20 September 2018
EMA/630775/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure No. EMEA/H/C/WS1369

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Elebrato Ellipta	fluticasone furoate / umeclidinium / vilanterol	EMEA/H/C/004781/WS1369/0001
Trelegy Ellipta	fluticasone furoate / umeclidinium / vilanterol	EMEA/H/C/004363/WS1369/0001

Worksharing applicant (WSA): GlaxoSmithKline Trading Services Limited

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

List of abbreviations

* This is a general list of abbreviations. Not all abbreviations will be used.

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
EU	European Union
EXACT-RS	Exacerbations of Chronic Pulmonary Disease Tool – Respiratory Symptoms
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)
kg	kilogram
LABA	long-acting $beta_2$ receptor agonist
LAMA	long-acting muscarinic receptor antagonist
LRTI	lower respiratory tract infection
LS	least square
MAA	Marketing Authorisation Application
MACE	Major Adverse Cardiac Event
mcg	milligram
MCID	minimum clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction

mMRC	modified Medical Research Council
NDA	New Drug Application
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
SAWP	Scientific Advice Working Party
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
SmPC	Summary of Product Characteristics
SMQs	Standardised MedDRA Queries
SS	Serial Spirometry (Population)
TDI	Transitional Dyspnoea Index
TDI-SAC	Transitional Dysponea Index-self administered computerised version
TIO	tiotropium
UK	United Kingdom
UMEC	umeclidinium bromide
URTI	upper respiratory tract infection
US	United States
VI	vilanterol
WM	weighted mean

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Trading Services Limited submitted to the European Medicines Agency on 13 February 2018 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extention of indication to modify the therapeutic indication for Elebrato Ellipta and Trelegy Ellipta into "maintenance treatment in adult patients with moderate to severe chronic obstructive pulmonary disease (COPD)".
As a consequence, the indication section (4.1), Undesirable effects section (4.8) and Pharmacodynamic Properties section (5.1), Pharmacokinetic properties section (5.2), Preclinical Safety data section (5.3) of the EU SmPC are updated. This is based on the result of study CTT116855 and study 200812 and the population PK report 208059.

The Package Leaflet is updated in accordance.

Additionally, an updated RMP (version 2.0) has also been submitted to introduce minor changes and bring it in line with the new template (rev.2).

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/0001/2015 on the granting of a class waiver.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed (Co-)Rapporteurs for the WS procedure:

Peter Kiely

Harald Enzmann

Timetable	Actual dates
Submission date	13 February 2018
Start of procedure:	3 March 2018
CHMP Rapporteur Assessment Report	2 May 2018
CHMP Co-Rapporteur Assessment Report	28 April 2018
PRAC Rapporteur Assessment Report	3 May 2018
PRAC members comments	7 May 2018
PRAC Outcome	17 May 2018
CHMP members comments	22 May 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	25 May 2018
Request for supplementary information (RSI)	31 May 2018
CHMP Rapporteur Assessment Report	21 August 2018
PRAC Rapporteur Assessment Report	24 August 2018
PRAC members comments	12 September 2018
Updated PRAC Rapporteur Assessment Report	6 September 2018
PRAC Outcome	6 September 2018
CHMP members comments	10,11 September 2018
Updated CHMP Rapporteur Assessment Report	14 September 2018
Opinion	20 September 2018

2. Scientific discussion

2.1. Introduction

FF/UMEC/VI (Trelegy Ellipta, Elebrato Ellipta) once-daily was approved in the European Union (EU) on 15 November 2017 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 ICS and LABA. FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, UMEC is a long acting muscarinic antagonist (LAMA) and VI is a selective long-acting, beta2-adrenergic agonist (LABA).

2.2. Rationale for the proposed change

The purpose of this variation application is to update the license for Trelegy Ellipta and Elebrato Ellipta to provide information relating to the comparison of FF/UMEC/VI with FF/VI and UMEC/VI, the comparison of FF/UMEC/VI with the open combination of FF/VI + UMEC, and the pharmacokinetics (PK) of FF, UMEC, and VI following inhalation of FF/UMEC/VI in patients with COPD. Specific revisions to the SmPC are proposed for Section 4.1 Therapeutic indications, Section 4.8 Undesirable effects, Section 5.1 Pharmacodynamic properties (Clinical Efficacy), and Section 5.2 Pharmacokinetic properties.

FF/UMEC/VI (Trelegy Ellipta, Elebrato Ellipta) once-daily is approved in the European Union (EU) 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 ICS and LABA.

The company is submitting a revised indication wording with changes strikethrough as follows*:*

Trelegy 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 revisions are primarily based on data from Study CTT116855 (IMPACT) that compared FF/UMEC/VI with FF/VI and UMEC/VI over 52 weeks in subjects with COPD using a primary endpoint of the annual rate of on-treatment moderate/severe exacerbations. Additional revisions are based on data from Study 200812 evaluating the non-inferiority FF/UMEC/VI compared with UMEC + FF/VI over 24 weeks in subjects with COPD and data from a population PK analysis (Study 208059) of FF, UMEC, and VI when administered from a single inhaler as FF/UMEC/VI or from separate inhalers as UMEC + FF/VI in subjects with COPD.

Changes have been proposed in the SmPC for sections 4.1, 5.1 & 5.2 & 5.3, with an updated AE table in section 4.8. The PL is amended accordingly.

2.3. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

However, the current wording in sections of the EU Summary of Product Characteristics (SPC) associated with nonclinical study data contains exposure multiples calculated using data from population PK analyses for FF/UMEC/VI conducted for a subset of 74 COPD subjects from study CTT116853.

Population PK analyses have been updated using a combined dataset from 821 COPD subjects administered FF/UMEC/VI in combination from studies 200812, CTT116853 and CTT116855 (see population PK report). Using exposure values from this larger data set has added robustness to the exposure multiples calculated for each active component when comparing with animal systemic exposure data. It is proposed to revise the nonclinical related exposure multiples in the SPC accordingly, thus aligning with other references to the 3-study combined population PK analysis-derived values in the current submission.

This was reviewed and agreed upon. Therefore the section 5.3 is updated to include the updated genotoxicity, carcinogenicity and reproductive toxicity figures.

2.3.1. Ecotoxicity / environmental risk assessment

An updated tailored Phase II Tier A environmental risk assessment was provided for the active ingredient fluticasone furoate (FF). For the active ingredients umeclidinium (UMEC) and vilanterol (VI) an update of the Phase I environmental risk assessments was not necessary.

Environmental Risk Assessments (ERAs) for all three ingredients have been previously undertaken in monotherapy and different combinations undertaken which have all been reviewed and approved in the EU via the Centralised Procedures.

The risk characterization has been updated by new sales data (total sales of FF in all medical products in the EU (IMS 2016: 74 kg) and 5 years forecast in EU).

PECsw–refined based on manufacturing forecast of all GSK registered products for the 5th year of sales in the EU is 0.0011 µg/L or 1.1 ng/L.

Table 1: PECgroundwater-refined = 0.25 x PECsw-refined = 0.00027 ng/L.

Matrix	*PEC [µg/L]*	*Species*	*NOEC [µg/L]*	*AF*	*PNEC [µg/L]*	*PEC/PNEC*	*Result*
Surface water-refined	0.0011	Fish	0.29	10	0.029	0.038	No risk
Groundwater-refined	0.000275	Daphnia	12	10	1.2	0.00023	No risk

Table 2: Summary of main study results

Substance (INN/Invented Name): Fluticasone furoate (GW685698)					
CAS-number (if available): 397864-44-7					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD117	2.61			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	2.61			not B
Persistence	OECD 304 A	DT50 > 137 d (12°C)			P
Toxicity	NOEC	0.29 µg/L			T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined on 5 years sales forecast for EU	0.0011	µg/L			> 0.01 threshold (N)
Other concerns (e.g. chemical class)	Fluticasone furoate is a glucocorticoid and, as such, is considered a potential endocrine disruptor and therefore the potential endocrine activity of this compound was investigated in an appropriate chronic test system with relevant endpoints				(Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Koc = 3,800 to 16,000mL/g (mean of 4 soils and 1 sediment: 9,600mL/g) Koc_{des} = 5,400 to 22,000mL/g (mean of 4 soils and 1 sediment: 13,000mL/g)			Report provided
Inherent Biodegradability Test	OECD 302 C	Not inherently biodegradable			Report provided
Inherent biodegradability in Soil	OECD 304 A	DT50 > 64d 3% mineralization in 64d			Reliable Report provided FF considered as P
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Acute toxicity to *Daphnia magna*	OECD 202	NOEC	4.2 (unfiltered 48h) 0.012 (filtered 48h)	mg/L	Report provided Not valid and not relevant for this ERA.
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	0.29	µg/L	Report provided
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	1000	mg/L	Report provided
Phase IIb Studies					
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	1000	mg/kg	Eisenia fetida LC_{50} (14 days) = 1,000 mg/kg Report

					provided

2.3.2. Discussion on non-clinical aspects

The outcome of the updated refined risk characterisation shows that fluticasone furoate is unlikely to present a relevant risk to organisms in the aquatic environment and in groundwater when fluticasone furoate will reach surface waters via wastewater by the use of the maximum recommended dose.

Therefore, further testing in the aquatic compartment will not be necessary and it can be concluded that the drug substance and/or its metabolites are unlikely to represent a risk to the aquatic environment.

2.3.3. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of fluticasone furoate, umeclidinium (UMEC) and vilanterol. In addition, updated figures are also inserted in section 5.3 of the Product Information for each monocomponent based on the population PK analyses submitted in the present application.

2.4. Clinical aspects

2.4.1. Introduction

The MAH is submitting this application to update the marketing authorisation for both Trelegy and Elebrato, based on the results of study CTT116855 and study 200812 and the population PK report 208059.

Study CTT116855 was a randomised, double-blind, parallel-group study that compared the efficacy and safety of FF/UMEC/VI with FF/VI and UMEC/VI for 52 weeks in subjects with COPD. This study was designed to evaluate the benefit of FF/UMEC/VI over the FF/VI and UMEC/VI dual component medications in subjects with advanced, symptomatic COPD and at risk of exacerbation using a primary endpoint of the annual rate of on-treatment moderate/severe COPD exacerbations.

Study 200812 was a randomised, double blind, parallel group study comparing FF/UMEC/VI administered in one Ellipta inhaler with FF/VI + UMEC administered in separate Ellipta inhalers over 24 weeks in subjects with COPD. This study was designed to demonstrate the non-inferiority of FF/UMEC/VI to FF/VI+UMEC using a primary endpoint of trough FEV1 at Week 24 with a margin of non-inferiority of 50 mL.

The population PK analysis (Study 208059) evaluated combined data from a subset of COPD patients that participated in 3 phase IIIa/b studies (CTT116855, CTT116853, 200812) to characterise the PK of FF, UMEC and VI following administration of FF/UMEC/VI or from separate inhalers as UMEC + FF/VI or as dual FF/VI or UMEC/VI from an Ellipta inhaler and to assess the effect of covariates on the PK of FF, UMEC and VI.

GCP

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

The MAH 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.

2.4.2. Pharmacokinetics

Pharmacokinetic interaction studies

The report of a population PK analysis (Study 208059) of FF, UMEC, and VI when administered from a single inhaler as FF/UMEC/VI or from separate inhalers as UMEC + FF/VI or as dual FF/VI or UMEC/VI in subjects with COPD is presented.

The primary objectives of the analyses were:

- to characterize the population PK of FF, UMEC and VI in adults with COPD following administration of FF/UMEC/VI in an ELLIPTA inhaler and following administration of FF/VI+UMEC, FF/VI, UMEC/VI.
- to identify influential covariates, among age, race, gender, weight, body mass index, smoking status, concurrent medications (cytochrome P450 inducers/inhibitors, Pgp inhibitors), lung function status in terms of reversibility post albuterol/salbutamol, percent predicted FEV1 at screening (PPFEV1) and creatinine clearance on the PK of FF, UMEC and VI in patients with COPD.

