and the number of randomised subjects

MMRM model.

There is an underlying assumption that the data are missing at random. All available scheduled post-baseline assessment were utilised and, via modelling of the within-subject correlation structure, the derived treatment differences were adjusted to take into account missing data.

Terms in the model:

Dependent variable: trough FEV1, trough FVC or SGRQ total score at each visit

Categorical: treatment group, smoking status (screening), geographical region, Visit

Continuous: baseline FEV1, baseline FVC or baseline SGRQ total score

Interaction: baseline*Visit, treatment*Visit

Repeated: Visit

Two models were fitted; one with a response variable of change from baseline and one with the response variable as the raw value. A separate analysis using the same model and including only the subjects in the EXT population was provided. The analysis of FEV1 (and FVC) data for this population included FEV1 (FVC) data at Weeks 2, 4, 12, 24, 36 and 52. The analysis of SGRQ total score included SGRQ total scores at Weeks 4, 24, and 52. Analysis of exacerbation data assumed a negative binomial distribution.

Sample Size

Sample size was based on the co-primary efficacy endpoints and prior internal data for the drug classes. It was expected that the mean treatment difference between an ICS/LABA/LAMA combination when compared with an ICS/LABA would be approximately 2 to 3 units. Based on these data 688 evaluable subjects per treatment arm would be required to provide 90% power to detect a difference of 2.5 units between FF/UMEC/VI and BUD/FOR for SGRQ total score, assuming a standard deviation of 12 units. The study had >90% power to detect a difference of 80 mL between FF/UMEC/VI and BUD/FOR for trough FEV1 at 24 weeks, using a SD of 240 mL, based on results from prior trials. As this was a single study to support the efficacy evidence, the powering provided was for a two sided significance level of 0.01. It was estimated that approximately 30% of subjects would discontinue study treatment without Week 24 data, data for subjects who discontinued study treatment prematurely were not explicitly imputed. Thus, to account for an approximately 30% withdrawal rate, 900 subjects were required for each treatment arm.

The Intent-to-Treat (ITT) Population comprised all randomised subjects, excluding those who were randomised in error. A subject who was recorded as a screen or run-in failure and also randomised was considered to be randomised in error. Any other subject who received a randomisation number was considered to have been randomised. Data for the ITT Population are presented t0 Week 24.

The Extension (EXT) Population: comprised all subjects in the ITT Population who were enrolled into the subset of subjects (approximately 400) with extension to 52 weeks.

Subjects in the extension subset were enrolled first thus all data from the subset were available at the conclusion of the study. Data from extension subjects up to Week 24 are also included in safety and efficacy data displays for the ITT Population. The EXT Population displays include efficacy and safety data from all visits, including the Week 36 and Week 52 visits. The primary summaries and analyses used the ITT Population and many were repeated for the EXT Population.

Results

Participant flow

A total of 2121 subjects from 15 countries gave informed consent. Of the consenting subjects 59 (3%) failed pre-screening and 252 (12%) failed screening. Most of the screen failures were due to failure to meet the inclusion/exclusion criteria (219 subjects [11%]). The most frequently reported reasons for inclusion criteria screen failure were severity of disease (140 subjects [56%]) and a score of <10 on the CAT at Screening (17 subjects [7%]). The most frequently reported reasons for exclusion criteria screen failure were pneumonia and/or COPD exacerbation (17 subjects [7%]) and abnormal chest X-ray (15 subjects [6%]).

The majority of subjects completed the study (89.6%). Of the subjects that prematurely discontinued from the study, the most common reasons were decision by subject or proxy, AEs, and lack of efficacy (Table 16).

Table 12 Number (%) of subjects completing – or prematurely discontinuing the study

	FF/UMEC/VI 100/62.5/25 N=911	BUD/FOR 400/12 N=899
Completed	840 (92)	782 (87)
Prematurely discontinued	71 (8)	117 (13)
Decision by subject or proxy	22 (2)	44 (5)
Adverse event	34 (4)	28 (3)
Lack of efficacy	10 (1)	37 (4)
Investigator discretion	1 (<1)	5 (<1)
Protocol deviation	4 (<1)	1 (<1)
Stopping criterion reached	0	1 (<1)
Lost to follow up	0	1 (<1)

A total of 1810 subjects were included in the ITT Population. The largest recruitment was from Germany (278 subjects [13%]) followed by Mexico (245 subjects [12%]), Ukraine (240 subjects [11%]), and the Russian Federation (227 subjects [11%]). The number of randomised subjects per study centre ranged from 2 to 47.

Baseline data / Numbers analysed

Table 13 Demographic and lung function characteristics at screening by treatment group data are group mean (s.d.)

	ITT (24 weeks)		EXT (52 weeks)	
	FF/UMEC/VI 100/62.5/25 N=911	BUD/FOR 400/12 N=899	FF/UMEC/VI 100/62.5/25 N=210	FF/UMEC/VI 100/62.5/25 N=210
Gender m/f (%)	74/26	74/26	75/25	74/26
Age (years)	64.2 (8.6)	62.7 (8.7)	63.7 (7.8)	63.3 (8.4)
BMI, kg/m^2	26.86 (5.18)	26.98 (5.10)	27.61 (5.27)	27.01 (5.07)
Current smoker n (%)	400 (44)	394 (44)	95 (45)	97 (44)
Pack years	39.5 (21.9)	39.2 (22.15)	39.8 (19.9)	39.6 (23.1)
Airways reversibility yes/no[1] (%)	15/85	17/83	16/84	80/80

Airways reversibility (mL)	88.4 (131.2)	99.0 (131.5)	90.4 (139.2)	110.5 (142.8)
Pre-bronchodilator FEV1 (L)	1.260 (0.46)	1.240 (0.46)	1.334 (0.49)	1.256 (0.48)
Pre-bronchodilator FEV1 % normal (%)	42.5 (13.0)	41.8 (13.5)	44.1 (13.4)	41.7 (14.1)
Oxygen saturation (%)	95.2 (2.60)	95.2 (2.59)	95.6 (2.11)	95.7 (2.13)

1 Reversible is an increase in FEV1 of ≥ 12% and ≥ 200 mL following administration of salbutamol.

Outcomes and estimation

Results efficacy

The majority of subjects in the ITT population provided data on the co-primary efficacy endpoints up to Week 24. A total of 895 out of 911 (98.2%) in the FF/UMEC/VI group and 874 out of 899 (97.2%) in the BUD/FOR group were included in the co-primary analysis of trough FEV1 up to Week 24 of whom 836 and 781, respectively, had analysable data at week 24. A total of 887 out of 911 subjects in the FF/UMEC/VI group and 866 out of 899 subjects in the BUD/FOR group were included in the co-primary analysis of SGRQ Total Score to Week 24.

Both co-primary endpoints met the criteria for declaring statistical significance (Table 18). At Week 24, a clinically meaningful and statistically significant improvement in trough FEV1 was observed with FF/UMEC/VI, compared with BUD/FOR (treatment difference 171 mL, $p<0.001$). Additionally, clinically meaningful improvements from baseline in SGRQ Total Score were observed in both treatment groups, and FF/UMEC/VI demonstrated statistically significant improvement compared with BUD/FOR of -2.2 units ($p<0.001$).

COPD exacerbation rates

ITT Population: The incidence of investigator-defined COPD exacerbations over the 24-week treatment period was 11% in the FF/UMEC/VI group and 16% in the BUD/FOR group (Table 18). Of the subjects who experienced exacerbations, most had only one that was moderate or severe; few subjects had mild exacerbations (1% in the FF/UMEC/VI group and 2% in the BUD/FOR group). The mean duration of the exacerbation was similar between the treatment groups. Thirteen subjects in the FF/UMEC/VI group and 25 subjects in the BUD/FOR group were hospitalised for a COPD Exacerbation. None of the exacerbations were fatal and all but two in the FF/UMEC/VI group resolved.

EXT Population: In general, a similar exacerbation profile to the ITT Population was observed, although the difference in the incidence of investigator-defined exacerbations between the treatment groups was larger over the 52-week treatment period. Fewer subjects in the FF/UMEC/VI group experienced exacerbations compared with the BUD/FOR group (18% vs. 30%). The incidence of mild exacerbations remained low (1% in the FF/UMEC/VI group and 3% in the BUD/FOR group). Eight subjects treated with FF/UMEC/VI and 24 subjects treated with BUD/FOR were hospitalised for a COPD Exacerbation. None of the exacerbations were fatal and all but one in the BUD/FOR group resolved.

Change from Baseline in EXACT-respiratory symptom (RS) Score

Reductions in EXACT-RS scores indicate improvement in symptoms with a clinically meaningful improvement score defined as a decrease in the 4-weekly mean score of ≥ 2 units from baseline.

ITT Population: At each 4-week interval over the 24-week treatment period, FF/UMEC/VI produced greater reductions from baseline in EXACT-RS scores (ranged from -1.45 to -2.43) compared with BUD/FOR (ranged from -0.50 to -1.09). Treatment differences between FF/UMEC/VI and BUD/FOR (ranged from -0. 95 to -1.41) were statistically significant at each 4-week interval ($p<0.001$).

EXT Population: At each 4-week interval over the 52-week treatment period, FF/UMEC/VI produced greater reductions from baseline in EXACT-RS scores (ranged from -1.24 to -2.64) compared with BUD/FOR (ranged from -0.61 to -1.53). Treatment differences between FF/UMEC/VI and BUD/FOR (ranged from -0.52 to -1.53) were statistically significant at almost all 4-week intervals ($p<0.05$) except Week 1-4.

TDI Focal Score

Lower TDI focal scores indicate more deterioration in severity of dyspnoea, a clinically meaningful improvement in dyspnoea was defined as an increase of at least 1 point in TDI focal score.

ITT Population: At Week 24, clinically meaningful TDI focal scores were observed in both treatment groups, and FF/UMEC/VI demonstrated a statistically significant improvement compared with BUD/FOR of 0.57 units ($p<0.001$).

EXT Population: At Weeks 24 and 52, clinically meaningful TDI focal scores were observed in both treatment groups but the treatment differences were not statistically significant.

Daily activity question Percentage of Days with a Score of 2

ITT Population: Over Weeks 1-24, the percentage of days with a score of 2 remained similar to baseline in both the FF/UMEC/VI (5.1%) and BUD/FOR (5.0%) groups; the treatment difference was not statistically significant.

EXT Population: Over Weeks 1-52, the percentage of days reporting a score of 2 remained similar to baseline in both the FF/UMEC/VI (4.6%) and BUD/FOR (4.9%) groups; the treatment difference was not statistically significant.

Serial FEV1

Mean baseline FEV1 in the serial spirometry (SS) Population was similar between the treatment groups: 1.381 L in FF/UMEC/VI group (n = 203) and 1.362 L in the BUD/FOR group (n = 203). On Day 1, FF/UMEC/VI produced larger mean increases from baseline in FEV1 (rang from 90 to 222 mL) compared with BUD/FOR (rang from 32 to 155 mL). Treatment differences in change from baseline FEV1 between FF/UMEC/VI and BUD/FOR were statistically significant ($p<0.05$) at most time points except at 15 and 30 minutes, and at 15 hours.