The primary endpoints of the analyses were:

- Non-linear mixed effects model (NONMEM) generated post-hoc estimates for FF, UMEC and VI population PK parameters and associated inter-subject variability and residual error: (Apparent clearance [CL/F], apparent volume of distribution (V/F), absorption rate constant [Ka]).
- Derived PK parameters: Area under the curve at steady state (AUC(ss)) and Cmax.

Methods

FF, UMEC and VI plasma concentration – time data were used for population PK analyses using non-linear mixed effects modelling with NONMEM v7.4. A model-based estimation approach was undertaken whereby the plasma data for FF, UMEC and VI from Studies 200812, CTT116853 and CTT116855 were combined. The previously reported population PK models for FF, UMEC and VI served as starting points for the structural model development (adequacy was assessed using Monte Carlo simulations). The data below the limit of quantification (BLQ) were treated as censored data and all data were analysed with the full likelihood approach (M3 method). Covariate analysis was undertaken once the base structural model had been developed. The adequacies of the population PK models were assessed through diagnostic plots and visual predictive checks. The post-hoc individual parameter estimates from each model for FF, UMEC and VI were utilized to estimate individual systemic exposure measures. The geometric mean and the associated 95% confidence intervals (CIs) for AUCss and Cmax at steady state were summarized for each analyte by study, treatment, geographic race and region.

Results

Analysis Population: A total of 821 subjects from 3 studies contributed to population PK analysis. Demographic and baseline characteristics of subjects were similar across each of the 3 population PK datasets (FF, UMEC and VI).

The PK of FF in 200812, CTT116853 and CTT116855 was well-described by a two-compartment model with first-order absorption and first-order elimination. The only covariates found to be statistically

significant were Japanese heritage and FF/VI treatment on inhaled clearance (CL/F) but no dose adjustment was warranted based on the predicted systemic exposure.

The PK of UMEC in 200812, CTT116853 and CTT116855 was well-described by a two-compartment model with first-order absorption and first-order elimination. Weight, age and smoking status were found to be significant covariates on CL/F and weight was also a significant covariate on the apparent volume of distribution of the central compartment (V2/F). However, no dose adjustment was warranted for these covariates based on the predicted systemic exposure.

The PK of VI in 200812, CTT116853 and CTT116855 was well-described by a two-compartment model with first-order absorption and first-order elimination. Weight and smoking status were found to be significant covariates on CL/F and V2/F, respectively. However, no dose adjustment was warranted for these covariates based on the predicted systemic exposures.

The final parameter estimates for the three population PK models are presented in the Table below.

Table 3: Final Population PK Model Parameters

FF		UMEC		VI	
Parameter	**Estimate [95% CI]**	**Parameter**	**Estimate [95% CI]**	**Parameter**	**Estimate [95% CI]**
CL/F [L/h]	513 [493, 534]	CL/F [L/h]	149 [138, 160]	CL/F [L/h]	73.5 [69.7, 77.3]
V2/F [L]	1.36 FIXED	V2/F [L]	1100 [1030, 1170]	V2/F [L]	352 [333, 371]
Q/F [L/h]	268 FIXED	Q/F [L/h]	854 FIXED	Q/F [L/h]	242 [230, 254]
V3/F [L]	111 FIXED	V3/F [L]	16200 FIXED	V3/F [L]	2250 [1670, 2830]
KA [h^{-1}]	0.0821 [0.0805, 0.0837]	KA [h^{-1}]	18.6 [16.2, 21.0]	KA [h^{-1}]	19.6 FIXED
Japanese heritage on CL/F	0.647 [0.628, 0.666]	Weight exponent on CL/F	0.580 [0.409, 0.751]	Weight exponent on CL/F	0.444 [0.281, 0.607]
FF/VI on CL/F	1.42 [1.38, 1.46]	Age exponent on CL/F	-0.648 [-0.979, -0.317]	Smoking effect on V2/F	1.46 [1.34, 1.59]
		Smoking effect on CL/F	1.28 [1.13, 1.45]		
		Weight exponent on V2/F	0.797 [0.614, 0.980]		

2.4.3. Discussion on clinical pharmacology

The report of a population PK analysis (Study 208059) of FF, UMEC, and VI when administered from a single inhaler as FF/UMEC/VI or from separate inhalers as UMEC + FF/VI or as dual FF/VI or UMEC/VI in 821 subjects with COPD is submitted.

A total of 821 subjects from 3 studies provided samples for the population PK analysis. Data for few subjects (16/821= 2%), at one or both visits could not be utilized due to discrepancy between dosing time record and PK sample collection time record and were considered as protocol deviations. There were 714, 622, and 817 COPD subjects with that contributed to final FF, UMEC and VI population PK datasets respectively from the combined data from CTT116855, 200812 and CTT116853 studies. FF, UMEC, and VI datasets contained 2948, 2589 and 3331 plasma concentration-time observations respectively. Approximately, 13% to 41% samples were BLQ.

All FF, UMEC, VI plasma concentrations were well interspersed with historical data.

FF, UMEC and VI PK were all adequately described by a two-compartment model with first-order absorption.

For FF, Japanese heritage and FF/VI treatment were significant covariates on apparent inhaled clearance. For UMEC, weight, age and smoking status on apparent inhaled clearance and weight on apparent volume of distribution were significant covariates. For VI, weight on apparent inhaled clearance and smoking status on apparent volume of distribution were significant covariates.

For Japanese heritage COPD subjects, FF CL/F was estimated to be 35% lower, but the increase in FF systemic exposure in subjects of Japanese heritage versus non-Japanese heritage as these systemic exposures remain well below the threshold for FF-induced reduction of serum cortisol.

The typical value of FF CL/F was 513 L/h for subjects receiving FF/UMEC/VI (100/62.5/25 mcg). For FF/VI (100/25 mcg) administration, FF CL/F was estimated to be 42% higher. However, such values in subjects receiving FF/VI versus FF/UMEC/VI is not likely to be clinically relevant as these systemic exposures remain well below the threshold for FF-induced reduction of serum cortisol.

In a similar manner, no clinically relevant change in UMEC or VI systemic exposure was estimated after accounting for the effect of the influential covariates namely age, weight and smoking status.

In summary, population PK analyses (similar to historical) demonstrated that the effects of these covariates on PK were marginal and no dose adjustment was deemed necessary for FF, UMEC or VI based on these covariates.

Steady state AUCss (geometric mean, pg*h/mL) and Cmax,ss (geometric mean, pg/mL) for FF/UMEC/VI were consistent with historical data for FF/VI and UMEC/VI and there was no clinically relevant difference in FF, UMEC or VI systemic exposure when administered as FF/UMEC/VI or UMEC+FF/VI.

2.4.4. Conclusions on clinical pharmacology

Population PK analyses for FF/UMEC/VI using combined data from Studies CTT116855, 200812 and CTT116853 were consistent with those for the components when given in dual combination. The models described adequately the PK of FF, UMEC and VI in patients with COPD. No dose adjustments are warranted based on age, weight, smoking status or race.

In conclusion, the results of the Population PK analysis are adequately reflected in the section 5.2 of the SmPC, including also an update to the elderly section.

2.5. Clinical efficacy

Two efficacy studies have been submitted in this variation. The MAH request for changes to the indication is based on study CTT116855 and on Study 200812 as supporting efficacy data.

The methods/design/populations will be presented separately for each study hereafter. However for the results analyses will be presented together.

Main study - Study CTT116855

Methods

Objective(s)

The primary objective of Study CTT116855 was to evaluate the efficacy of FF/UMEC/VI to reduce the annual rate of moderate/severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in subjects with COPD.

The primary objective of Study 200812 was to compare the effect of FF/UMEC/VI with FF/VI+UMEC on lung function after 24 weeks of treatment.

Study design

CTT116855 study was a randomised, double-blind, parallel-group study that compared the efficacy and safety of FF/UMEC/VI with FF/VI and UMEC/VI for 52 weeks in subjects with COPD. This study was designed to evaluate the benefit of FF/UMEC/VI over the FF/VI and UMEC/VI dual component medications in subjects with advanced, symptomatic COPD and at risk of exacerbation using a primary endpoint of the annual rate of on-treatment moderate/severe COPD exacerbations.

At total of 10,355 subjects were randomized in the Intent-to-Treat (ITT) Population at study centres in 37 countries. The total duration of subject participation was approximately 55 weeks, consisting of a 2-week Run-in Period, 52-week Treatment Period, and a 1-week Safety Follow-up Period. Clinic visits occurred at pre-screening/screening, Randomization (Day 1), and after 4, 16, 28, 40, and 52 weeks of treatment. In addition, there was a safety follow-up telephone contact or clinic visit conducted one week after completing the last study visit.

Eligible subjects were randomized (2:2:1) to the FF/UMEC/VI, FF/VI, and UMEC/VI treatment groups.

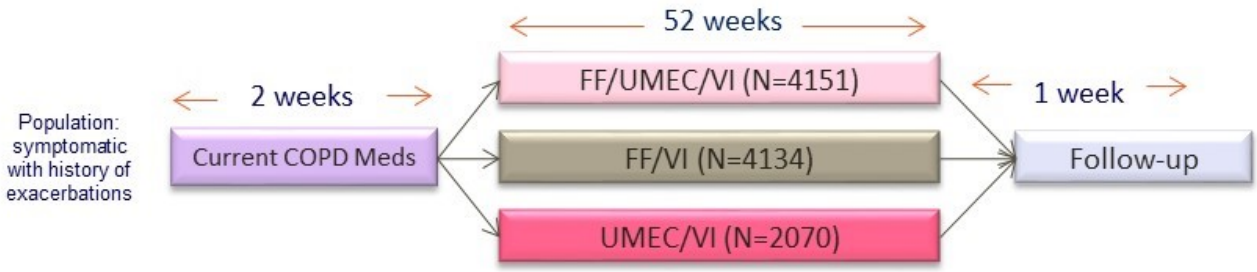


Figure 1: Study Schematic

Discussion of Study Design

Use of the FF/VI and UMEC/VI active comparator groups is consistent with the CHMP Note for Guidance on Fixed Dose Combination Medicinal Products which suggest studies be conducted preferably against the component medications [EMA/CHMP/158268/2017]. Moreover, use of these active comparators extends the previous development work that supported the approval of Trelegy Ellipta/Elebrato Ellipta by using partial factorial analysis to demonstrate the contribution of both the UMEC and FF components of Trelegy Ellipta/Elebrato Ellipta based on comparisons of FF/UMEC/VI with the FF/VI and UMEC/VI dual components, respectively. This approach was done in agreement with Scientific Advice from CHMP (EMEA/H/SA/2498/1/2012/II and EMEA/H/SA/2498/1/FU/1/2013/II).

Study population

The enrolment criteria for Study CTT116855 were consistent with those from Study CTT116853 which supported the initial MAA application. As Study CTT116855 was designed to assess benefit on exacerbations, patients with advanced, symptomatic COPD and at risk of an exacerbation were enrolled. Additionally, CTT116855 was intentionally designed to be as inclusive as possible with regards to the enrolment of subjects with significant CV disease. For example, subjects with a past history of previous myocardial infarction (MI) (>6 months prior to Screening) and New York Heart Association Class 1–3 heart failure were eligible for inclusion in the study. In addition, patients with first degree heart block, second degree heart block Mobitz Type 1, and corrected QT interval using Friedicia's formula (QTc[F]) measurements up to 530 msec in patients with a QRS >120 msec could be enrolled.

Basic inclusion criteria were: male or female subjects, 40-years of age or older with a diagnosis of COPD, a history of cigarette smoking of ≥10 pack-years, a post-albuterol FEV1/forced vital capacity (FEV1/FVC) ratio of <0.70, with symptomatic COPD based on a score of ≥10 on the CAT. Requirements for severity of airflow obstruction and exacerbation history requirements were either:

- a post-bronchodilator FEV1 < 50% predicted normal and a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months or,
- a post-bronchodilator 50% ≤ FEV1 < 80% predicted normal and a documented history of ≥ 2 moderate COPD exacerbations or a documented history of ≥ 1 severe COPD exacerbation (hospitalized) in the previous 12 months.

Additionally, consistent with CHMP follow-up advice on the study design, subjects must have been receiving daily maintenance treatment for their COPD for at least 3 months prior to screening.

Subjects who had a current diagnosis of asthma, COPD caused by α1-antitrypsin deficiency, other significant respiratory disorders (e.g., active tuberculosis, lung cancer, pulmonary hypertension), lung resection within the previous 12 months, or other clinically significant diseases in the opinion of the investigator, were excluded from the study.

Treatments

Investigational Products and Reference Therapy

Table 4: Study Treatments Supplied for Study CTT116855

Study Treatment	Formulation	Strength	Batch Numbers
FF/UMEC/VI	First strip: FF blended with lactose Second strip: UMEC and VI blended with lactose and magnesium stearate	100 mcg per blister 62.5 mcg and 25 mcg per blister, respectively	R654258, R654259, R682331, R682332, R706369, R706455, R737215, R737216, R750268, and R761665

FF/VI	First strip: FF blended with lactose Second strip: VI blended with lactose and magnesium stearate	100 mcg per blister 25 mcg per blister	R643600, R660895, R660896, R677960, R677977, R692155, R708434, R708435, R744923, R744928, R763259, and R775856
UMEC/VI	First strip: UMEC blended with lactose and magnesium stearate Second strip: VI blended with lactose and magnesium stearate	62.5 mcg per blister 25 mcg per blister	R602192, R661669, R693417, R701920, and R733950

Salbutamol (rescue medication) via a metered-dose inhaler (MDI) with a spacer was issued for reversibility testing at Screening. Salbutamol MDI or NEBULES were provided to the subjects at Screening for as-needed use throughout the study.

Outcomes / endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was the annual rate of moderate/severe exacerbations on patients treated with FF/UMEC/VI compared with both FF/VI and UMEC/VI.

The rate of moderate/severe COPD exacerbations is an established clinically relevant endpoint based on known associations with disease morbidity and mortality. Exacerbations of moderate severity were defined as those requiring treatment with oral/systemic corticosteroids and/or antibiotics while severe exacerbations were defined as those requiring in-patient hospitalisation or resulted in death. Mild exacerbations were defined as those self-managed by the subjects and were not associated with the use of corticosteroids or antibiotics or hospitalisation.

Secondary Efficacy Endpoints

The secondary efficacy endpoints included:

- Change from Baseline trough FEV1 at Week 52 comparing FF/UMEC/VI with FF/VI
- Change from Baseline SGRQ Total Score at Week 52 comparing FF/UMEC/VI with FF/VI
- Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI
- Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count $\geqslant$150 cells/µL
- Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of subjects with a blood eosinophil count $\geqslant$150 cells/µL
- Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

To further investigate the potential for blood eosinophil levels to predict the exacerbation response to an ICS in COPD, the annual rate of on-treatment moderate/severe exacerbations and the time to first on-

treatment moderate/severe exacerbation in the subset of subjects with a blood eosinophil count ≥ 150 cells/µl for the comparison of FF/UMEC/VI with UMEC/VI (evaluating the effect of FF) were defined as secondary endpoints.

Trough FEV1 at Week 52 was chosen as a secondary endpoint for evaluation of lung function as it is a robust, well established and objective means of demonstrating bronchodilator efficacy and duration of effect. Additional assessments of trough FEV1 were obtained throughout the trial to evaluate response over time.

The SGRQ was selected as a widely-accepted measure to evaluate change in disease-specific HRQoL. Subjects completed the SGRQ for COPD (SGRQ-C), a COPD-specific version of the SGRQ designed to measure the impact of the disease on their HRQoL. The primary analysis of SGRQ Total score was at Week 52 (secondary endpoint). The minimum clinically important difference (MCID) for this instrument of a 4-unit reduction in SGRQ Total Score from baseline was used for the responder analysis. The CAT was used to measure COPD-specific health status with the MCID of a >2-unit improvement (decrease in score) from baseline used for the responder analysis. Symptom assessments, all defined as 'other' endpoints included the TDI using the 1 unit TDI score as the accepted MCID for responder analysis and diary assessments of rescue medication use and night-time awakenings. An additional efficacy endpoint of note was all-cause mortality. Inclusion of this endpoint was considered appropriate for evaluation based on the COPD severity of the patient population under study, the association of exacerbations with mortality, and the large sample size and duration of the study. While all-cause mortality was categorized as an efficacy endpoint to assess potential benefit, this endpoint may also be used as a safety endpoint.

Safety Assessments for Study CTT116855

In consideration of the classes of medications studied and the co-morbidities associated with COPD, this study was also designed to provide a full assessment of safety by evaluating adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), in particular CV events and pneumonia, CV effects (ECGs, including evaluation of QTc(F), and vital signs), and clinical laboratory tests. All deaths and non-fatal serious adverse event reports were adjudicated by an independent Clinical Endpoint Committee (CEC) and a pre-specified Major Adverse Cardiac Event (MACE) analysis was conducted.

Safety endpoints included:

- Incidence of AEs
- Adjudicated Serious Adverse Reports
- Incidence of pneumonia.
- Incidence of CV events (including MACE and CV AEs of special interest [AESI] group)
- Events in the pneumonia AESI group and moderate/severe exacerbations composite
- Events in the pneumonia AESI group leading to hospitalisation or prolonged hospitalisation or death and severe exacerbations
- Time to first event in the pneumonia AESI group resulting in hospitalisation or prolonged hospitalisation or death, severe exacerbation and event in the CV AESI group resulting in hospitalisation or prolonged hospitalisation or death
- ECG measurements
- Vital signs

- Haematological and clinical chemistry parameters
- Oropharyngeal examinations (abnormalities reported as part of the AEs)
- Incidence of bone fractures

Statistical Methods/Sample size

In study CTT116855, sample size calculations were based on the primary endpoint, the annual rate of on treatment moderate/severe exacerbations for the co-primary treatment comparisons of FF/UMEC/VI with FF/VI and with UMEC/VI. A total of 10,000 subjects were needed to provide 90% power to detect a reduction in the annual rate of moderate and severe exacerbations in the FF/UMEC/VI arm compared with the UMEC/VI arm (assuming a true 15% reduction) and a reduction compared with the FF/VI arm (assuming a true 12% reduction). Calculations were based on a negative binomial regression model and used a two-sided 1% significance level.

For the analysis, the overall type I error was controlled at $\alpha=0.05$. Multiplicity across the co-primary treatment comparisons was accounted for by using the truncated Hochberg procedure with a truncation parameter of $\gamma=0.6$.

Additionally, multiplicity was controlled across the key secondary endpoints/treatment comparisons using a hierarchical, closed testing procedure. The secondary hypothesis tests were grouped sequentially in two blocks of two comparisons each (lung function and symptoms, and time to first exacerbation event). Each block of comparisons was also adjusted for multiplicity using the truncated Hochberg method as described for the primary endpoint analysis with a truncation parameter of $\gamma=0.6$ for the first block and a truncation parameter of $\gamma=1$ for the second block.

The primary analysis of the number of moderate/severe COPD exacerbations was performed using a generalized linear model assuming the negative binomial distribution. The primary analysis used data for the ITT population collected while subjects were on study treatment. The model included terms for treatment group, gender, exacerbation history ($\leq$ 1, $\geq$ 2 moderate/severe), smoking status at Screening, baseline disease severity (as post-bronchodilator % predicted FEV1) and geographical region, with the logarithm of time on treatment as an offset variable. A sensitivity analysis was performed where all available data collected until the time of study withdrawal was used. For this sensitivity analysis, the total number of events and the total time in the study (both on-treatment and off-treatment) prior to study withdrawal were used in the analysis model. Further, several additional sensitivity analyses were performed to evaluate the impact of missing data on the primary analysis of the primary endpoint.

The secondary endpoints of trough (pre-dose in morning) FEV1 and SGRQ Total score were analysed using mixed model repeated measures (MMRM) with covariates of treatment group, smoking status at Screening, baseline, geographical region, and visit, plus interaction terms for visit by baseline and visit by treatment group. The proportion of responders according to SGRQ Total Score was analysed using a generalized linear mixed model with a logit link function, including terms for treatment group, smoking status (Screening), geographical region, visit, baseline SGRQ Total Score and baseline by visit and treatment group by visit interactions.

The analysis of the secondary endpoint of time to first moderate/severe exacerbation used Cox's proportional hazards model, adjusting for treatment group, gender, exacerbation history ($\leq$ 1, $\geq$ 2

moderate/severe), smoking status at Screening, baseline disease severity (as % post-bronchodilator predicted FEV1) and geographical region.

The secondary endpoint of annual rate of severe exacerbations was analysed in the same way as the primary endpoint.

Rescue use (mean number of occasions per day and percentage of rescue-free days) and mean number of night-time awakenings per night were analysed in a similar way to trough FEV1.

Populations Analysed

A total of 10,367 subjects were randomised to receive blinded study treatment. Of these, 12 subjects were randomised in error and recorded as screen failures, leaving 10,355 subjects included in the ITT Population. Subjects were randomised using a 2:2:1 ratio to the FF/UMEC/VI (N=4151), FF/VI (N=4134), and UMEC/VI (N=2070) groups, respectively.

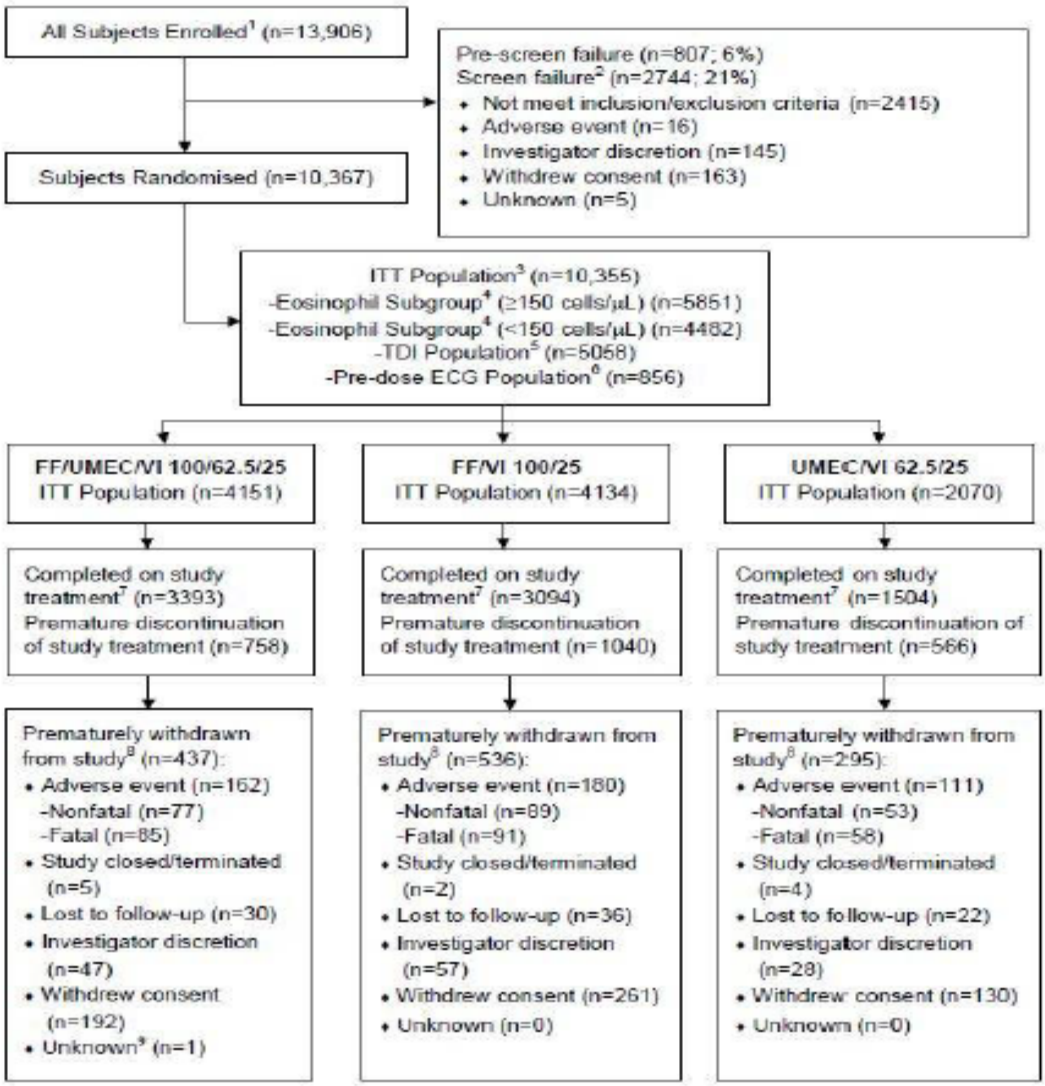


Figure 2: Subject Disposition (Study CTT116855)

1. All subjects who signed informed consent and for whom a record exists on the study database.
2. Percentage was based on the number of subjects who attended the Screening Visit.