At Week 24 mean increases from baseline with FF/UMEC/VI ranged from 160 to 339 mL changes with BUD/FOR ranged from -32 to 140 mL. Treatment differences in change from baseline FEV1 between FF/UMEC/VI and BUD/FOR ranged from 156 to 231 mL and were statistically significant at every time point ($p<0.001$).

Table 14 Overview of Efficacy endpoints Study CTT116853

	ITT (24 weeks)		EXT (52 weeks)	
	FF/UMEC/VI 100/62.5/25 N=911	BUD/FOR 400/12 N=899	FF/UMEC/VI 100/62.5/25 N=210	BUD/FOR 400/12 N=220
	Co-primary endpoints			
Change in FEV1 mL (s.e.)	142 (8.3)	-29 (8.5)	126 (17.0)	-53 (17.2)
	Treatment difference 171 mL 95% C.I 148, 194 p < 0.001		Treatment difference 179 mL 95% C.I 131, 226 p < 0.001	
Change in SGRQ total score	-6.6 (0.45)	-4.3 (0.46)	-4.6 (1.01)	-1.9 (1.03)
	Treatment difference -2.2 95% C.I. -3.5,		Treatment difference -2.7 95% C.I. -5.5, 0.2	

	-1.0 p <0.001		p =0.065	
	Secondary endpoints			
Mild moderate/severe COPD exacerbations No. (% patients) rate/100 patient.yrs	95 (10%) rate 0.22	126 (14%) rate 0.34	34 (16%) Rate 0.20	60 (27%) Rate = 0.36
	Annual rate ratio 0.65 95% C.I. 0.49, 0.86 p= 0.002		Annual rate ratio 0.56 95% C.I. 0.37, 0.85 p= 0.006	
COPD exacerbations leading to hospitalisation No. (% exacerbations)	13 (10)	25 (14)	8 (17)	24 (29)
TDI score (s.e) at week 24 or Week 52	2.29 (0.096)	1.72 (0.099)	1.74 (0.22)	1.39 (0.22)
	Treatment difference 0.57 95% C.I. 0.30, 0.84 p < 0.001		Treatment difference 0.34 95% C.I. -0.28, 0.97 p = 0.28	
Chang in EXACT RS score weeks 21 - 24 (s.d)	-2.46 (4.74)	-1.13 (4.84)		
Change in daily activity % of days with a score of 2 - i.e. increased activity (s.e)	0.0 (0.38)	-0.1 (0.39)	0.0 (0.70)	0.3 (0.69)
	Treatment difference 0.1 95% C.I. -0.9, -1.1 p = 0.82		Treatment difference -0.3 95% C.I. -2.1, 1.6 p = 0.77	

Summary of main efficacy results

The following table summarises the efficacy results from the main study supporting the present application it should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 15 Summary of efficacy for trial CTT116853

Title: A Phase III, 24 week, randomised, double blind, double dummy, parallel group study (with an extension to 52 weeks in a subset of subjects) comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI administered once daily in the morning via a dry powder inhaler with budesonide/formoterol 400mcg/12mcg administered twice-daily via a reservoir inhaler in subjects with chronic obstructive pulmonary disease		
Study identifier	CTT116853	
Design	A Phase III, 24 week, randomised, double blind, double dummy, parallel group comparison of the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI (100/62.5/25 mcg) administered once daily in the morning via a dry powder inhaler with budesonide/formoterol 400mcg/12mcg administered twice-daily subjects with chronic obstructive pulmonary disease.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks with 52-week sub-population 2 weeks not applicable

Hypothesis	Superiority		
Treatments groups	Test product		FF/UMEC/VI 24 weeks n = 911
	Test product sub-group		FF/UMEC/VI 52 weeks n = 210
	Reference product		BUD/FOR 24 weeks n = 899
Endpoints and definitions	Δ FEV1	mL	Standard lung function variable
	Δ SGRQ	Score 0 – 40	Patient reported symptom and QoL score
	COPD exacerbations	Rate/100 patient.yrs	
Database lock	09 Jun 2016		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	FF/UMEC/VI/ 24 weeks	BUD/FOR 24 weeks
	Number of subject	911	899
	Δ FEV1	145 mL	-22 mL
	95% CI	126, 158	-046, -013
	Δ SGRQ total score	-6.6	-4.3
	95% CI	-7.4, -5.7	-5.2, -3.4
	Exacerbation rate 95% CI	0.22 0.49, 0.86	0.34 0.37, 0.85
Effect estimate per comparison	Δ FEV1	FF/UMEC/VI	BUD/FOR
		Treatment difference p <0.001	
	Δ SGRQ score	Treatment difference p <0.001	
	COPD exacerbation rate	Treatment difference p =0.002	

Supportive studies

1. Study 200109

Study 200109 was a comparison of the addition of umeclidinium bromide (UMEC) to fluticasone furoate (FF)/vilanterol (VI), with placebo plus FF/VI in subjects with Chronic Obstructive Pulmonary Disease (COPD).

This was a multicentre study with 55 investigators conducted at 13 centres in the United States of America (USA), 12 centres in Canada, 12 centres in Chile, 8 centres in Argentina and 10 centres in Romania it was carried out from October 2013 to April 2014.

Objectives

The primary objective was to evaluate the efficacy and safety of the addition of UMEC 125 mcg to FF/VI 100/25 mcg once-daily and the addition of UMEC 62.5 mcg to FF/VI 100/25 mcg once-daily, compared with placebo plus FF/VI 100/25 mcg once-daily over 12 weeks in subjects with COPD.

The secondary objective was to evaluate the addition of UMEC 125 mcg to FF/VI 100/25 mcg once-daily and the addition of UMEC 62.5 mcg to FF/VI 100/25 mcg once-daily, compared with placebo plus FF/VI 100/25 mcg once-daily on COPD-related health status assessments over 12 weeks in subjects with COPD.

Methods

Study design and treatments

The study was a randomised, double-blind, parallel-group, multi-centre evaluation of the efficacy and safety of two doses of UMEC (62.5 mcg and 125 mcg once daily) added to FF/VI once-daily as a triple therapy compared to placebo plus FF/VI. Subjects who met the inclusion criteria and none of the exclusion criteria at Visit 1 (Screening) entered a 4-week open Run-In period with FF/VI 100/25 mcg administered once daily via the ELLIPTA dry powder inhaler. Subjects were provided with salbutamol to be used as needed for symptomatic relief during both the Run-In and treatment periods.

At the end of the Run-In period subjects who met the randomisation criteria were assigned to receive one of the following three treatments (1:1:1) while continuing treatment with open-label FF/VI 100/25 mcg once daily in the AM during a 12-week treatment period:

- UMEC (62.5 mcg) administered once daily via a DPI
- UMEC (125 mcg) administered once daily via a DPI
- Matching placebo administered once daily via a DPI

Inclusion Criteria

Male and female subjects (females of non-reproductive potential or using study specified contraceptive methods), treated as outpatients, 40 years of age and older with a history of COPD, as defined by the American Thoracic Society/European Respiratory Society [Celli, 2004], with a smoking history (current or former) of at least 10 pack-years were eligible. Subjects also had a pre and post-albuterol/salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 and a pre- and post-albuterol/salbutamol FEV1 of no more than 70% of predicted normal values calculated using National Health and Nutrition Examination Survey (NHANES) III reference equations and a dyspnoea score of ≥2 on the modified Medical Research Council (mMRC) Dyspnoea Scale at Visit 1 (Screening). Subjects were required to have met the following corrected QT interval (QTc) Criteria: corrected QT interval using Fridericia's formula (QTc(F) <450 msec or QTc(F) <480 msec for patients with QRS duration ≥ 120 msec.

Exclusion Criteria

Subjects could not have a current diagnosis of asthma, have been hospitalised for COPD or pneumonia within 12 weeks prior to Visit 1, have had lung volume reduction surgery within the 12 months prior to Visit 1, have had a lower respiratory tract infection requiring antibiotic use within 6 weeks of Visit 1, use long-term oxygen therapy (prescribed for greater than 12 h a day), or have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1.

Subjects could not have evidence of concurrent respiratory disease, or other clinically significant medical conditions including an abnormal and clinically significant ECG finding from the 12-lead ECG conducted at Visit 1, have severe milk protein allergy or drug allergies.

Prior and Concomitant Medications and Non-Drug Therapies

All COPD medications used within 30 days prior to Visit 0 (Pre-screening visit) and onwards were to be recorded in the eCRF including any changes. Beginning at Visit 1 and throughout the rest of the study, all non-COPD medications were to be recorded in the eCRF including any changes. Study provided albuterol/salbutamol, open-label FF/VI and double-blind study drug were not to be recorded in the eCRF. Medications initiated after completion of Visit 7 or the Early Withdrawal Visit were not to be recorded in the eCRF, with the exception of those used to treat a COPD exacerbation or SAE that occurred between Visit 7 (or the Early Withdrawal Visit) and the follow-up contact.

Primary Efficacy Endpoint

The primary efficacy endpoint was trough FEV1 on Day 85 defined as the mean of the FEV1 values obtained 23 and 24 h after dosing. Baseline trough FEV1 was the mean of the 2 assessments made at -30 and -5 minutes pre-dose on Treatment Day 1.

Secondary Efficacy Endpoint

The secondary efficacy endpoint was weighted mean (WM) 0-6 h FEV1 obtained post-dose on Day 84. The WM was calculated from the pre-dose FEV1 and post-dose FEV1 measurements at 15 minutes, 30 minutes, 1 h, 3 h and 6 h.

Other Efficacy Endpoints

- Proportion of subjects achieving an increase of at least 100 mL above baseline in trough FEV1
- Trough FEV1 and WM FEV1 over 0-6 h post-dose at other time points
- Proportion of subjects achieving an increase in FEV1 of ≥ 12% and ≥ 200 mL above baseline at any time during 0-6 h post-dose on Day 1
- Serial FEV1 over 0 to 6 h (at each time point)
- Peak FEV1
- Time to onset (defined as an increase of 100 mL above baseline in FEV1) during 0-6h post-dose on Treatment Day 1 (Visit 2) (This is an additional endpoint not specified in the protocol, which has been included to further characterise the lung function response to treatment.)
- Serial and trough forced vital capacity (FVC)

Health-Related Quality of Life / Health Outcomes

The health-related quality of life and health outcome endpoints were: COPD Assessment Test (CAT), St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C).

Statistical methods

Summary statistics for raw and change from baseline in trough FEV1 at each clinic visit and for each treatment are based on the ITT population. The primary endpoint of trough FEV1 on Day 85 was analysed using a mixed model repeated measures (MMRM) analysis, including covariates of baseline FEV1, smoking status, Day, treatment, Day by baseline interaction and Day by treatment interaction, where Day is nominal. The model used all available trough FEV1 values recorded on Days 2, 28, 56, 84 and 85. Missing data are not directly imputed in the analysis. The 0-6 h weighted mean FEV1 on Day 84 will be analysed for the ITT Population using MMRM analysis as for the primary variable.

Sample Size Assumptions

Sample size calculations were based on the primary endpoint of trough FEV1 at Day 85 and assume 90% power, a two-sided 5% significance level, an estimate of residual standard deviation of 220 mL based on analyses of previous studies in COPD and a treatment difference of 80 mL. Under these assumptions, 160 evaluable subjects on each treatment (480 in total) were required. The variability for the secondary endpoint of 0-6h WM FEV1 at Day 84 was expected to be the same as that for trough FEV1. The treatment difference for this endpoint was expected to be greater than that for trough, and therefore the sample size required for the primary trough endpoint provided sufficient power for comparisons on the secondary WM endpoint. It was estimated that approximately 20% of subjects would withdraw during the treatment period, data for subjects who withdrew prematurely were not explicitly imputed. Hence, to account for a 20% withdrawal rate, approximately 600 subjects (200 subjects per treatment) were randomised. 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.

Results

PATIENT DEMOGRAPHY AND DISPOSITION

A total of 727 subjects were enrolled in the study of whom 705 attended the screening visit; 70 were screen failures. The most common reasons for screen failure were failure to meet inclusion/exclusion criteria (63 subjects) and withdrawal of consent (7 subjects).

A total of 619 subjects were randomised across 13 centres in the United States (26% of subjects), 12 centres in Chile (21% of subjects), 12 centres in Canada (20% of subjects), 10 centres in Romania (17% of subjects) and 8 centres in Argentina (16% of subjects). All randomised subjects were included in the ITT population. Overall, 575 subjects (93%) in the ITT Population completed the study; 93% of the placebo group, 95% of the UMEC 62.5 group and 91% in the UMEC 125 group.

Table 16 overview of patient demography and baseline characteristics

	Placebo + FF/VI 100/25 n=206	**UMEC 62.5 + FF/VI 100/25 n=206**	**UMEC 125 + FF/VI 100/25 n=207**
Mean (s.d) age in years	64.7 (7.9)	64.9(8.7)	63.8 (7.7)
Male/female (%)	68/32	67/33	61/39
BMI (kg/m^2)	26.82 (5.4)	27.40 (6.0)	28.58 (6.8)
Current smoker n (%)	90 (44)	81 (39)	87 (42)
Pre-bronchodilator FEV1 (L)	1.156 (0.45)	1.117 (0.45)	1.158 (0.45)
% Predicted normal FEV1	45.9 (13.0)	44.2 (13.4)	45.6 (12.8)
Post ipratropium FEV1 (L)	1.367 (0.47)	1.349 (0.51)	1.377 (0.48)
% reversibility to salbutamol and ipratropium	20.9 (16.5)	22.6 (14.5)	21.4 (16.1)

Outcomes / results

The outcome for the primary efficacy endpoint trough FEV1 at Day 85 is shown in Table 21 and was statistically significantly superior to placebo for both doses of UMEC. Trough FEV1 at Day 2, Day 28, Day 56 and Day 84 were "Other" efficacy endpoints and were significantly superior to placebo $p < 0.001$ at all time points.

Statistically significant improvements in LS mean change from baseline in the secondary endpoint 0-6 h WM FEV1 were demonstrated for both the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups compared with the placebo + FF/VI treatment group at Day 84. Significant improvements in the LS mean change from baseline in 0-6 h WM FEV1 were also demonstrated for both the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups compared with the placebo + FF/VI group for the "Other" efficacy endpoints at Days 1 and 28.

Greater proportions of subjects in the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups achieved an FEV1 increase from baseline of at least 12% and 200 mL compared with the placebo + FF/VI group during 0-6 h post-dose on Day 1. The odds of achieving this increase versus not achieving it were statistically significantly greater for the UMEC groups compared with the placebo ($p<0.001$ for both groups).

Subjects in the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups had a statistically significantly higher odds of achieving an FEV1 increase from baseline of at least 100 mL versus not achieving that increase compared with the placebo + FF/VI treatment group at Days 2, 28, 56, 84 and Day 85.

Median time to onset of additional bronchodilation was shorter in both UMEC + FF/VI (30 minutes for each) treatment groups compared with the placebo + FF/VI treatment group (180 minutes); the hazard ratios for both treatment comparisons (based on analysis of time to onset of additional bronchodilation) were statistically significant ($p<0.001$)

At baseline, the mean daily use of rescue salbutamol ranged from 2.1 to 2.4 puffs/day across the treatment groups. Over Weeks 1-12, a statistically significant reduction from baseline in rescue salbutamol use was demonstrated in the UMEC 62.5+ FF/VI (-0.4 puffs/day) treatment group and in the UMEC 125+ FF/VI (-0.2 puffs/day) treatment group compared with the placebo + FF/VI treatment group.

Mean total SGRQ scores at baseline were similar across the treatment groups (range: 44.48 to 45.48). Least squares mean improvements from baseline were observed in all treatment groups at Day 28 and Day 84, with a greater improvement from placebo seen only in the UMEC 62.5 + FF/VI treatment group. None of the improvements reached the minimal clinically important difference (MICD) of 4 units. The differences between the two UMEC + FF/VI treatment groups versus the placebo + FF/VI treatment group were not statistically significant and did not reach the MCID of -4 units.

Table 17 overview of efficacy endpoints

	Placebo + FF/VI 100/25 n=206	UMEC 62.5 + FF/VI 100/25 n=206	UMEC 125 + FF/VI 100/25 n=207
	Primary endpoint		
Mean (s.e.) trough FEV1 at D 85 L	1.215 (0.01)	1.338 (0.01)	1.343 (0.01)
		Treatment difference to placebo 0.124 95% CI 0.093, 0.154 p < 0.001	Treatment difference to placebo 0.128 95% CI 0.098, 0.159 p < 0.001
	Secondary endpoint		
Weighted mean (SE) 0-6 h FEV1 on Day 84	1.270 (0.012)	1.422 (0.012)	1.410 (0.012)
		Treatment difference to placebo 0.153 95% CI 0.118, 0.187 p < 0.001	Treatment difference to placebo 0.140 95% CI 0.106, 0.175 p < 0.001
	Other endpoints		
No. (%) of patients having an increase from baseline of ≥ 12% and ≥ 200 mL at 0-6 h post dose on Day 1	27 (13)	95 (46)	98 (48)
		Odds ratio to placebo 6.1 95% CI 3.7, 10.0 p < 0.001	Odds ratio to placebo 6.3 95% CI 3.8, 10.3 p < 0.001
Proportion of patients having a trough FEV1≥ 100 mL above baseline No. at D 85 (%)	27 (13)	94 (46)	89 (43)
Median time in minutes to onset (Δ ≥ FEV1 100 mL) on D1	180	30	30
		Hazard ratio to placebo 2.1 95% CI 1.7, 2.7 p < 0.001	Hazard ratio to placebo 2.1 95% CI 1.6,2.6 p < 0.001
Mean (s.e.) change from baseline in number of puffs of reduction in rescue medication.	-0.3 (0.08)	-0.7 (0.08)	-0.6 (0.08)
		Treatment difference to placebo0.4 95% CI -0.7, -0.2 p < 0.001	Treatment difference to placebo -0.2 95% CI -0.5, 0.0 p =0.04
Mean (s.e) change from baseline in total SGRQ score at D 84	-2.23 (0.70)	-3.05 (0.69)	-1.77 (0.70)
		Treatment difference to placebo -0.82 95% CI -2.76, 1.12 p = 0.41	Treatment difference to placebo 0.46 95% CI -1.49, 2.41 p = 0.65

2.Study 200110

Study 200110 was a comparison of the addition of umeclidinium bromide (UMEC) to fluticasone furoate (FF)/vilanterol (VI), with placebo plus FF/VI in subjects with Chronic Obstructive Pulmonary Disease (COPD).

This was a multi-centre study with 59 investigators in 4 countries. Study centre(s): 30 centres in Germany, 15 centres in the United States of America, 8 centres in the Republic of Korea and 6 centres in the Czech Republic it was carried out from October 2013 to April 2014.**Study design/methods**

A total of 730 subjects were enrolled in the study of whom 715 attended the screening visit; 85 were screen failures. The most common reasons for screen failure were failure to meet inclusion/exclusion criteria (10% of subjects) and withdrawal of consent and adverse events (<1% for each).

A total of 620 subjects were randomised and 619 were included in the ITT population across 30 centres in Germany (46% of subjects), 15 centres in the United States (29%), 8 centres in the Republic of Korea (11%) and 6 centres in the Czech Republic (14%). Overall, 575 subjects (93%) in the ITT Population completed the study. At least 93% of subjects attended each clinic visit including Follow-Up. Attendance was slightly higher at Days 56, 84 and 85 in the UMEC+FF/VI groups than the placebo +FF/VI group which can be attributed to the higher withdrawal rate from the placebo +FF/VI group this was mainly due to withdrawals due to lack of efficacy in the placebo group (5%) compared to the UMEC groups 2% and 1%. Also, 5% of subjects withdrew due to exacerbations in the placebo group compared to 1% in both UMEC groups.

Table 18 overview of patient demography and baseline characteristics

	Placebo + FF/VI 100/25 n=206	**UMEC 62.5 + FF/VI 100/25 n=206**	**UMEC 125 + FF/VI 100/25 n=207**
Mean (s.d) age in years	62.6 (9.0)	62.6 (8.1)	63.4 (7.5)
Male/female (%)	61/39	66/34	63/37
BMI (s.d.) (kg/m^2)	21.72 (5.4)	27.60 (6.2)	27.31 (5.3)
Current smoker n (%)	119 (58)	120 (58)	116 (56)
Pre-bronchodilator FEV1 (L)	1.287 (0.47)	1.240 (0.44)	1.271 (0.48)
% Predicted normal FEV1	47.4	46.3	47.9
Post ipratropium FEV1 (L)	1.470 (0.50)	1.473 (0.48)	1.484 (0.51)
% reversibility to salbutamol and ipratropium	16.1 (15.74)	20.7 (16.29)	18.6 (15.24)

Results

The outcome for the primary efficacy endpoint trough FEV1 at Day 85 is shown in Table 22 and was statistically significantly superior to placebo for both doses of UMEC. Trough FEV1 at Day 2, Day 28, Day 56 and Day 84 were "Other" efficacy endpoints and were significantly superior to placebo $p < 0.001$ at all time points.

Statistically significant improvements in LS mean change from baseline in the secondary endpoint 0-6 h WM FEV1 were demonstrated for both the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups compared with the placebo + FF/VI treatment group at Day 84. Significant improvements in the LS mean change from baseline in 0-6 h WM FEV1 were also demonstrated for both the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups compared with the placebo + FF/VI group for the "Other" efficacy endpoints at Days 1 and 28.

Greater proportions of subjects in the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups achieved an FEV1 increase from baseline of at least 12% and 200 mL compared with the placebo + FF/VI group during 0-6 h post-dose on Day 1. The odds of achieving this increase versus not achieving it were statistically significantly greater for the UMEC groups compared with the placebo ($p<0.001$ for both groups).

Subjects in the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups had a statistically significantly higher odds of achieving an FEV1 increase from baseline of at least 100 mL versus not achieving that increase compared with the placebo + FF/VI treatment group at Days 2, 28, 56, 84 and Day 85.