3. All randomised subjects, excluding those randomised in error that did not receive study treatment.
4. ITT subjects who have a baseline eosinophil assessment.
5. ITT subjects who completed a BDI assessment on Day 1.
6. ITT subjects from sites included in the ECG substudy that have a pre-dose ECG assessment at Week 4.
7. A subject was considered to have completed treatment if they did not prematurely discontinue study treatment and attended the Week 52 visit.
8. A subject was considered to have completed the study if they had either attended the Week 52 visit or had a phone contact at Week 52. Subjects could have only one primary reason for study withdrawal. One subject randomised to FF/UMEC/VI completed the study but was reported as prematurely withdrawn in the eCRF in error. This subject is summarised as “Prematurely withdrawn,” primary reason: Investigator discretion.
9. One subject did not complete the study but reason for non-completion was not entered in the eCRF.

Table 5: Subject Populations (Study CTT116855, Randomised Subjects)

Population	Number of Subjects by Region, Country, Site	Number (%) of Subjects			
		FF/UMEC/VI 100/62.5/25	FF/VI 100/25	UMEC/VI 62.5/25	Total
Randomised, N	---	4155	4139	2073	10,367
ITT[1], N	RAP Table 1.07	4151	4134	2070	10,355
Pre-dose ECG[2, 3]	RAP Table 1.08	367 (9)	332 (8)	157 (8)	856 (8)
TDI3,4	RAP Table 1.09	2029 (49)	2014 (49)	1015 (49)	5058 (49)
Eosinophil subgroup[3] n		4143	4125	2065	10,333
<150 cells/µL		1844 (45)	1769 (43)	869 (42)	4482 (43)
≥150 cells/µL		2299 (55)	2356 (57)	1196 (58)	5851 (57)

Subject Disposition

A total of 13,906 subjects from 37 countries were enrolled (signed an ICF) in this study.

Of the subjects enrolled, 807 (6%) failed pre-screening and of those who attended the Screening Visit, 2744 (21%) failed screening (Table 5). Most of the screen failures were due to subjects not meeting the inclusion/exclusion criteria (2415 subjects [18%]). The most frequently failed inclusion criteria were history of exacerbations (753 subjects [27%]), severity of COPD disease (533 subjects [19%]), and CAT score at Screening (324 subjects [12%]). The most frequently failed exclusion criteria were unresolved pneumonia and/or moderate/severe COPD exacerbation (358 subjects [13%]), abnormal chest X-ray (133 subjects [5%]), and non-compliance (124 subjects [5%]). A subject could have only one primary reason as determined by the Investigator for screen failure, but more than one inclusion/exclusion criterion could have been selected.

A total of 10,367 subjects were randomised, but 12 were randomised in error (screen failures); thus, 10,355 subjects were included in the ITT Population. The largest subject participation was from the US (2406 subjects [23%]) followed by Germany (1187 subjects [11%]), Argentina (972 subjects [9%]), China (535 subjects [5%]), and Spain (499 subjects [5%]). The number of subjects included in the ITT Population per study site ranged from 1 to 52.

The majority of subjects completed study treatment (77%) and completed the study (88%). Of the 23% of subjects who were prematurely discontinued from study treatment, the most frequently reported reasons were AE (7%), decision by subject or proxy (7%), and lack of efficacy (6%). Of the 12% of subjects who were prematurely withdrawn from the study, the most frequently reported reasons were withdrawal of consent (6%) and AE (4%).

Overall, the percentage of subjects who prematurely discontinued study treatment was lower in the FF/UMEC/VI group (18%) than in the FF/VI (25%) and UMEC/VI (27%) groups. The percentage of subjects who prematurely discontinued study treatment due to AE or lack of efficacy was lower in the FF/UMEC/VI group (AE: 6%; lack of efficacy: 4%) than in the FF/VI (AE: 8%; lack of efficacy: 8%) and UMEC/VI (AE: 9%; lack of efficacy: 8%) groups. The time to premature discontinuation of study treatment is shown in Figure 4. The percentage of subjects who prematurely discontinued study

treatment was lower in the FF/UMEC/VI group than in the FF/VI or UMEC/VI groups through the course of the study.

Overall, the percentage of subjects who were prematurely withdrawn from the study was slightly lower in the FF/UMEC/VI group (11%) than in the FF/VI (13%) and UMEC/VI (14%) groups. The reasons for premature study withdrawal were similar across treatment groups. The percentage of subjects who prematurely withdrew from the study was slightly lower in the FF/UMEC/VI group than in the FF/VI or UMEC/VI groups through the course of the study.

Table 6 Subject Disposition (Study CTT116855, ITT Population)

Status	Number (%) of Subjects			
	FF/UMEC/VI 100/62.5/25 N=4151	FF/VI 100/25 N=4134	UMEC/VI 62.5/25 N=2070	Total N=10,355
Study Treatment Completion Status				
Completed [1]	3393 (82)	3094 (75)	1504 (73)	7991 (77)
Prematurely discontinued	758 (18)	1040 (25)	566 (27)	2364 (23)
Adverse event	249 (6)	325 (8)	186 (9)	760 (7)
Lack of efficacy	163 (4)	313 (8)	172 (8)	648 (6)
Protocol deviation	32 (<1)	41 (<1)	19 (<1)	92 (<1)
Noncompliance with study treatment	22 (<1)	22 (<1)	12 (<1)	56 (<1)
Noncompliance with daily diary	11 (<1)	10 (<1)	6 (<1)	27 (<1)
Subject reached protocol defined stopping criteria	4 (<1)	1 (<1)	2 (<1)	7 (<1)
Liver chemistry	0	0	0	0
Pregnancy	0	0	0	0
QTc	4 (<1)	1 (<1)	2 (<1)	7 (<1)
Study closed/terminated	5 (<1)	2 (<1)	5 (<1)	12 (<1)
Lost to follow-up	21 (<1)	25 (<1)	14 (<1)	60 (<1)
Investigator discretion	33 (<1)	36 (<1)	15 (<1)	84 (<1)
Decision by subject or proxy	250 (6)	296 (7)	153 (7)	699 (7)
Subject relocated	31 (<1)	31 (<1)	20 (<1)	82 (<1)
Frequency of visits	8 (<1)	13 (<1)	6 (<1)	27 (<1)
Burden of procedures	51 (1)	49 (1)	38 (2)	138 (1)
Other	155 (4)	203 (5)	94 (5)	452 (4)
Unknown [2]	1 (<1)	1 (<1)	0	2 (<1)
Study Completion Status				
Completed [3]	3714 (89)	3598 (87)	1775 (86)	9087 (88)
Prematurely withdrawn	437 (11)	536 (13)	295 (14)	1268 (12)
Adverse event	162 (4)	180 (4)	111 (5)	453 (4)
Outcome non-fatal	77 (2)	89 (2)	53 (3)	219 (2)
Outcome fatal	85 (2)	91 (2)	58 (3)	234 (2)
Study closed/terminated	5 (<1)	2 (<1)	4 (<1)	11 (<1)
Lost to follow-up	30 (<1)	36 (<1)	22 (1)	88 (<1)
Investigator discretion	47 (1)	57 (1)	28 (1)	132 (1)
Withdrew consent	192 (5)	261 (6)	130 (6)	583 (6)
Subject relocated	20 (<1)	27 (<1)	14 (<1)	61 (<1)
Frequency of visits	9 (<1)	8 (<1)	6 (<1)	23 (<1)
Burden of procedures	44 (1)	64 (2)	30 (1)	138 (1)
Other	123 (3)	177 (4)	86 (4)	386 (4)
Unknown [4]	1 (<1)	0	0	1 (<1)

Demographic and Baseline Characteristics

Based on common enrolment criteria and overlap in participating countries, the populations in Studies CTT116855 and 200812 were similar with respect to demographics and key baseline characteristics of smoking status, smoking history, severity of impairment in airflow obstruction, reversibility status, exacerbation history and CAT score. Subjects enrolled in both studies were primarily White, the majority were male, and the average age was 65 to 66 years. Subjects were symptomatic based on a mean CAT score of 19 to 20, had severe airflow obstruction based on a mean percent predicted FEV1 of 41 to 45% and virtually all subjects experienced ≥1 moderate or severe exacerbation in the 12 months prior to screening.

Table 7 Demographic characteristics

	CTT116855			200812	
Demographic/Baseline Characteristic	**FF/UMEC/VI N=4151**	**FF/VI N=4134**	**UMEC/VI N=2070**	**FF/UMEC/VI N=527**	**FF/VI + UMEC N=528**
Gender: Male, n (%)	2766 (67)	2748 (66)	1356 (66)	391 (74)	394 (75)
Mean age, yr	65.3	65.3	65.2	66.7	65.9
Race: White[1], n (%)	3200 (77)	3179 (77)	1604 (77)	416 (79)	416 (79)
Mean BMI, kg/m	26.61	26.66	26.58	26.23	26.76
Current smoker, n (%)	1436 (35)	1423 (34)	728 (35)	209 (40)	192 (36)
Mean smoking pack-yrs	46.7	46.4	47.0	43.4	44.2
GOLD Grade, n (%)					
1 (≥80 % predicted FEV_1)	10 (<1)	8 (<1)	4 (<1)	0	1 (<1)
2 (≥50% to <80 % predicted FEV_1)	1535 (37)	1455 (35)	729 (35)	174 (34)	189 (37)
3 (≥30% to <50 % predicted FEV_1)	1934 (47)	2031 (49)	1017 (49)	251 (49)	253 (49)
4 (<30 % predicted FEV_1)	666 (16)	639 (15)	319 (15)	90 (17)	69 (13)
Mean % predicted FEV[2]	41.9	41.6	41.8	44.5	45.5
Reversible to salbutamol[3] n, (%)	734 (18)	810 (20)	366 (18)	73 (14)	74 (14)
Total Moderate or Severe exacerbations[4], n					
0	2 (<1)	5 (<1)	2 (<1)	0	0
1	1853 (45)	1907 (46)	931 (45)	236 (45)	227 (43)
≥2	2296 (55)	2222 (54)	1137 (55)	291 (55)	301 (57)
Mean CAT Score	20.1	20.1	20.2	19.6	20.1

Subjects were required to be on COPD maintenance therapy for at least 3 months prior to study entry and consistent with the severity of the study populations the majority of subjects were using various combinations of COPD maintenance therapies. In Study CTT116855, the most common COPD maintenance medications reported at entry were ICS + LABA + LAMA (34%), ICS + LABA (26%), LABA + LAMA (8%), and LAMA (7%). Similar results were obtained in Study 200812.

Supportive study - Study 200812

Study 200812 was a randomised, double blind, parallel group study comparing FF/UMEC/VI administered in one Ellipta inhaler with FF/VI + UMEC administered in separate Ellipta inhalers over 24 weeks in subjects with COPD. This study was designed to demonstrate the non-inferiority of FF/UMEC/VI to

FF/VI+UMEC using a primary endpoint of trough FEV1 at Week 24 with a margin of non-inferiority of 50 mL.