Median time to onset of additional bronchodilation was shorter in both UMEC + FF/VI (30 minutes for each) treatment groups compared with the placebo + FF/VI treatment group (182 minutes); the hazard ratios for both treatment comparisons (based on analysis of time to onset of additional bronchodilation) were statistically significant ($p<0.001$)

At baseline, the mean daily use of rescue salbutamol ranged from 1.5 to 2.1 puffs/day across the treatment groups. Over Weeks 1-12, a statistically significant reduction from baseline in rescue salbutamol use was

demonstrated in the UMEC 62.5+ FF/VI (-0.3 puffs/day) treatment group and a reduction was observed in the UMEC 125+ FF/VI (-0.2 puffs/day) treatment group compared with the placebo + FF/VI treatment group.

Mean total SGRQ scores at baseline were similar across the treatment groups (range: 41.78 to 44.14). Least squares mean improvements from baseline were observed in all treatment groups at Day 28 and in the UMEC treatment groups at Day 84. Greater improvements from baseline were seen in the UMEC+FF/VI treatment groups compared with the placebo +FF/VI group. The differences between the two UMEC+FF/VI treatment groups versus the placebo +FF/VI treatment group were statistically significant for UMEC 62.5 + FF/VI at Day 84. None of the differences reached the Minimally Clinically Important Difference (MCID) of -4 units

Table 19 overview of efficacy endpoints

	Placebo + FF/VI 100/25 n=206	**UMEC 62.5 + FF/VI 100/25 n=206**	**UMEC 125 + FF/VI 100/25 n=207**
	Primary endpoint		
Mean (s.e.) trough FEV1 at D 85 L	1.355 (0.011)	1.476 (0.011)	1.466 (0.011)
		Treatment difference to placebo 0.122 95% CI 0.091, 0.152 p < 0.001	Treatment difference to placebo 0.111 95% CI 0.081, 0.141 p < 0.001
	Secondary endpoint		
Weighted mean (s.e.) 0-6 h FEV1 on Day 84	1.402 (0.012)	1.548 (0.012)	1.537 (0.011)
		Treatment difference to placebo 0.147 95% CI 0.114, 0.179 p < 0.001	Treatment difference to placebo 0.153 95% CI 0.103, 0.167 p < 0.001
	Other endpoints		
No. (%) of patients having an increase from baseline of ≥ 12% and ≥ 200 mL during 0-6 h post-dose on Day 1	29 (14)	93 (45)	95 (46)
		Odds ratio to placebo 5.0 95% CI 3.1, 8.1 p < 0.001	Odds ratio to placebo 5.3 95% CI 3.2, 8.5 p < 0.001
Proportion of patients having a trough FEV1≥ 100 mL above baseline No. at D 85 (%)	28 (14)	88 (43)	84 (41)
		Hazard ratio to placebo 4.8 95% CI 2.9,7.8 p < 0.001	Hazard ratio to placebo 4.4 95% CI 2.7, 7.2 p < 0.001
Median time in minutes to onset (Δ ≥ FEV1 100 mL) on D1	182	30	30

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant presents three completed clinical safety and efficacy trials in support of the marketing authorisation.

CTT116853 was a 24-week evaluation, with an extension up to 52-weeks for a subset of subjects, of the efficacy and safety of FF/UMEC/VI compared with BUD/FOR. It was conducted to a randomised, double-blind, double-dummy, parallel-group, multi-centre design comparing the candidate treatment, once-daily FF/UMEC/VI (100/62.5/25 – Trelegy Ellipta and Elebrato Ellipta) against twice-daily BUD/FOR (400/12 Symbicort Turbuhaler) in subjects with advanced COPD at risk of exacerbation.

The co-primary endpoints were change from baseline in trough FEV1 and change from baseline in SGRQ Total Score at Week 24. Secondary efficacy endpoints were the annual rate of on-treatment moderate or severe COPD exacerbations, assessment of respiratory symptoms using the Exacerbations of COPD Tool (EXACT) – Respiratory Symptoms (EXACT-RS) - Score and subscale (breathlessness, cough/sputum production, and chest symptoms) scores, Transitional Dyspnea Index (TDI) focal score at Week 24 and Daily Activity Question.

The CHMP SAWP initially agreed that the proposed comparator study (CTT116853) of FF/UMEC/VI versus BUD/FOR, together with the supporting UMEC + FF/VI studies (200109 and 200110) could form the basis of an initial MAA. However, the CHMP recommended that use of FF/VI as an active comparator would be more appropriate taking into account current knowledge. However, the CHMP acknowledged that an authorisation may be possible with superiority demonstrated only against one authorised fixed dose combination (ICS/LABA or LAMA/LABA), provided that demonstrated superiority in efficacy is compelling and that data from other supportive studies allow demonstration of efficacy against LAMA/LABA and/or ICS/LABA.

Studies 200109 and 200110 were of similar design, randomised, double-blind, parallel-group, 12-week evaluations of the efficacy and safety of two strengths of UMEC (62.5 and 125 mcg) in addition to FF/VI compared to placebo added to the same combination of FF/VI in patients with moderate to very severe COPD. The primary endpoint of the supporting studies was trough FEV1 on Day 85; the secondary endpoint was weighted mean FEV1 over 0-6 hour post-dose on Day 84. The FF/UMEC/VI dose (100/62.5/25) was selected based on the doses that have been licenced for COPD for the FF/VI (100/25) and UMEC/VI (62.5/25) dual combinations through extensive studies in the mono and dual therapy programmes. Because it is no longer intended to commercialise a dose of UMEC 125 µg the two studies could be interpreted as a comparison of the UMEC 62.5 + FF/VI 100/25 µg (similar to Elebrato but not a fixed combination) compared with FF/VI alone at the same doses and/or a comparison of UMEC 62.5 µg with placebo. In both studies the triple combination shows superiority for most endpoints which is what would be expected.

During the assessment, the applicant informed about an issue involving the statistical analysis of the clinical reversibility results for the supportive clinical trial 200109, the results of which have been relied upon in part to support the efficacy of the product. The root-cause of the issue relates to a programming error for the conversion of numerical data from Base 10 to binary, which was not initially picked up by the internal QC controls of the applicant.

The results of Study CTT116853 show that the triple fixed dose combination of FF/UMEC/VI has statistically significant and clinically relevant improvements in trough FEV1 on week 24 over the approved comparator BUD/FOR. The difference between the two treatments of 171 ml is very marked. Therefore, we can raise the question of whether the BUD/FOR treatment arm was sufficient to match the needs of the population recruited i.e. whether participants in that arm were under treated. However, considering the results from both supporting studies 200109 and 200110 showing also a statistically significant and clinically relevant improvement in trough FEV1 on Day 85 over FF/VI (treatment differences of 122 mL and 124 mL), the evidence of a positive effect of the triple combination in lung function in COPD patients already receiving ICS/LABA combination is not questioned. No further analyses are necessary."While this error does not seem

to have had any significant effect on the outcome of the trials nor have led to any patient safety issues, the applicant has been advised to review their procedures to minimise the possibility of recurrence, which they have committed to doing.

Efficacy data and additional analyses

The results of Study CTT116853 show that the triple fixed dose combination of FF/UMEC/VI has statistically significant and clinically relevant benefits over the approved comparator BUD/FOR. The study is in line with advice given by EMA/CHMP on the clinical development programme. Considering the PK data and the additional data from studies 200109 and 200110 is therefore considered acceptable. No further analyses are necessary.

2.5.3. Conclusions on clinical efficacy

Study CTT116853 convincingly demonstrates the advantage of a triple fixed dose combination of LABA/LAMA/ICS over an approved double (LABA/ICS) combination and is in line with scientific advice provided by CHMP. The design of study CTT116853 included, however, direct comparisons with an authorised ICS/LABA combination only, which in itself would not have been sufficient to grant the indication sought by the applicant.

That being said, the company provided additional scientific data from two small supportive studies (200109 and 200110) showing that the triple combination showed superiority over a dual combination of FF/VI -. While these additional studies further clarify the clinical efficacy of the combination product, there remains a lack of evidence to claim a step-up indication from LAMA+LABA due to the absence of LAMA+LABA as a comparator in the pivotal Phase III study. The applicant was therefore advised that the therapeutic indication should reflect the clinical trial and be more accurately tailored to the COPD population studied in the clinical programme.

While the clinical efficacy results did show a beneficial effect on the rate of exacerbations, the clinical studies were not powered to allow this aspect to be reflected in the indication. It was agreed, however, that this information would be of benefit to clinicians, and so should be included in the product information. These data have therefore been included in section 5.1 as supportive information.

2.6. Clinical safety

Patient exposure

The clinical development programme to support the MAA for FF/UMEC/VI in patients with COPD comprises five completed studies: a single (principal) 24 week Phase III study (CTT116853) with a subset extension to 52 weeks, two 12 week supporting Phase III studies (200109 and 200110), and two Phase I clinical pharmacology studies (CTT116415 and 200587).

Data from supportive studies 200109 and 200110 were integrated since they were replicate studies. The results for comparator treatment arms UMEC (62.5 mcg) + FF/VI (100/25 mcg) and [placebo] FF/VI (100/25 mcg) [only] are presented as they represent the proposed dose for each of the components in the FF/UMEC/VI triple combination (100/62.5/25 mcg).

Safety data from the principal study CTT116853 and the supporting studies 200109and 200110 were not integrated as it was considered inappropriate to calculate annualised event rates from studies of short duration, and because of the different sample sizes between the studies (i.e., considerably larger volume of information obtained from CTT116853 relative to 200109/200110).

The number of patient by study and treatment arm is shown in Table 23. A total of 911 subjects were randomised to the FF/UMEC/VI group in the CTT116853 ITT population and 412 subjects were randomised

and treated with UMEC 62.5 + FF/VI in the 200109 and 200110 ITT populations (206 subjects in each study). A total of 430 subjects (24%) were included in the CTT116853 extension (52 week) 210 (23%) in the FF/UMEC/VI group and 220 (24%) in the BUD/FOR group.

Table 20 Summary of Subject Exposure (Studies CTT116853, 200109, 200110 ITT populations)

Study Grouping/ Study Number	Number of Patients				
	FF/UMEC/VI 100/62.5/25	BUD/FOR 400/12	Pbo + FF/VI 100/25	UMEC 62.5 + FF/VI 100/25	Total
CTT1168531	911	899	-	-	1810
Supporting Studies 2	-	-	412	412	824
200109	-	-	206	206	-
200110	-	-	206	206	-

Adverse events

- Summary of On-Treatment Adverse Events

CTT116853

ITT Population: The overall incidence of AEs and SAEs was 38.9% and 5.4%, respectively in the FF/UMEC/VI group and for the BUD/FOR group 37.7% and 5.7%, respectively. The incidence of non-fatal SAEs was 4.9% in the FF/UMEC/VI group and for the BUD/FOR group it was 5.2%. Two subjects (0.2%) in the FF/UMEC/VI group and 1 subject (0.1%) in the BUD/FOR group had SAEs considered related to study treatment by the investigator.