Eligible subjects were randomized (1:1) to FF/UMEC/VI and placebo or FF/VI and UMEC for 24 weeks (N=1055). The randomization was stratified by the number of long-acting bronchodilators received during the Run-in. The total duration of subject participation was approximately 27 weeks, consisting of a 2-week Run-in period, 24-week Treatment Period and a 1-week Safety Follow-up Period. Clinic visits occurred at Pre-screening/Screening, Randomization (Day1), and after 4, 12, and 24 weeks of treatment. In addition, there was a safety follow-up telephone contact or clinic visit conducted 1 week after completing the last study visit.

Study population

To maintain consistency across patient populations, the enrolment criteria were the same as those described for Study CTT116855. Additionally, consistent with Study CTT116855, subjects must have been receiving daily maintenance treatment for their COPD for at least 3 months prior to screening.

Table 8: Study Treatments Supplied for Study 200812

Study Treatment	Formulation	Strength	Batch Numbers
FF/UMEC/VI	First strip: FF blended with lactose Second strip: UMEC and VI blended with lactose and magnesium stearate	100 mcg per blister 62.5 mcg and 25 mcg per blister	R762708
Placebo (to match UMEC)	Lactose	N/A	R715717, R780908
FF/VI	First strip: FF blended with lactose Second strip: VI blended with lactose and magnesium stearate	100 mcg per blister 25 mcg per blister	R763258, R763259
UMEC	UMEC blended with lactose and magnesium stearate	62.5 mcg per blister	R760232

Salbutamol (rescue medication) via a metered-dose inhaler (MDI) with a spacer was issued for reversibility testing at Screening. Salbutamol MDI or NEBULES were provided to the subjects at Screening for as-needed use throughout the study.

Outcomes / endpoints

Efficacy endpoints in Study 200812 include:

Primary efficacy endpoint

- Change from baseline in trough FEV1 at Week 24.

Secondary efficacy endpoints

- Proportion of responders based on the SGRQ total score at Week 24.
- Change from baseline in SGRQ total score at Week 24.
- Proportion of responders based on TDI focal score at Week 24.

- TDI focal score at Week 24.
- Time to first moderate or severe COPD exacerbation.
- Mean change from baseline in trough FEV1 at the end of Period 1.
- Mean change from baseline in daily AM and PM PEF averaged over Period 1.
- Mean change from baseline in the percentage of symptom-free 24-hour periods during Period 1.
- Mean change from baseline in the percentage of rescue-free 24-hour periods during Period 1.
- Mean change from baseline in ACT score at the end of Period 1.
- Proportion of subjects with ACT score ≥ 20 at the end of Period 1.

The safety endpoints were similar to those in the pivotal trial,

- Incidence of AEs.
- Incidence of AESIs.
- ECG measurements.
- Vital signs.
- Haematological and clinical chemistry parameters.

Overall the choice of efficacy and safety endpoints were appropriate for the population and interventions.

Statistical Methods/Sample size

The treatment comparison of primary interest was to evaluate the non-inferiority of FF/UMEC/VI to FF/VI+UMEC for the primary efficacy endpoint of trough FEV1 at Week 24. No p values for treatment comparisons were reported as the primary objective of the study was to test the non-inferiority of FF/UMEC/VI to FF/VI+UMEC. No inference on non-inferiority or superiority was drawn for the secondary and other efficacy endpoints.

The planned sample size of 816 evaluable subjects provided 90% power to determine non inferiority of FF/UMEC/VI to FF/VI+UMEC based on change from baseline in of trough FEV1 at Week 24, when the margin of non-inferiority was 50 mL and the true mean treatment difference was assumed to be 0 mL. This used a one sided 2.5% significance level and an estimated residual standard deviation (SD) for change from baseline in trough FEV1 at Week 24 of 220 mL (based on MMRM analyses of previous Phase IIIa studies in COPD subjects).

It was estimated that approximately 20% of subjects who were randomized would either discontinue study treatment or be excluded from the Modified Per Protocol (mPP) Population at Week 24, therefore approximately 1020 subjects were required to be randomized. The mPP Population comprised all subjects in the ITT Population who did not have a full protocol deviation considered to impact efficacy. Any data following a moderate or severe COPD exacerbation or pneumonia were excluded from mPP analysis due to the potential impact of the exacerbation, pneumonia, or the medications used to treat these events, on the study findings. Subjects with partial protocol deviations considered to impact efficacy were included in the mPP Population but had their data excluded from analyses from the time of partial protocol deviation onwards.

The primary efficacy analyses used the mPP Population. The secondary and other efficacy, and safety summaries and analyses used the ITT Population.

The change from baseline in trough FEV1 at Week 24 was analysed using a MMRM analysis including trough FEV1 recorded at each of Week 4, Week 12, and Week 24. No imputation was made for any missing numerical data. Covariates included baseline FEV1, stratum (number of long acting bronchodilators used during the Run in period: 0/1 or 2), visit number, geographical region, treatment, visit-by-baseline interaction, and visit-by-treatment interaction. Least squares means and LS mean change from baseline values for each treatment group with associated standard error (SE) and 95% CIs were calculated. The estimated treatment difference along with corresponding SE and 95% CI was also calculated. The variance covariance matrix was assumed to be unstructured. Two models were fitted: one with a response variable of trough FEV1, and one with a response variable of change from baseline in trough FEV1.

The change in SGRQ total score from baseline and the TDI focal score were analysed using a MMRM analysis. No imputation was made for any missing numerical data. Covariates included baseline SGRQ score or Baseline Dyspnoea Index (BDI) (as applicable), stratum (number of long-acting bronchodilators used during the Run in period: 0/1 or 2), visit number, geographical region, treatment, visit-by-baseline/BDI (as applicable) interaction, and visit-by-treatment interaction. Least squares means and LS mean change from baseline values for each treatment group with associated SE and 95% CI were calculated. The estimated treatment difference along with corresponding SE and 95% CI was also calculated.

The proportion of responders at Week 24 for SGRQ and TDI total, using cut-off as defined for Study 200812 was analysed using a generalized linear mixed model including data at Week 12 and Week 24. Covariates included baseline SGRQ score or BDI (as applicable), treatment group, stratum (number of long acting bronchodilators used during the Run in period: 0/1 or 2), geographical region, visit number, visit by baseline/BDI (as applicable) interaction, and visit-by-treatment interaction.

Time to first moderate or severe COPD exacerbation was analysed using Cox's proportional hazards model. Covariates included treatment group, gender, exacerbation history (0 to 1, or ≥2 moderate or severe exacerbations within 12 months prior to Screening), stratum (number of long acting bronchodilators used during the Run in period: 0/1 or 2), geographical region, and baseline FEV1 (percent predicted normal).

Populations Analysed

In study 200812, a total of 1055 subjects were randomized to receive blinded study treatment.

Table 9: Subject Populations (ASE Population, Study 200812)

Population	Number of subjects, n (%) [1]		
	FF/UMEC/VI	FF/VI+UMEC	Total
ASE Population, N	527	528	1311
Randomized, N	527(100)	528 (100)	1055
ITT Population mPP	478 (91)	478 (91)	1055 (100)
Population			956 (91)

Subject Disposition

A total of 1311 subjects over 12 countries were pre-screened and 1278 subjects were screened. There were 33 pre-screen failures, 175 screen failures, and 48 Run-in failures. A total of 1055 subjects were randomized and received study treatment and 94% of subjects completed the study.

- **Results for both studies CTT116855 and 200812**

Efficacy results

Efficacy results will be presented for the pivotal trial in the first instance, but where endpoints were common across both clinical studies these results will be presented in tandem.

a) Pivotal Study – CTT116855

Primary endpoint: Annual Rate of On-Treatment Moderate/Severe Exacerbations

Study CTT116855 used well established criteria to define COPD exacerbations, consistent with regulatory authority guidance on COPD drug development. The diagnosis of an exacerbation was made and recorded by the investigator after contact with the subject. Symptoms of COPD were recorded daily by subjects using an eDiary and specific criteria for worsening symptoms were used to trigger contact with the investigator. The symptoms and criteria were consistent with those used in previous exacerbations studies for the salmeterol/fluticasone propionate combination product and FF/VI.

The results for the primary analysis of the primary endpoint of the annual rate of on-treatment moderate/severe exacerbations of COPD in Study CTT116855 are summarized below. FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on-treatment moderate/severe exacerbations compared with FF/VI and UMEC/VI ($p<0.001$ for both comparisons).

Table 10: Analysis of On-Treatment Moderate/Severe COPD Exacerbations Using Negative Binomial Model (CTT116855, ITT Population)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Number subjects	4145	4133	2069
Model estimated exacerbation rate	0.91	1.07	1.21
95% CI	(0.87, 0.95)	(1.02, 1.12)	(1.14, 1.29)
FF/UMEC/VI vs Column			
Rate ratio		0.85	0.75
95% CI		(0.80, 0.90)	(0.70, 0.81)
p-value		<0.001	<0.001
Percentage reduction in rate		15%	25%
95% CI		(10%, 20%)	(19%, 30%)

The supportive analysis of the annual rate of on-treatment moderate/severe exacerbations using the Poisson regression model and sensitivity analyses investigating the impact of missing data, which included analyses using both on- and off-treatment data, using on-treatment data and the Jump to Reference (J2R) assumption for missing data following treatment discontinuation, and using on- and off-treatment data and the J2R assumption for missing data following study withdrawal were supportive of the findings for the primary analysis for the comparisons of FF/UMEC/VI with FF/VI and UMEC/VI.

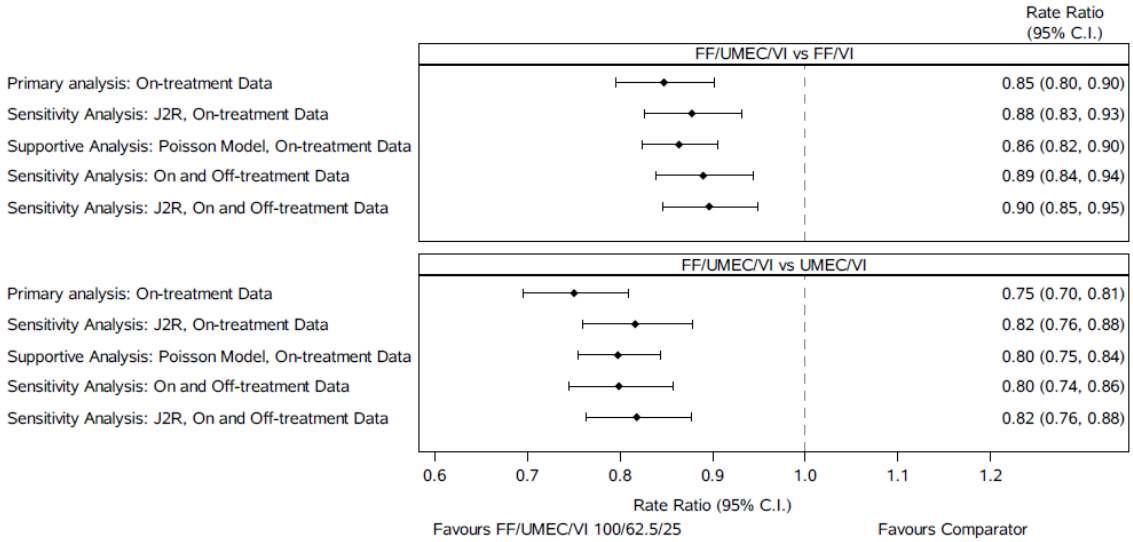


Figure 3: Forest Plot of Adjusted On-treatment Moderate/Severe COPD Exacerbation Rate Ratios and Associated Sensitivity Analyses (CTT116855)

The effect of FF/UMEC/VI on the annual rate of moderate/severe COPD exacerbations was maintained when both on- and off-treatment data were included in the analysis. For this analysis, FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of moderate/severe COPD exacerbations compared with FF/VI (11% reduction, p<0.001) and UMEC/VI (20% reduction, p<0.001).

Annual Rate of On-Treatment Severe Exacerbations

FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on-treatment severe exacerbations (i.e., resulting in hospitalisation/prolonged hospitalisation or death) compared with UMEC/VI (p<0.001). The reduction in the annual rate of on-treatment severe COPD exacerbations for FF/UMEC/VI compared with FF/VI was not statistically significant.

Table 11: Analysis of On-treatment Severe COPD Exacerbations Using Negative Binomial Model (CTT116855, ITT Population)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Number subjects	4145	4133	2069
Model estimated exacerbation rate	0.13	0.15	0.19
95% CI	(0.12, 0.14)	(0.13, 0.16)	(0.17, 0.22)
FF/UMEC/VI vs Column			
Rate ratio		0.87	0.66
95% CI		(0.76, 1.01)	(0.56, 0.78)
p-value		0.064	<0.001
Percentage reduction in rate		13%	34%
95% CI		(-1%, 24%)	(22%, 44%)

Time to First Moderate or Severe COPD Exacerbation

As this endpoint was studied in both clinical trials, results from both trials will be summarised here.

CTT116855

FF/UMEC/VI demonstrated a statistically significant decreased risk of a moderate/severe COPD exacerbation compared with FF/VI and UMEC/VI (p<0.001 for both comparisons)

Table 12: Time to First On-treatment Moderate/Severe COPD Exacerbation (Study CTT116855, ITT Population)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Number subjects with event (%)	1959 (47)	2039 (49)	1036 (50)
Number of subjects without an event (censored) (%)	2192 (53)	2095 (51)	1034 (50)
Probability of having event (%)	49.9	53.7	53.3
95% CI	(48.3, 51.5)	(52.1,55.4)	(51.0, 55.6)
First quartile time to onset (days)	112	81	73
FF/UMEC/VI vs Column			
Hazard ratio		0.85	0.84
95% CI		(0.80, 0.91)	(0.78, 0.91)
Percentage reduction in risk		14.8%	16.0%
95% CI		(9.3%, 19.9%)	(9.4%, 22.1%)
p-value		<0.001	<0.001

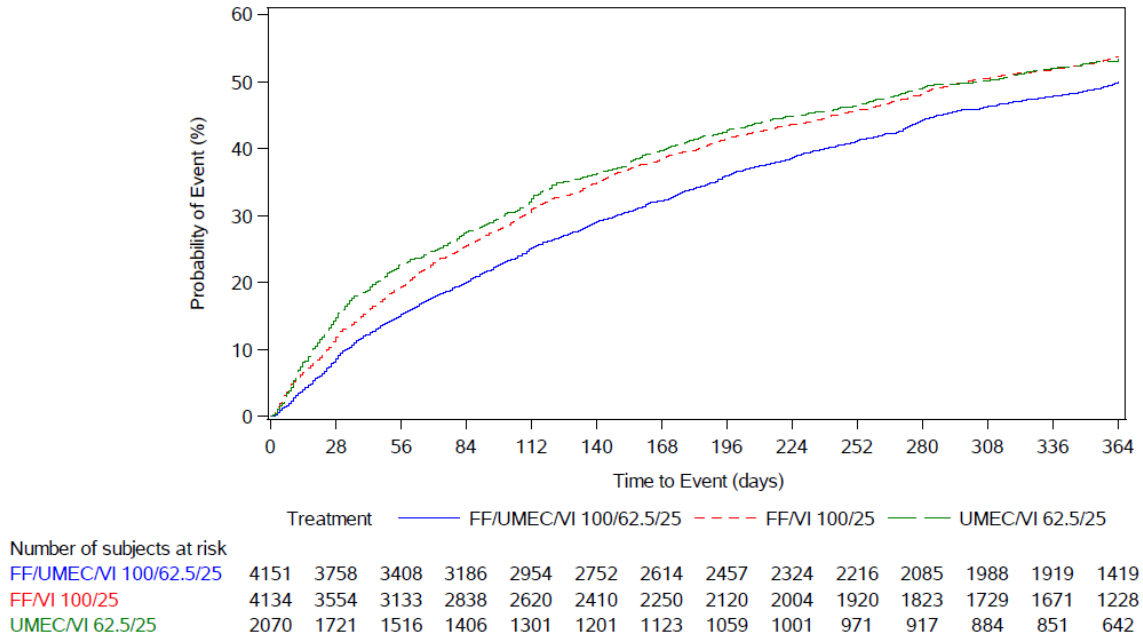


Figure 4: Kaplan-Meier Plot of Time to First On-treatment Moderate/Severe COPD Exacerbation (Study CTT116855, ITT Population)

Similar results were obtained when both on- and off-treatment data were included in the analysis of time to first moderate/severe exacerbation with risk reductions of 12.8% for FF/UMEC/VI compared with FF/VI and 14.5% for FF/UMEC/VI compared with UMEC/VI (p<0.001 for both comparisons).

200812

A similar number of subjects reported an on treatment moderate/severe COPD exacerbation in the FF/UMEC/VI and FF/VI+UMEC treatment groups (24% and 27%, respectively) with a similar risk of an exacerbation event based on time to first analysis.

Table 13: Time to First On-Treatment Moderate/Severe COPD Exacerbation (ITT Population, Study 200812)

	FF/UMEC/VI (N=527)	FF/VI+UMEC (N=528)
Number subjects with event (%)	129 (24)	142 (27)
Number of subjects without an event (censored) (%)	398 (76)	386 (73)
Probability of having event (%)	25.2	26.8
95% CI	(21.6, 29.2)	(23.2, 30.8)
First quartile time to onset, days	166.0	150.0
FF/UMEC/VI vs FF/VI+UMEC		
Hazard ratio	0.87	
95% CI	(0.68, 1.12)	

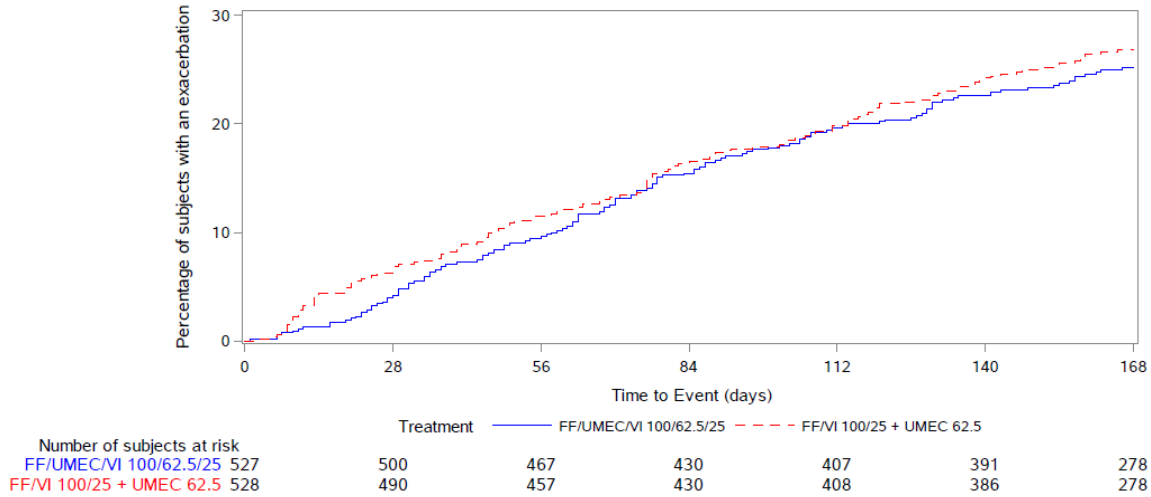


Figure 5: Kaplan-Meier Plot of Time to First On-Treatment Moderate/Severe COPD Exacerbation (ITT Population, Study 200812)

Lung Function

CTT116855

At Week 52, a statistically significant improvement in trough FEV1 was observed for FF/UMEC/VI compared with FF/VI (treatment difference: 97 mL; 95% CI: 85 mL, 109 mL; p<0.001) and compared with UMEC/VI (treatment difference: 54 mL; 95% CI: 39 mL, 69 mL; p<0.001).

Table 14: Analysis of LS Mean Change from Baseline in Trough FEV_1 (L) at Week 52 for FF/UMEC/VI versus FF/VI or UMEC/VI (Study CTT116855, ITT Population)

	FF/UMEC/VI 100/62.5/25 N=4151	FF/VI 100/25 N=4134	UMEC/VI 62.5/25 N=2070
Number subjects with analysable data at Week 52	3366	3060	1490
LS Mean (SE)	1.274 (0.0042)	1.177 (0.0044)	1.220 (0.0063)
95% CI	(1.265, 1.282)	(1.168, 1.185)	(1.208, 1.232)
LS Mean Change from baseline (SE)	0.094 (0.0042)	-0.003 (0.0044)	0.040 (0.0063)
95% CI	(0.086, 0.102)	(-0.012, 0.006)	(0.028, 0.052)
FF/UMEC/VI vs Column			
Difference (SE)		0.097 (0.0061)	0.054 (0.0076)
95% CI		(0.085, 0.109)	(0.039, 0.069)
Unadjusted p-value		<0.001	<0.001
Adjusted p-value[1]		<0.001	

Improvements in trough FEV1 observed for FF/UMEC/VI compared with FF/VI and UMEC/VI at the first time point assessed (Week 4) were maintained at all subsequent visits (all p<0.001).

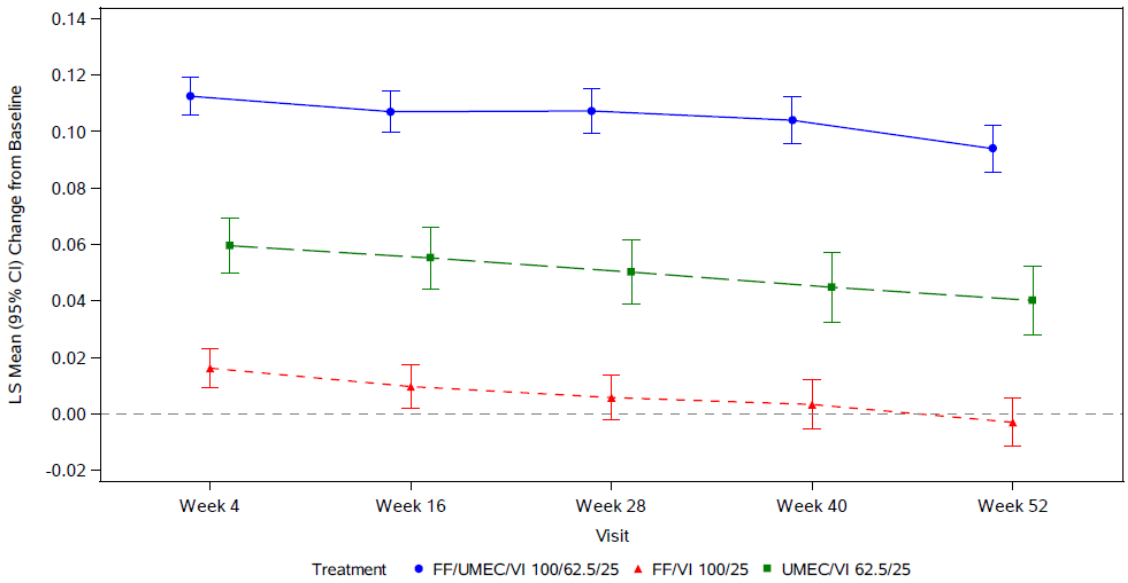


Figure 6: Least-squares Mean (95% CI) Change from Baseline in Trough FEV_1 (L) (Study CTT116855, ITT Population)

Heath-Related Quality of Life

CTT116855

FF/UMEC/VI demonstrated a clinically meaningful improvement in SGRQ Total Score with a LS mean change from baseline of -5.5 units at Week 52 (compared with the MCID of 4 units) and a statistically significant difference compared with FF/VI (between group difference of -1.8 units; 95% CI: -2.4, -1.1; p<0.001) and compared with UMEC/VI (between group difference of -1.8 units; 95% CI: 2.6, 1.0; p<0.001). Additionally, the odds of being an SGRQ responder versus a non-responder at Week 52 were statistically significantly higher for FF/UMEC/VI compared with FF/VI and UMEC/VI (p<0.001), indicative of clinically meaningful improvements in HRQoL with FF/UMEC/VI over the dual combinations.