EXT Population: In the FF/UMEC/VI group the overall incidence of AEs and SAEs was 47.6% and 10.0%, respectively and for the BUD/FOR group it was 55.5% and 12.7%, respectively. The incidence of AEs considered related to study treatment by the investigator was 3.8% in the FF/UMEC/VI group and 7.7% in the BUD/FOR group. The incidence of non-fatal SAEs was 9.0% in the FF/UMEC/VI group and 12.3% in the BUD/FOR group. No subjects in the FF/UMEC/VI group and 1 subject (0.5%) in the BUD/FOR group had SAEs considered related to study treatment by the investigator.

Table 21 Overview of On-Treatment Adverse Events (CTT116853 – ITT and EXT Populations)

On-treatment Adverse Event Type	Number (%) of Subjects			
	ITT Population (24 weeks)		EXT Population (52 weeks)	
	FF/UMEC/VI 100/62.5/25 N=911	BUD/FOR 400/12 N=899	FF/UMEC/VI 100/62.5/25 N=210	BUD/FOR 400/12 N=220
Any AE	354 (38.9)	339 (37.7)	100 (47.6)	122 (55.5)
Drug-related [1]	46 (5.0)	41 (4.6)	8 (3.8)	17 (7.7)
Led to permanent discontinuation of study treatment or withdrawal from study	28 (3.1)	25 (2.8)	10 (4.8)	9 (4.1)

Any SAE	49 (5.4)	51 (5.7)	21 (10.0)	28 (12.7)
Drug-related [1]	2 (0.2)	1 (0.1)	0	1 (0.5)
Non-fatal	45 (4.9)	47 (5.2)	19 (9.0)	27 (12.3)
Fatal	4 (0.4)	6 (0.7)	2 (1.0)	1 (0.5)
Drug-related [1] fatal	0	0	0	0

1. Investigator's judgement of causality

2.

200109/200110 combined

In 200109/200110, the overall incidence of AEs was 34% in the UMEC + FF/VI group and 37% in the FF/VI group. The incidence of SAEs by category (fatal, non-fatal, fatal drug-related, and non-fatal drug-related) was similar between the treatment groups. The incidence of AEs considered related to study drug by the investigator or that led to permanent discontinuation of study treatment or withdrawal from the study was similar between the treatment groups (5% and 2%, respectively, in the UMEC + FF/VI group and 5% and 3%, respectively, in the FF/VI group).

Table 22 Overview of On-Treatment Adverse Events (200109/200110 – ITT population)

	Number (%) of Subjects	
On-treatment Adverse Event Type	**FF/VI 100/25 N=412**	**UMEC 62.5 + FF/VI 100/25 N=412**
Any AE	153 (37)	142 (34)
Any Drug-Related[1] AE	22 (5)	21 (5)
Any AE Leading to Permanent Discontinuation of Study Treatment or Withdrawal from Study	14 (3)	10 (2)
Any Non-fatal Drug-Related[1] SAE	1 (<1)	0
Any Fatal Drug-Related[1] SAE	0	0
Any Non-fatal SAE	12 (3)	9 (2)
Any Fatal SAE	5 (1)	1 (<1)

1. Investigator's judgement of causality.

Common Adverse Events

Frequently-Reported On-Treatment Adverse Events

CTT116853

ITT Population: The most frequently reported AEs were nasopharyngitis, which was reported for 7% of subjects in the FF/UMEC/VI group and 5% in the BUD/FOR group, and headache, which was reported for 44 subjects (5%) in the FF/UMEC/VI group and 53 subjects (6%) in the BUD/FOR group. The remaining most frequent AEs were reported for no more than 3% of subjects in either treatment group and with a generally similar incidence in both treatment groups. Although the incidence of blood pressure increased was less than 1% in both treatment groups, there as a lower event rate per 1000 subject-years) in the FF/UMEC/VI group (9.8 [4 events]) compared with the BUD/FOR group (56.5 [22 events]).

There was a higher incidence of pneumonia in the FF/UMEC/VI group (19 subjects [2%]) compared with the BUD/FOR group (7 subjects [<1%]). There was a numerical imbalance for COPD, which was reported for 15 subjects (2%) in the FF/UMEC/VI group compared with 23 subjects (3%) in the BUD/FOR group.

There was an increased risk (i.e., 95% confidence interval [CI] of hazard ratio does not include 1) of pneumonia for the FF/UMEC/VI group and of rhinorrhoea for the BUD/FOR group (Figure 9). The 95% CIs for all other frequent on-treatment AEs in the ITT Population included 1 i.e. was not statistically significant.

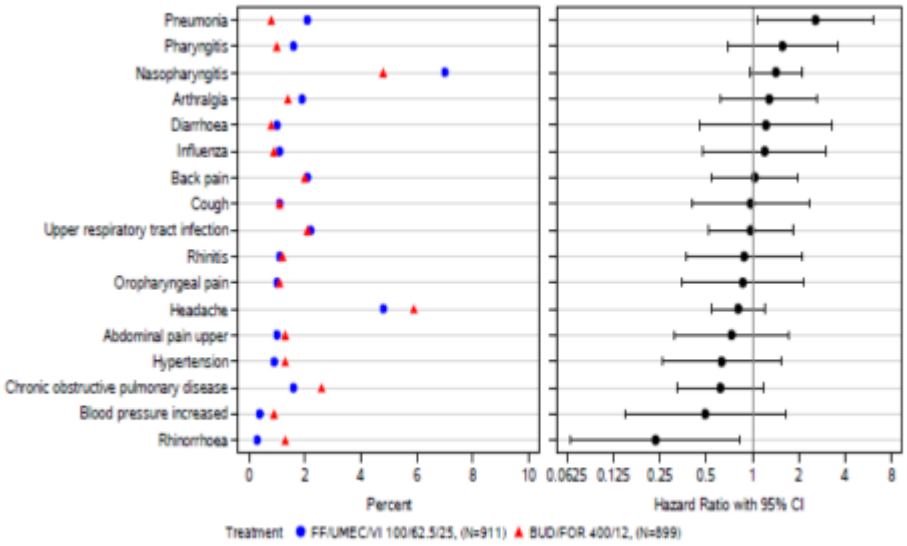


Figure 6. CTT116853 ITT population to Week 25 common on-treatment AEs

EXT Population: The most frequently reported AE was nasopharyngitis, which was reported for 23 subjects (11%) in the FF/UMEC/VI group and 22 (10%) in the BUD/FOR group. The second most frequent AE was headache, which was reported for 17 subjects (8%) in the FF/UMEC/VI group and 22 (10%) in the BUD/FOR group. The next most frequent AE was COPD, which was reported less in the FF/UMEC/VI group (5 subjects [2%]) compared with the BUD/FOR group (22 subjects [10%]). The remaining most frequent AEs were reported for no more than 5% of subjects in either treatment group and with a generally similar incidence in both treatment groups. Pneumonia was reported for 4 subjects (2%) in the FF/UMEC/VI group and 4 subjects (2%) in the BUD/FOR group.

Table 23 the ten Most Frequent On-Treatment Adverse Events in Each Treatment Group (CTT116853 – ITT and EXT Populations)

Adverse Event (Preferred Term)	FF/UMEC/VI 100/62.5/25		BUD/FOR 400/12	
	n (%)	Rate [1] [# Events]	n (%)	Rate [1] [# Events]
ITT Population (24 weeks), N	**911**		**899**	
Nasopharyngitis	64 (7)	179.3 [73]	43 (5)	125.9 [49]
Headache	44 (5)	186.7 [76]	53 (6)	200.3 [78]
URTI [2]	20 (2)	66.3 [27]	19 (2)	64.2 [25]
COPD Back	15 (2)	39.3 [16]	23 (3)	66.8 [26]
pain	19 (2)	61.4 [25]	18 (2)	48.8 [19]
Arthralgia	17 (2)	44.2 [18]	13 (1)	41.1 [16]
Pneumonia	19 (2)	49.1 [20]	7 (<1)	18.0 [7]
Pharyngitis	15 (2)	41.8 [17]	9 (1)	25.7 [10]
Abdominal Pain Upper	9 (<1)	27.0 [11]	12 (1)	33.4 [13]
Rhinitis Cough	10 (1)	24.6 [10]	11 (1)	38.5 [15]
Hypertension	10 (1)	24.6 [10]	10 (1)	25.7 [10]
Oropharyngeal pain	8 (<1)	19.7 [8]	12 (1)	41.1 [16]
Influenza	9 (<1)	24.6 [10]	10 (1)	28.3 [11]
Diarrhoea	10 (1)	24.6 [10]	8 (<1)	23.1 [9]
Rhinorrhoea	9 (<1)	24.6 [10]	7 (<1)	18.0 [7]
Blood pressure increased	3 (<1)	9.8 [4]	12 (1)	33.4 [13]
EXT Population (52 weeks), N	**210**		**220**	
Nasopharyngitis	23 (11)	172.6 [34]	22 (10)	138.7 [27]
Headache COPD	17 (8)	198.0 [39]	22 (10)	185.0 [36]
URTI	5 (2)	40.6 [8]	22 (10)	133.6 [26]
Hypertension	6 (3)	40.6 [8]	10 (5)	92.5 [18]
Arthralgia Back	7 (3)	35.5 [7]	6 (3)	41.1 [8]
pain Pneumonia	5 (2)	30.5 [6]	6 (3)	41.1 [8]
Rhinitis	4 (2)	30.5 [6]	5 (2)	30.8 [6]
Dizziness	4 (2)	25.4 [5]	4 (2)	20.6 [4]
Oropharyngeal pain	3 (1)	15.2 [3]	5 (2)	41.1 [8]
Pharyngitis	1 (<1)	5.1 [1]	6 (3)	41.1 [8]
Respiratory tract infection viral	6 (3)	30.5 [6]	1 (<1)	5.1 [1]
Abdominal pain upper	5 (2)	25.4 [5]	1 (<1)	10.3 [2]
Blood pressure increased	3 (1)	25.4 [5]	3 (1)	20.6 [4]
Dyspnoea	1 (<1)	5.1 [1]	3 (1)	20.6 [4]
Vertigo	0	0	4 (2)	20.6 [4]
Candida infection Gastrooesophageal	0	0	4 (2)	20.6 [4]
reflux disease Oral fungal infection	0	0	4 (2)	20.6 [4]
	0	0	3 (1)	20.6 [4]
	0	0	3 (1)	20.6 [4]

1. Event rate per 1000 subject-years calculated as the number of events x 1000, divided by the total treatment exposure.

Serious adverse events and deaths

Serious adverse events included any untoward medical occurrence that, at any dose, resulted in: death; was life-threatening; required hospitalisation or prolongation of existing hospitalisation; resulted in

disability/incapacity; was a congenital anomaly/birth defect; was an important medical event that may not have been immediately life-threatening or resulted in death or hospitalisation but may have jeopardised the subject or may have required medical or surgical intervention to prevent one of the other outcomes defined as SAEs; or any event of possible drug-induced liver injury with hyperbilirubinaemia, defined as alanine aminotransferase (ALT) ≥3x upper limit of normal (ULN) and bilirubin ≥2xULN (>35% direct) (or ALT ≥3xULN and international normalised ratio (INR) >1.5, if INR measured) termed 'Hy's Law' events (INR measurement was not required and the threshold value stated did not apply to patients receiving anticoagulants).