Table 15: Total Score and Responder Analysis at Week 52 (Study CTT116855, ITT Population)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
SGRQ Total Score			
n with analysable data at Week 52	3318	3026	1470
LS mean (SE)	45.0 (0.23)	46.8 (0.24)	46.8 (0.35)
LS mean change from Baseline (SE)	-5.5 (0.23)	-3.7 (0.24)	-3.7 (0.35)
FF/UMEC/VI vs Column			
Difference (SE)		-1.8 (0.34)	-1.8 (0.42)
95% CI		(-2.4, -1.1)	(-2.6, -1.0)
p-value		<0.001	<0.001
Responders According to SGRQ Total Score			
n	4108	4092	2050
Responder[1], n (%)	1723 (42)	1390 (34)	696 (34)
Non-responder, n (%)	2385 (58)	2702 (66)	1354 (66)
FF/UMEC/VI vs Column			
Odds ratio		1.41	1.41
95% CI		(1.29, 1.55)	(1.26, 1.57)
p-value		<0.001	<0.001

200812

Both treatments demonstrated similar clinically meaningful improvements in HRQoL as measured by change from baseline SGRQ Total Score at Week 24 with a similar proportion of subjects defined as responders by SGRQ Total Score.

Table 16: SGRQ Total Score and Responder Analysis at Week 24 (Study 200812, ITT Population)

	FF/UMEC/VI (N=527)	FF/VI+UMEC (N=528)
SGRQ Total Score		
n (Analyzable Data at Week 24)	489	483
LS Mean Change (SE)	-5.841 (0.5870)	-4.935 (0.5904)
95% CI	(-6.993, -4.689)	(-6.094, -3.777)
FF/UMEC/VI vs FF/VI+UMEC		
Difference (SE)	-0.906 (0.8327)	
95% CI	(-2.540, 0.728)	
Responders According to SGRQ Total Score		
n	489	483
Responder[1], n (%)	243 (50)	247 (51)
Non-Responder, n (%)	246 (50)	236 (49)
FF/UMEC/VI vs FF/VI+UMEC		
Odds Ratio	0.92	
95% CI	(0.71, 1.20)	

TDI Focal Score

In both studies, the self-administered computerised versions of the TDI and BDI questionnaires were used.

CTT116855

All analyses presented for this study are based on the TDI Population which comprised of 5058 subjects at selected sites who completed a pre-dose BDI assessment at Day 1.

At Week 52, FF/UMEC/VI demonstrated a statistically significant improvement in TDI focal score compared with FF/VI (p=0.020). The treatment difference for FF/UMEC/VI compared with UMEC/VI at Week 52 did not meet statistical significance. The odds of being a TDI responder versus non-responder at Week 52 were statistically significantly higher for FF/UMEC/VI compared with FF/VI and UMEC/VI.

Table 17: TDI Focal Score and Responder Analysis at Week 52 (Study CTT116855, TDI Population)

	FF/UMEC/VI N=2029	FF/VI N=2014	UMEC/VI N=1015
TDI Focal Score			
n analysable data	1959	1861	930
n with analysable data at Week 52	1549	1392	670
LS mean (SE)	0.98 (0.079)	0.71 (0.083)	0.89 (0.120)
95% CI	(0.82, 1.13)	(0.55, 0.87)	(0.65, 1.12)
FF/UMEC/VI vs Column			
Difference (SE)		0.27 (0.115)	0.09 (0.144)
95% CI		(0.04, 0.49)	(-0.19, 0.37)
p-value		0.020	0.522
Responders According to TDI Focal Score			
n	2029	2014	1015
Responder[1], n (%)	730 (36)	591 (29)	302 (30)
Non-responder, n(%)	1299 (64)	1423 (71)	713 (70)
FF/UMEC/VI vs Column			
Odds ratio		1.36	1.33
95% CI		(1.19, 1.55)	(1.13, 1.57)
p-value		<0.001	<0.001

Study 200812

Findings for the TDI focal score indicated similar benefit of FF/UMEC/VI and FF/VI + UMEC to improve dyspnoea at Week 24. Both treatments resulted in clinically meaningful improvement in dyspnoea as measured by TDI at Week 24 based on TDI focal scores of ≥1. TDI focal scores and the odds of being a TDI responder versus non-responder were similar between groups at Week 24.

Table 18: TDI Focal Score and Responder Analysis at Week 24 (Study 200812, ITT Population)

	FF/UMEC/VI (N=527)	FF/VI+UMEC (N=528)
TDI Focal Score		
n (Analyzable Data at Week 24)	482	481
LS Mean Change (SE)	2.029 (0.1252)	1.892 (0.1254)
95% CI	(1.784, 2.275)	(1.646, 2.138)
FF/UMEC/VI vs FF/VI+UMEC		
Difference (SE)	0.137 (0.1773)	
95% CI	(-0.211, 0.485)	
Responders According to TDI Focal Score		
n (Analyzable Data at Week 24)	482	481
Responder[1], n (%)	268 (56)	271 (56)
Non-Responder, n (%)	214 (44)	210 (44)
FF/UMEC/VI vs FF/VI+UMEC		
Odds Ratio	0.95	
95% CI	(0.72, 1.25)	

Rescue Medication Use

Rescue medication use was evaluated in Study CTT116855 only.

Across treatment groups, there was a slight trend for increased use of rescue medication over time, although this was less apparent in the FF/UMEC/VI treatment group.

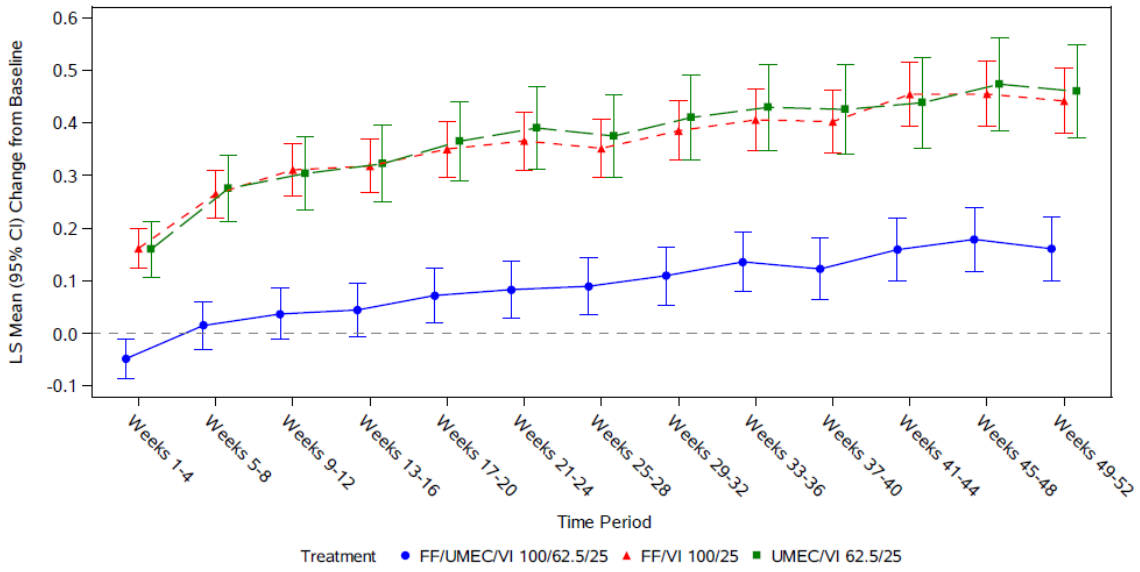


Figure 7: Least-squares Mean (95% CI) Change from Baseline Mean Number of Occasions of Rescue Use per Day by 4-Weekly Periods (Study CTT16855, ITT Population)

Over Weeks 49 to 52, there was a statistically significant lower mean change in number of occasions of rescue medication use per day in the FF/UMEC/VI compared with FF/VI and UMEC/VI ($p<0.001$). Similarly, the change in the percentage of rescue free days, reflecting increase use across groups, was smaller with FF/UMEC/VI compared with FF/VI and UMEC/VI ($p<0.001$).

Table 19: Rescue Medication Use over Weeks 49 to 52 (Study CTT116855, ITT Population)

	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
Mean Number of Occasions of Rescue Medication Use per Day			
Number subjects with analysable data	3322	3002	1462
LS Mean (SE)	1.75 (0.031)	2.03 (0.032)	2.05 (0.045)
95% CI	(1.69, 1.81)	(1.97, 2.09)	(1.96, 2.14)
LS Mean Change (SE)	0.16 (0.031)	0.44 (0.032)	0.46 (0.045)
95% CI	(0.10, 0.22)	(0.38, 0.50)	(0.37, 0.55)
FF/UMEC/VI vs Column			
Difference (SE)		-0.28 (0.044)	-0.30 (0.055)
95% CI		(-0.37, -0.19)	(-0.41, -0.19)
p-value		<0.001	<0.001
Percentage of Rescue–free Days			
Number subjects with analysable data	3322	3002	1462
LS Mean (SE)	42.5 (0.61)	37.3 (0.62)	38.1 (0.89)
95% CI	(41.4, 43.7)	(36.1, 38.6)	(36.4, 39.9)
LS Mean Change (SE)	-1.9 (0.61)	-7.1 (0.62)	-6.3 (0.89)
95% CI	(-3.1, -0.7)	(-8.3, -5.9)	(-8.0, -4.6)

Night-time Awakenings

Night-time awakenings were evaluated in Study CTT116855 only.

Over Weeks 49 to 52, FF/UMEC/VI demonstrated a statistically significant reduction in in the mean number of night-time awakenings per night compared with FF/VI and compared with UMEC/VI ($p \leq 0.005$)

Table 20: Analysis of Night-time Awakenings Due to COPD over Weeks 49 to 52 for FF/UMEC/VI versus FF/VI or UMEC/VI (Study CTT116855, ITT Population)

Night-time Awakenings per Night Due to COPD (Weeks 49 to 52)	FF/UMEC/VI N=4151	FF/VI N=4134	UMEC/VI N=2070
n	3322	3002	1462
LS Mean (SE)	0.48 (0.012)	0.53 (0.013)	0.58 (0.018)
95% CI	(0.46, 0.51)	(0.51, 0.56)	(0.54, 0.61)
LS Mean Change (SE)	-0.21 (0.012)	-0.16 (0.013)	-0.12 (0.018)
95% CI	(-0.24, -0.19)	(-0.19, -0.14)	(-0.15, -0.08)
FF/UMEC/VI vs Column			
Difference (SE)		-0.05 (0.018)	-0.10 (0.022)
95% CI		(-0.08, -0.01)	(-0.14, -0.05)
p-value		0.005	<0.001

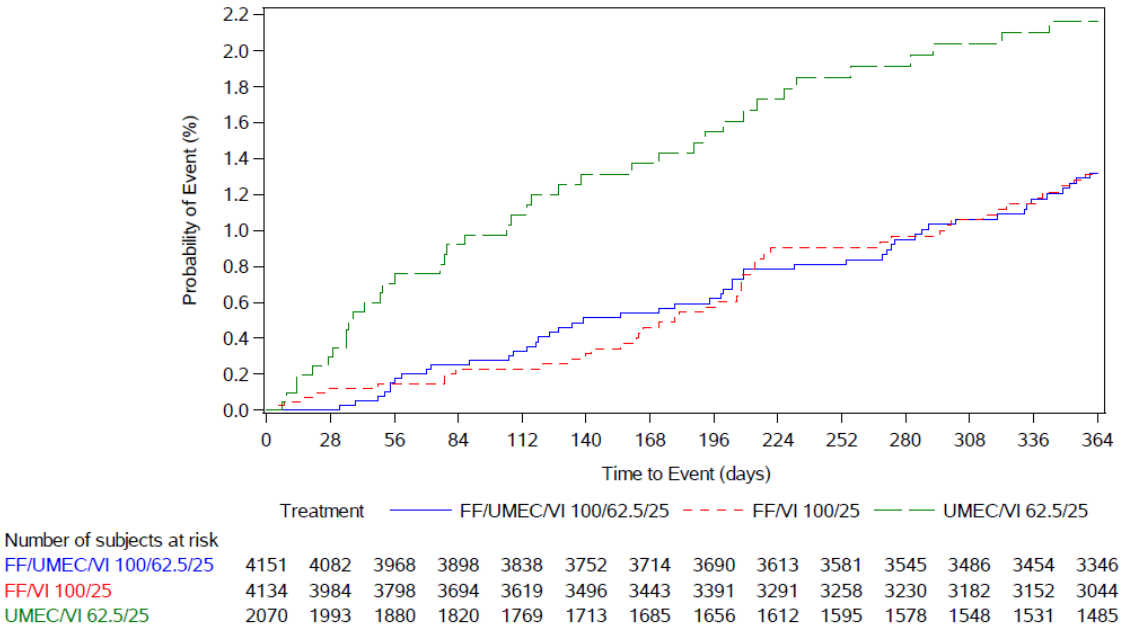
All-Cause Mortality

This endpoint was evaluated in Study CTT116855 only.