Deaths

In CTT116853, all SAE reports (fatal and non-fatal) were adjudicated by the clinical events committee, in studies 200109 and 200110, SAEs were not adjudicated.

A total of 18 on-treatment deaths occurred during the clinical development is programme; 12 deaths in CTT116853 and 6 deaths in 200109/200110.

In StudyCTT116853 ITT population up to Week 24 fatal SAEs were reported for 4 subjects (0.4%) in the FF/UMEC/VI group and 6 subjects (0.7%) in the BUD/FOR group, none of which were considered related to study treatment.

In Study CTT116853 EXT population up to Week 52 fatal SAEs were reported for 2 subjects (1.0%) in the FF/UMEC/VI group and 1 subject (0.5%) in the BUD/FOR group, none of which were considered related to study treatment. One subject with a fatal SAE was included in both the ITT and EXT counts.

In studies 200109 and 200110 fatal SAEs were reported for 1 subject (<1%) in the UMEC + FF/VI group and 5 subjects (1%) in the FF/VI group, none of which were considered related to study drug by the investigator.

Serious adverse events [including fatal SAE]

CTT116853

ITT Population: On-treatment SAEs (fatal and non-fatal) were reported for 49 subjects (5.4%) in the FF/UMEC/VI group and by 51 subjects (5.7%) in the BUD/FOR group. The most common on-treatment SAEs were COPD and pneumonia. There was a numerical imbalance for the incidence of COPD in the FF/UMEC/VI group (12 subjects [1.3%]) compared with the BUD/FOR group (21 subjects [2.3%]). There was a higher incidence of pneumonia in the FF/UMEC/VI group (9 subjects [1.0%]) compared with the BUD/FOR group (3 subjects [0.3%]). There was also a numerical imbalance for the incidence of any events in the cardiac disorders system organ class in the FF/UMEC/VI group (3 subjects [0.3%]) compared with the BUD/FOR group (9 subjects [1.0%]).

Post-treatment SAEs were reported for 3 subjects (0.3%) in the FF/UMEC/VI group and by 8 subjects (0.9%) in the BUD/FOR group.

EXT Population: On-treatment SAEs were reported for 21 subjects (10.0%) in the FF/UMEC/VI group and by 28 subjects (12.7%) in the BUD/FOR group. The most common on-treatment SAEs were COPD and pneumonia. The incidence of COPD was lower in the FF/UMEC/VI group (5 subjects [2.4%]) compared with the BUD/FOR group (20 subjects [9.1%]). There were 4 subjects (1.9%) in the FF/UMEC/VI group and 4 subjects (1.8%) in the BUD/FOR group who experienced pneumonia.

Drug-related SAEs were reported for two subjects (0.2%) in the FF/UMEC/VI group and one subject (0.1%) in the BUD/FOR group. Cardiac failure, lung infection, and pneumonia were the only reported on-treatment drug-related non-fatal SAEs reported in the FF/UMEC/VI group and atrial flutter was the only

event reported in the BUD/FOR group. In the extension population pneumonia was the only reported on-treatment drug-related non-fatal SAE and was reported by a single subject in the BUD/FOR group.

Table 24 Adjudicated Non-Fatal Serious Adverse Reports (CTT116853 – ITT and EXT Populations)

Non-Fatal Serious Adverse Report Category-Subcategory	Number (%) of Subjects			
	ITT Population (24 weeks)		EXT Population (52 weeks)	
	FF/UMEC/VI 100/62.5/25 N=911	BUD/FOR 400/12 N=899	FF/UMEC/VI 100/62.5/25 N=210	BUD/FOR 400/12 N=220
On-Treatment				
Total	45 (4.9)	47 (5.2)	19 (9.0)	27 (12.3)
Cardiovascular	7 (0.8)	6 (0.7)	3 (1.4)	1 (0.5)
Myocardial infarction/ischemic heart disease	3 (0.3)	2 (0.2)	1 (0.5)	0
Congestive heart failure	1 (0.1)	0	0	0
Other cardiovascular cause	3 (0.3)	4 (0.4)	2 (1.0)	1 (0.5)
Respiratory	21 (2.3)	27 (3.0)	8 (3.8)	23 (10.5)
COPD exacerbation	14 (1.5)	22 (2.4)	5 (2.4)	21 (9.5)
With evidence of pneumonia	4 (0.4)	3 (0.3)	2 (1.0)	5 (2.3)
Without evidence of pneumonia	11 (1.2)	19 (2.1)	3 (1.4)	16 (7.3)
Pneumonia/respiratory tract infection without COPD exacerbation Other respiratory cause Cancer	8 (0.9)	3 (0.3)	3 (1.4)	2 (0.9)
Lung	0	3 (0.3)	0	1 (0.5)
Colorectal	4 (0.4)	4 (0.4)	4 (1.9)	1 (0.5)
Other cancer cause	1 (0.1)	2 (0.2)	2 (1.0)	1 (0.5)
Unknown	1 (0.1)	0	1 (0.5)	0
Inadequate information	2 (0.2)	2 (0.2)	1 (0.5)	0
	0	1 (0.1)	0	1 (0.5)
Post-Treatment				
Cardiovascular	1 (0.1)	1 (0.1)	---	---
Myocardial infarction/ischemic heart disease	1 (0.1)	1 (0.1)	---	---
Respiratory	1 (0.1)	2 (0.2)	---	---
COPD exacerbation	1 (0.1)	2 (0.2)	---	---
Cancer	0	2 (0.2)	---	---
Other cancer cause	0	2 (0.2)	---	---

Studies 200109/200110

In 200109/200110, the incidence of non-fatal SAEs was similar between the treatment groups in the ITT Subpopulation: UMEC + FF/VI (9 subjects [2%]) and FF/VI (12 subjects [3%]). The most common non-fatal SAEs were COPD, which was reported for 3 subjects (<1%) in the UMEC + FF/VI group and 4 subjects (<1%) in the FF/VI group, and pneumonia (2 subjects [<1%] in each group). Other non-fatal SAEs were reported with an incidence of <1% in either group.

Laboratory findings

In CTT116853, routine non-fasting clinical laboratory tests (haematology and clinical chemistry) were performed at Screening, Week 12, Week 24 and Week 52 for subjects participating in the study extension or at the Study Treatment Discontinuation Visit, if applicable. Glucose and potassium were evaluated as part of the routine laboratory assessments during the study. Hypothalamic-pituitary-adrenal (HPA) axis effects, including adrenal suppression and decreased serum cortisol, are recognised class effects of ICS. While no specific laboratory evaluation of cortisol was conducted during the programme, AESIs related to adrenal suppression were evaluated. A minor error in the derivation of 'worst case post-baseline' flags relative to the normal range was identified for subjects with changes in the laboratory reference values occurring during the clinical trial, but these errors were not considered to have significantly affect the safety results of the trials.

In 200109 and 200110, clinical chemistry and haematology assessments were only conducted at Screening for the purpose of assisting investigators with determination of subject eligibility. At the discretion of the investigator, AEs could have been followed up with clinical chemistry or haematology assessments.

CTT116853

No clinically relevant trends or unexpected abnormalities in clinical chemistry (including glucose and potassium) or haematology parameters were observed. One subject in the BUD/FOR group had elevated liver function tests (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) that met the protocol defined stopping criteria while on treatment; the elevations subsequently resolved. A second subject (FF/UMEC/VI group) who was hepatitis C positive at screening had elevations in ALT and AST which were reported during a concurrent AE of worsening chronic virus hepatitis C.

ECG data

In study CTT116853, a single 12-lead ECG was recorded after measurement of vital signs and spirometry at Screening and approximately 15-45 minutes after dosing at Week 4 and Week 24 (and Week 52 for subjects participating in the study extension) or Study Treatment Discontinuation Visit as applicable. At selected study sites, a subset of subjects provided 24-hour Holter monitoring data at Screening and 24 hours prior to the Week 24 Visit. No emerging safety signals from ECGs, or Holter monitoring data at any time points were observed in study CTT116853.

In studies 200109 and 200110, a 12-lead ECG was performed at Screening (Visit 1) only. Holter monitoring was not conducted during the 200109 and 200110 studies."

Study CTT116853

Adverse Events by Gender

ITT Population Compared with the Overall ITT Population, a higher incidence of on-treatment AEs was reported for females in both treatment groups. There were no remarkable differences based on gender for the incidence of on-treatment drug-related AEs, SAEs, adjudicated non-fatal serious adverse reports, or AEs leading to discontinuation of study treatment or withdrawal from the study for either treatment group compared with the Overall ITT Population.

EXT Population Compared with the Overall EXT Population, a higher incidence of on-treatment AEs was reported for females in the FF/UMEC/VI group and lower incidences of on-treatment drug-related AEs, SAEs, and adjudicated non-fatal serious adverse reports were reported for females in the BUD/FOR treatment group. There were no remarkable differences based on gender for the incidence of on-treatment AEs leading to discontinuation of study treatment or withdrawal from the study for either treatment group compared with the Overall EXT Population.

Table 25 Summary of On-Treatment Adverse Events by Gender (CTT116853 – ITT and EXT Populations)

	Number (%) of Subjects			
	ITT Population (24 weeks)		EXT Population (52 weeks)	
	FF/UMEC/VI 100/62.5/25 N=911	BUD/FOR 400/12 N=899	FF/UMEC/VI 100/62.5/25 N=210	BUD/FOR 400/12 N=220
Any On-Treatment AE				
Overall Population	354 (38.9)	339 (37.7)	100 (47.6)	122 (55.5)
Male	251 (37)	231 (35)	72 (46)	89 (55)
Female	103 (44)	108 (46)	28 (53)	33 (57)
Any On-Treatment Drug-Related AE[1]				
Overall Population	46 (5.0)	41 (4.6)	8 (3.8)	17 (7.7)
Male	32 (5)	28 (4)	7 (4)	15 (9)
Female	14 (6)	13 (6)	1 (2)	2 (3)
Any On-Treatment SAE				
Overall Population	49 (5.4)	51 (5.7)	21 (10.0)	28 (12.7)
Male	41 (6)	41 (6)	16 (10)	26 (16)
Female	8 (3)	10 (4)	5 (9)	2 (3)
Any On-Treatment Adjudicated Non-Fatal Serious Adverse Report				
Overall Population	45 (4.9)	47 (5.2)	19 (9.0)	27 (12.3)
Male	38 (6)	37 (6)	14 (9)	25 (15)
Female	7 (3)	10 (4)	5 (9)	2 (3)
Any On-Treatment AE Leading to Discontinuation of Study Treatment or Withdrawal from Study				
Overall Population	28 (3.1)	25 (2.8)	10 (4.8)	9 (4.1)
Male	25 (4)	23 (3)	9 (6)	8 (5)
Female	3 (1)	2 (<1)	1 (2)	1 (2)

1. Investigator's judgement of causality.

Adverse Events by Age

ITT Population: Compared with the Overall ITT Population, higher incidences of on-treatment AEs, SAEs, adjudicated non-fatal serious adverse reports, and AEs leading to discontinuation of study treatment or withdrawal from the study were reported for subjects 75 to 84 years of age in the FF/UMEC/VI group but not in the BUD/FOR group. However, the conditions customarily more common in elderly (e.g., nervous system disorders, psychiatric disorders, cardiac disorders, vascular disorders, postural hypotension/falls/black outs/syncope/dizziness/ataxia/fractures) were seen with similar incidence in the FF/UMEC/VI and BUD/FOR groups. There were no remarkable differences based on age for the incidence of on-treatment drug-related AEs for either treatment group compared with the Overall ITT Population (Table 3.64). The number of subjects at least 85 years of age was small (n=9 total), and therefore, it is difficult to make conclusions on these data.

EXT Population: Compared with the Overall EXT Population, lower incidences of on-treatment SAEs and adjudicated non-fatal serious adverse reports were reported for subjects 65 to 74 years of age in the FF/UMEC/VI group. There were no remarkable differences based on age for the incidence of on-treatment AEs, drug-related AEs, or AEs leading to discontinuation of study treatment or withdrawal from the study for either treatment group compared with the Overall EXT Population. The number of subjects 75 to 84 years

of age was small (n=39 total) and therefore it is difficult to make conclusions on these data; there were no subjects at least 85 years of age.

Immunological events

The only relevant events are classified as hypersensitivity reactions and the clinical details available are insufficient to make any meaningful evaluation.

Safety related to drug-drug interactions and other interactions

As agreed with CHMP as part of Scientific Advice, no drug-drug interaction studies were conducted for FF/UMEC/VI, based on information from the previous development programmes for FF/VI, UMEC/VI, and UMEC monotherapy. The known drug interactions of FF/VI, UMEC/VI, and UMEC monotherapy are provided in the prescribing information for each product.

Discontinuation due to AES

CTT116853

ITT Population AEs that led to permanent discontinuation of study treatment or withdrawal from the study was twenty-eight subjects (3%) in the FF/UMEC/VI group and 25 (3%) in the BUD/FOR group.

EXT Population AEs leding to permanent discontinuation of study treatment or withdrawal from the study were reported for ten subjects (5%) in the FF/UMEC/VI group and nine (4%) in the BUD/FOR group.

Table 26 Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study in 2 or More Subjects (CTT116853 – ITT and EXT Populations)

AE Leading to Discontinuation of Study Treatment or Withdrawal from the Study (Preferred Term)	FF/UMEC/VI 100/62.5/25		BUD/FOR 400/12	
	n (%)	Rate [1] [# Events]	n (%)	Rate [1] [# Events]
ITT Population (24 weeks), N	**911**		**899**	
Any AE leading to discontinuation of treatment or withdrawal from study	28 (3)	86.0 [35]	25 (3)	84.8 [33]
Respiratory, thoracic and mediastinal disorders				
COPD	11 (1)	27.0 [11]	11 (1)	30.8 [12]
Dyspnoea				
Infections and infestations	7 (<1)	17.2 [7]	2 (<1)	5.1 [2]
Pneumonia	2 (<1)	4.9 [2]	4 (<1)	10.3 [4]
Neoplasms benign, malignant and unspecified (including cysts and polyps)	7 (<1)	17.2 [7]	2 (<1)	5.1 [2]
Lung neoplasm malignant	4 (<1)	9.8 [4]	1 (<1)	2.6 [1]
Cardiac disorders Cardiac failure Gastrointestinal disorders Nervous system disorders	2 (<1)	4.9 [2]	5 (<1)	15.4 [6]
General disorders and administration	0	0	2 (<1)	7.7 [3]
site conditions	0	0	6 (<1)	15.4 [6]
Investigations	0	0	2 (<1)	5.1 [2]
	2 (<1)	7.4 [3]	2 (<1)	5.1 [2]
	3 (<1)	9.8 [4]	1 (<1)	5.1 [2]
	1 (<1)	2.5 [1]	2 (<1)	5.1 [2]

EXT Population (52 weeks), N	210		220	
Any AE leading to discontinuation of treatment or withdrawal from study Respiratory, thoracic and mediastinal disorders	10 (5)	60.9 [12]	9 (4)	51.4 [10]
COPD	3 (1)	20.3 [4]	4 (2)	20.6 [4]
Cardiac disorders				
Infections and infestations Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (<1) 1 (<1) 2 (<1)	10.2 [2] 5.1 [1] 10.2 [2]	3 (1) 2 (<1) 1 (<1)	15.4 [3] 10.3 [2] 5.1 [1]

1. Event rate per 1000 subject-years calculated as the number of events x 1000, divided by the total treatment exposure

200109/200110

AEs leading to permanent discontinuation of study drug or withdrawal from study were reported for UMEC + FF/VI (10 subjects [2%]) and FF/VI (14 subjects [3%]). The most frequently reported AEs leading to withdrawal (incidence all <1%) were COPD (2 subjects in UMEC + FF/VI group and 4 subjects in FF/VI group), MI (1 subject in UMEC + FF/VI group and 4 subjects in FF/VI group), and pneumonia (2 subjects in UMEC + FF/VI group and 3 subjects in FF/VI group)

2.6.1. Discussion on clinical safety

The safety population supporting the FF/UMEC/VI clinical development comprised a total of 911 subjects treated with the closed triple combination FF/UMEC/VI 100/62.5/25 for up to 24 weeks in Study CTT116853 and 412 subjects treated with the open triple combination UMEC 62.5 + FF/VI 100/25 for up to 12 weeks in Studies 200109 and 200110. A subset of subjects in CTT116853 were treated with FF/UMEC/VI (N=210) for up to 52 weeks and provided long-term safety data.

In Study CTT116853 the mean age was 64 years, 26% were females, 44% were current smokers with about a 39 pack-year history, about two-thirds of subjects had at least one cardiovascular risk factor at baseline. Approximately two-thirds had at least one moderate/severe exacerbation in the previous year, and about 10% of subjects had a history of pneumonia prior to study entry which is representative of the target COPD population.

In CTT116853, the most frequently reported AEs were nasopharyngitis and headache in both treatment groups, and a similar profile was observed in the 200109/200110 studies. The most frequently reported AEs reported during the FF/UMEC/VI programme were consistent with those observed in the previous development programmes for FF/VI, UMEC/VI, and UMEC monotherapy.

In CTT116853, the most common on-treatment SAEs (fatal and non-fatal) were COPD exacerbations and pneumonia in both treatment groups. There was a numerical imbalance for the incidence of COPD in the BUD/FOR group compared with the FF/UMEC/VI group. COPD has been shown to be a risk factor for the development of pneumonia. Pneumonia is also a recognised risk associated with the use of ICS treatments in COPD. Review of SAE and AE data in the ITT Population up to 24 weeks (n=1810) in CTT116853 demonstrated a higher incidence of pneumonia AESI compared to BUD/FOR (2.2% vs 0.8%) which was not observed in the EXT Population up to 52 weeks (n=430), where a similar incidence of pneumonia AESI was observed in both treatment groups (1.9% vs 1.8%). In CTT116853, chest imaging confirmed pneumonias and SAE reports adjudicated as pneumonia (based on independent blinded adjudication) were in line with investigator-reported data. Based on data collected using the pneumonia eCRF, in the ITT Population up to 24 weeks, in the FF/UMEC/VI group, there were 10 subjects (1%) with pneumonia supported by X-ray/CT scan and 11 hospitalisations, and in the BUD/FOR group, there were 3 subjects (<1%) with pneumonia supported by X-ray/CT scan and 3 hospitalisations. In the EXT Population up to 52 weeks, in both the

FF/UMEC/VI and BUD/FOR groups, there were 4 subjects (2%) with pneumonia and 4 hospitalisations. There was one fatal pneumonia in CTT116853; this subject was in the FF/UMEC/VI group.

The incidence of pneumonia with FF/UMEC/VI in CTT116853 was in line with the incidence of pneumonia reported in 24-week studies with FF/VI (<1 to 2% with FF/VI 100/25) and less than that observed in 52-week exacerbation studies with FF/VI (6% with FF/VI 100/25).

Cardiovascular safety was monitored in CTT116853 via AE reporting with categorisation and analysis of adverse events of special interest including cardiac arrhythmia, cardiac failure, ischaemic heart disease, hypertension, and central nervous system haemorrhages and cerebrovascular conditions. There was a high prevalence of concurrent CV disease approximately two-thirds of subjects reported CV risk factors at baseline. Events in the hypertension subgroup were reported with a numerically higher incidence in BUD/FOR compared with FF/UMEC/VI in the ITT Population up to 24 weeks and with a similar incidence in the EXT Population up to 52 weeks. Small numerical differences in the incidence of MACE events were observed between treatments in the study with higher incidence in the BUD/FOR group in the ITT Population up to 24 weeks and higher incidence in FF/UMEC/VI group in the EXT Population up to 52 weeks. There were no emerging safety signals from vital signs, ECGs, or Holter data in the study. In addition, the independently adjudicated data were in line with the investigator-reported data.

A change in the classification of some adverse events which occurred during the clinical trials was reported by the applicant at the late stage of assessment. This related to a change in the reference intervals for some biochemical and laboratory normal values, which subsequently resulted in some patients initially classified as “High” later being reclassified as “Normal” and vice versa. This raised an uncertainty around the incidence of such adverse event reports from the affected clinical trials, but the ultimate clinical significance of this is minimal. Additional analyses were requested by CHMP and clarification was provided by the applicant. Both were considered acceptable. The applicant is however reminded that accurate document version control is an imperative in ensuring the integrity of data collected in clinical trials.

2.6.2. Conclusions on clinical safety

The safety profile of FF/UMEC/VI in the supporting clinical studies was in line with the pharmacologic class of each component and with the dual combinations FF/VI and UMEC/VI, and no new safety signals emerged in the populations studied.

2.7. Risk Management Plan

Safety concerns

Table 27

Summary of safety concerns	
Important identified risks	Pneumonia
Important potential risks	Serious Cardiovascular Events
	Decreased bone mineral density and associated fractures
Missing information	Safety in pregnancy and lactation
	Safety in severe hepatic impairment

Pharmacovigilance plan

Table 28

Study	Description of activity (or study title if known)	Milestone(s)	Due Date(s)
1	Study CTT116855 A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination FF/UMEC/VI with the fixed dose dual combinations of FF/VI and UMEC/VI, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease (Category 3)	Study start30 June 2014	1H2018
		Study finish: 3Q2017	
		Final report: 1H2018	

Risk minimisation measures

Table 29

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Pneumonia	Prescription-only medication See EU SmPC: Section 4.4 Warnings and Precautions:	Not applicable
Serious Cardiovascular Events	Prescription-only medication See EU SmPC: Section 4.4 Warnings and Precautions Events of cardiovascular events are listed in SmPC section 4.8: ***Cardiac Disorders*** *Uncommon: Supraventricular tachyarrythmia, Tachycardia, Atrial fibrillation*	Not applicable
Decreased Bone Mineral Density and Associated Fractures	Prescription-only medication See EU SmPC: Section 4.4 Warnings and Precautions Event of fracture is listed in SmPC section 4.8 ***Musculoskeletal and connective tissue disorders*** *Uncommon: Fractures*	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Safety in Pregnancy and lactation	Prescription-only medication. See EU SmPC: Section 4.6 Fertility, pregnancy and lactation	Not applicable
Safety in severe hepatic impairment	Prescription-only medication. See EU SmPC: Section 4.2 Posology and method of administration: Hepatic impairment 5.2 Pharmacokinetic properties Hepatic impairment	Not applicable

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable . The bridging report submitted by the applicant has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

COPD is strongly linked to tobacco smoking, particularly cigarette smoking and is a male predominant condition, in COPD clinical trials in developed countries generally about two thirds of included patients are male and for both males and females the average age tends to be in the early sixties. In poor countries the male predominance is not as marked as women may develop COPD as a result of cooking over open fires. The prevalence is quite variable on a local basis with higher prevalence linked to lower affluence and social status. Screening would be possible by mass measurement of lung function which is cheap, easy, and non-invasive, but is not done in practice. There have been no substantial trials of the value of screening for COPD. Tobacco smoking cessation or non/never smoking is an effective measure and societal efforts have been made in that direction rather than into screening programmes.

COPD is characterised by cough, excess sputum production, airways narrowing leading to air trapping and hyperinflation of the chest, and loss of lung tissue (emphysema). In its more advanced stages it causes strain and eventually failure, of the cardiac right ventricle.

3.1.2. Available therapies and unmet medical need

Management of the condition relies on smoking cessation, pharmacological intervention with bronchodilators and anti-inflammatory agents and, when necessary treatment of respiratory infections, physical rehabilitation is aimed primarily at muscle strengthening, and in advanced cases long term domiciliary oxygen administration is helpful and has a proven benefit on lung function. Some patients are suitable for lung volume reduction surgery to reduce non-gas exchanging thoracic space. Once developed the condition is only partly reversible so more treatment options are always welcome.

3.1.3. Main clinical studies

The main phase 3 clinical studies supporting this application are one pivotal study (CTT116853) and two supportive studies (200109 and 200100)

CTT116853 was a 24-week evaluation, with an extension up to 52-weeks for a subset of subjects, of the efficacy and safety of FF/UMEC/VI compared with BUD/FOR. It was conducted to a randomised, double-blind, double-dummy, parallel-group, multi-centre design comparing the candidate treatment, once-daily FF/UMEC/VI (100/62.5/25 – Trelegy Ellipta and Elebrato Ellipta) against twice-daily BUD/FOR (400/12 Symbicort Turbuhaler) in subjects with advanced COPD at risk of exacerbation.

Trough FEV1 endpoints and were significantly superior to placebo $p < 0.001$ at alltime points. Clinically meaningful improvements from baseline in SGRQ Total Score were observed in both treatment groups, and FF/UMEC/VI demonstrated statistically significant improvement compared with BUD/FOR.

In studies 200109 and 200110, the outcome for the primary efficacy endpoint change from baseline at trough FEV1 at Day 85 was statistically significantly superior to placebo for both doses of UMEC in patients who are not adequately treated. Statistically significant improvements in LS mean change from baseline in the secondary endpoint 0-6 h WM FEV1 were demonstrated for both the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups compared with the placebo + FF/VI treatment group at Day 84. Significant improvements in the LS mean change from baseline in 0-6 h WM FEV1 were also demonstrated for both the UMEC 62.5 + FF/VI and the UMEC 125 + FF/VI treatment groups compared with the placebo + FF/VI group

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Median time to onset of additional bronchodilation was shorter in both UMEC + FF/VI (30 minutes for each) treatment groups compared with the placebo + FF/VI treatment group (182 minutes); the hazard ratios for both treatment comparisons (based on analysis of time to onset of additional bronchodilation) were statistically significant ($p<0.001$).

Studies 200109 and 200110 were of similar design, randomised, double-blind, parallel-group, 12-week evaluations of the efficacy and safety of two strengths of UMEC (62.5 and 125 mcg) in addition to FF/VI compared to placebo added to the same combination of FF/VI in patients with moderate to very severe COPD. The primary endpoint of the supporting studies was trough FEV1 on Day 85; the secondary endpoint was weighted mean FEV1 over 0-6 hour post-dose on Day 84. The FF/UMEC/VI dose (100/62.5/25) was selected based on the doses that have been licenced for COPD for the FF/VI (100/25) and UMEC/VI (62.5/25) dual combinations through extensive studies in the mono and dual therapy programmes. The dose of UMEC 125 µg used in the clinical programme will not be marketed. Therefore , the two studies could be interpreted as a comparison of the UMEC 62.5 + FF/VI 100/25 µg (similar to Elebrato but not a fixed combination) compared with FF/VI alone at the same doses and/or a comparison of UMEC 62.5 µg with placebo. In both studies the triple combination shows superiority for most endpoints.

3.2. Favourable effects

Elebrato contains three active components the bronchodilators vilanterol and umeclidinium which work by complementary mechanisms of action on airways autonomic nerve and muscle and the anti-inflammatory inhaled corticosteroid fluticasone furoate. All three are considered to have beneficial effects on the airways inflammation and narrowing which is a key pathology in COPD and as their actions are complementary then their combination is logical. There is evidence that the treatments used in combination of two or three reduce the frequency of moderate to severe COPD exacerbations thus avoiding patient distress and inconvenience and reducing the burden that COPD places on health care resources. For individual patients the progression of COPD often appears to be punctuated by exacerbations – the patient never fully regains his/her pre-exacerbation state. However, at a population level it is generally agreed that pharmacological intervention dose not modify the rate of deterioration of lung function.

3.3. Uncertainties and limitations about favourable effects

The present application is in effect supported by a single clinical trial CTT116853 which compared the likely commercial product Elebrato to an authorised and widely used fixed dose combination of budesonide/formoterol over 24 weeks and in a smaller sub-population over 52 weeks. Not unexpectedly the triple combination showed advantages over the double with respect to change from baseline in lung function. An advantage was also shown in the patients symptom and quality of life score SGRQ again this is not surprising but the magnitude of the benefit is as it is unusual for inhaled (or other) therapies to reach or exceed the boundary of a reduction of four points which is taken to indicate clinical relevance of the benefit.

Much the greater proportion of patients were studied for 24 weeks (n = 1810) and the smaller proportion for 52 weeks (n = 430). Because COPD exacerbations are highly seasonal (more frequent in winter) anything less than a 12 month study is considered sub-optimal to measure exacerbation rates and this should be taken into consideration is evaluating the results of Study CTT116853.

The two supportive studies 200109 and 200110 were only of twelve weeks duration which in the context of COPD is too short to give a reliable readout on anything other than spirometric variables (e.g. FEV1). In addition the treatment arms involving an ‘excess’ dose 125 µg of umeclidinium are not fully relevant due to the current lower strength applied for by the applicant.

3.4. Unfavourable effects

The unfavourable effects are those associated with the class of active substances. For the LABA tremor, tachycardia, agitation, increase of blood pressure, hypokalaemia, hyperglycaemia, for the LAMA dry mouth, blurring of vision, urinary retention, and for the ICS oropharyngeal candidiasis, vocal cord atrophy, hyperglycaemia, and most important pneumonia. They can be expected individually and in combination. It is important to note a signal in respect of pneumonia which occurred more frequently in the Elebrato treatment arm of the main study than in the comparator arm. The significance of this, if any, is uncertain as both arms contained an inhaled corticosteroid and it is unknown if there are differences within the class for ICS propensity to cause pneumonia.

3.5. Uncertainties and limitations about unfavourable effects

For this application the uncertainties about unfavourable effects are limited as the active components of this FDC are well known when administered on an individual basis or in some fixed combinations. It is highly unlikely that bringing them together in a single administration device will cause a change in their safety profiles.

However, a change in the classification of some adverse events which occurred during the clinical trials was reported by the applicant at the late stage of assessment. This raised an uncertainty around the incidence of such adverse event reports from the affected clinical trials. The ultimate clinical significance was however considered minimal by CHMP. The applicant is however reminded that accurate document version control is an imperative in ensuring the integrity of data collected in clinical trials.

Table 30 Effects Table for TRELEGY ELLIPTA AND ELEBRATO ELLIPTA, COPD patients

Effect	Short Description	Unit	FF/UMEC/VI	Symbicort®	Uncertainties/ Strength of evidence	References
Favourable Effects						
Trough FEV1	Change from baseline in Trough FEV1 at Week 24	L	0.142 (0.126; 0.158)	-0.029 (-0.046; -0.013)	Adjusted Mean 0.171 (95% CI 0.148; 0.194), p-value < 0.001	Study CTT116853considered to be a meaningful benefit for this COPD group D
SGRQ	Change from baseline in SGRQ Total Score at Week 24	L	-6.6 (-7.4; -5.7)	-4.3 (-5.2; -3.4)	Adjusted mean difference (95% CI) -2.2 (-3.5; -1.0), p-value < 0.001	
COPD exacerbation rate	Annual rate of moderate/severe COPD exacerbations, week 24		0.22	0.34	Adjusted mean difference (95% CI) 0.65 (0.49; 0.86), p-value = 0.002	Study CTT116853, was not powered for COPD exacerbation rate
	Annual rate of moderate/severe COPD exacerbations, week 24		0.20	0.36	Adjusted mean difference (95% CI) 0.56 (0.37; 0.85), p-value = 0.006	
Unfavourable Effects						
Pneumonia		n (%)	20 (2%)	7 (<1%)	ICS-containing treatments are known to increase the risk of pneumonia in COPD patients.	Study CTT116853

MACE		n (%)	4 (0.4%)	7 (0.8%)	There is no evidence of an additive effect when UMEC and VI are administered together.	
Class effects of ICS/LABA/ LAMA	Muscle spasms, dry mouth, oral candidiasis, dysphonia, headache, oropharyngeal pain, sinus tachycardia	Event rate			Treatment adverse events ranged from 38.9% to 37.7% across treatment arms and were of similar natures. No particular pattern or concern emerges with respect to FF/UMEC/VI	

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

In the pivotal clinical study the applicant demonstrates advantages for fixed triple inhalational therapy over dual therapy. The variables concerned are; lung function, frequency of exacerbations, and patient quality of life all may be considered valuable to patients and health care providers and to be quite long lasting – months rather than weeks or days. Overall, the results represent current opinion/knowledge about the management of COPD. Compelling results were demonstrated compared to the comparator arm dual therapy. A caveat is that the results for the candidate treatment might be unduly flattering since the comparator arm (dual treatment) were undertreated for their degree of severity of COPD (mostly GOLD D) and might have benefited from additional treatment.

In contrast to the benefits, the risks are infrequent or less frequent may be reversible with cessation or moderation of treatment and are well understood for each component on an individual basis.

3.6.2. Balance of benefits and risks

Overall, the benefit-risk balance is considered to be positive in the population with moderate to severe chronic obstructive pulmonary disease (COPD). In addition, there is lack of evidence to claim a step-up indication from LAMA+LABA due to the absence of LAMA+LABA as a comparator in the Phase III study. Elebrato should be used as maintenance treatment in adult patients with moderate to severe COPD and who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist.

3.7. Conclusions

The overall B/R of Elebrato is positive for maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Elebrato Ellipta is favourable in the following indication:

Elebrato Ellipta is indicated as a maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD) who are not adequately treated by a combination of an inhaled corticosteroid and a long-acting β2-agonist (for effects on symptom control see section 5.1).

The CHMP 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.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.