The analysis for on-treatment all-cause mortality included deaths that occurred up to 7 days after the last day of treatment and was based on the actual date of death. Twenty three percent of subjects prematurely discontinued study treatment prior to Week 52. The incidence of on treatment deaths was low across groups with 1.20% for FF/UMEC/VI, 1.19% for FF/VI, and 1.88% for UMEC/VI. The most common primary causes of death across treatment groups were CV (including sudden death) and respiratory (all <1% across groups). Death was adjudicated as associated with COPD for 18 of 50 subjects in the FF/UMEC/VI group, 14 of 49 subjects in the FF/VI group, and 15 of 39 subjects in the UMEC/VI group.

The FF/UMEC/VI group demonstrated a statistically significant reduction in the risk of on-treatment all-cause mortality compared with the UMEC/VI group (HR: 0.58; 95% CI: 0.38, 0.88; p=0.011, corresponding to a risk reduction of 42.1%). For the comparison of FF/UMEC/VI and FF/VI, the risk of on treatment all-cause mortality was similar (HR: 0.95; 95% CI: 0.64, 1.40, p=0.780, corresponding to a risk reduction of 5.5%).

Table 21: Kaplan-Meier Plot of On-treatment Time to All-cause Mortality (Study CTT116855, ITT Population)



Number of subjects at risk														
FF/UMEC/VI 100/62.5/25	4151	4082	3968	3898	3838	3752	3714	3690	3613	3581	3545	3486	3454	3346
FF/VI 100/25	4134	3984	3798	3694	3619	3496	3443	3391	3291	3258	3230	3182	3152	3044
UMEC/VI 62.5/25	2070	1993	1880	1820	1769	1713	1685	1656	1612	1595	1578	1548	1531	1485

Off-treatment data for all-cause mortality included data collected from subjects after discontinuation of study treatment whether or not they remained in the study. When on and off-treatment data were included in the analysis, vital status was available for 9781 subjects (94%) of the study population at Week 52.

When both on-and off treatment mortality data were included in the analysis, the significant risk reduction in all-cause mortality was maintained for FF/UMEC/VI compared with UMEC/VI, indicating a robustness of treatment effect. Specifically, FF/UMEC/VI significantly reduced the risk of on- and off-treatment all-cause mortality compared with UMEC/VI (HR 0.71; 95% CI: 0.51, 0.99; p=0.043, corresponding to a risk reduction of 28.6%). The risk of all-cause mortality was similar for FF/UMEC/VI compared with FF/VI (HR: 0.90, 95% CI: 0.67, 1.20; p=0.458).

Efficacy in Subgroups

Subgroup analyses were performed for Study CTT116855 only.

For Study CTT116855, an assessment was performed for the ITT Population to determine whether the effect of treatment on the primary endpoint was modified by the different levels of the following subgroups: gender, age group, race, geographical region, exacerbation history, and CV risk.

No significant interactions of treatment with gender, race, geographical region, or number of CV risk factors were observed on the primary endpoint. A significant subgroup-by-treatment interaction was observed for exacerbation history (p=0.010) and age group (p=0.052).

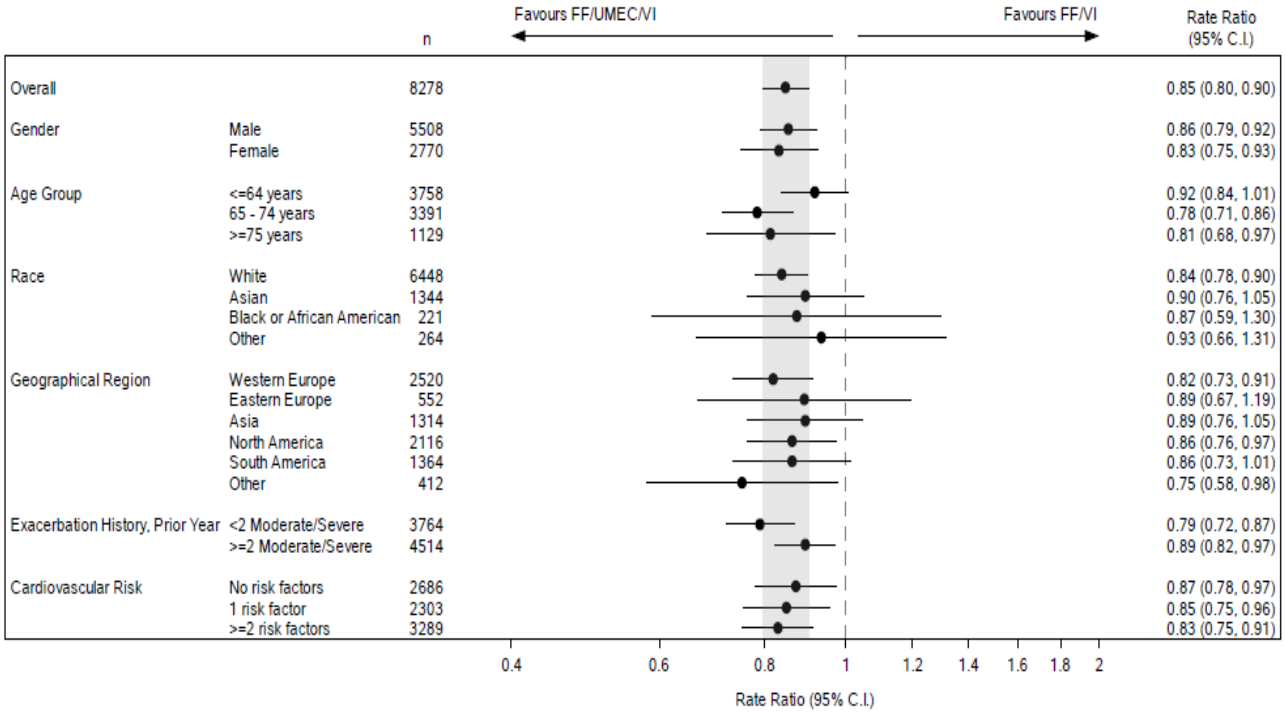
Further investigation of the significant interaction of treatment with age showed that the point estimate for the HR favoured FF/UMEC/VI over both FF/VI and UMEC/VI for each age category. The significant interaction is likely due to a difference in the magnitude of the rate ratio, which was greater in the 65 to 74 year age category and lower in the ≤64 year category for both treatment comparisons.

Relative to the comparison of FF/UMEC/VI with FF/VI in the overall ITT Population, there were no clinically relevant differences in the annual rate of moderate/severe exacerbations in any subgroup categories

(Figure 8). All point estimates of the rate ratio favoured FF/UMEC/VI with some variation in the magnitude of rate reduction.

For the subgroups of gender and number of CV risk factors, point estimates for the FF/UMEC/VI versus FF/VI rate ratio were all contained within the 95% CI of the comparison within the overall ITT Population. At least one of the point estimates for a category within the race, geographical region, exacerbation history, and age subgroups fell outside the 95% CI of the comparison within the overall ITT Population (Figure 8). These results tended to occur in smaller subgroup categories and were not considered clinically relevant due to overlapping 95% CI with other categories within the respective subgroup.

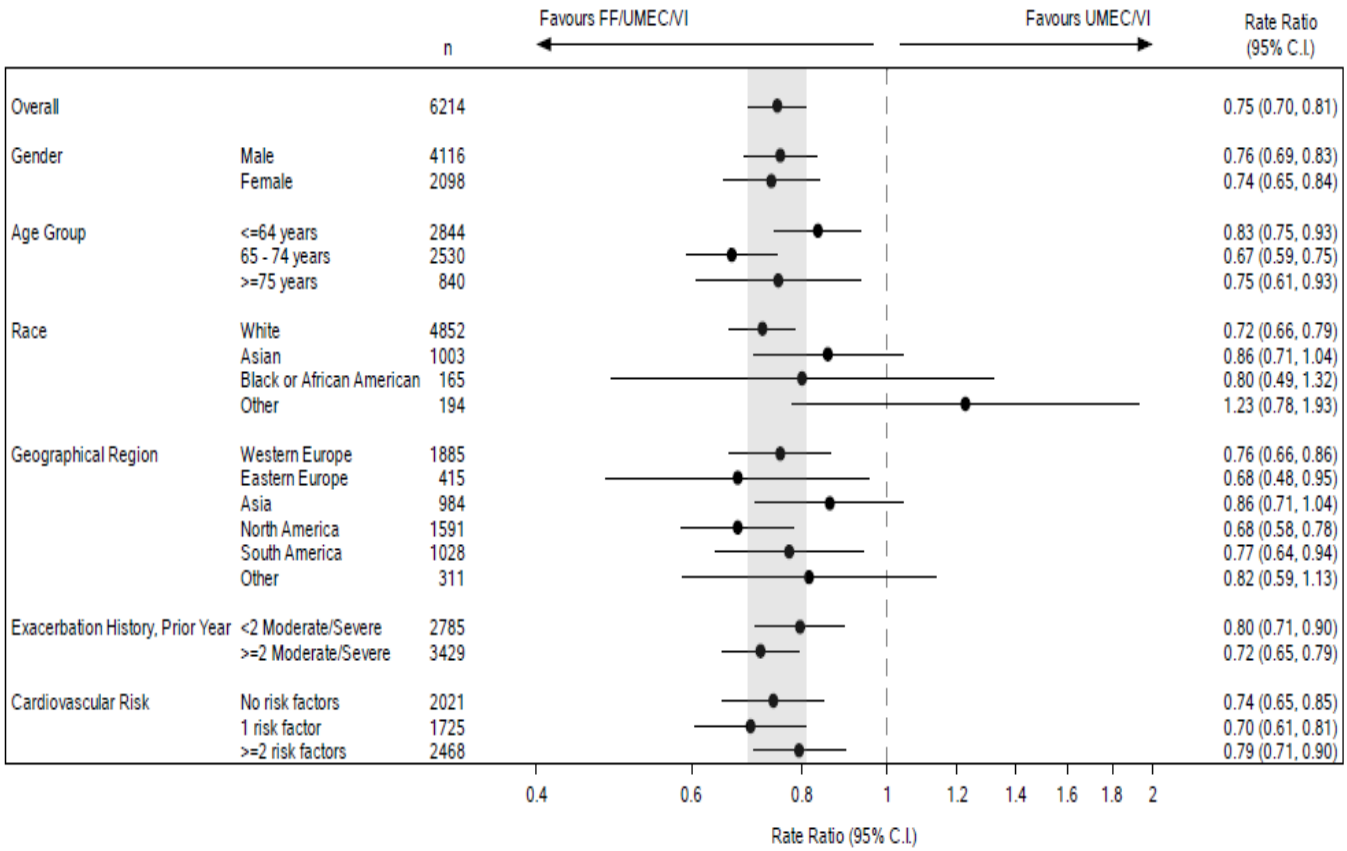
Figure 8: Forest Plot of On-treatment Moderate/Severe Exacerbation Rate Ratio Overall and by Subgroup – FF/UMEC/VI vs FF/VI (Study CTT116855, ITT Population)



Relative to the comparison of FF/UMEC/VI with UMEC/VI in the overall ITT Population, there were no clinically relevant differences in the annual rate of moderate/severe exacerbations in any subgroup category. All point estimates of the rate ratio for these subgroups favoured FF/UMEC/VI with some variation in the magnitude of rate reduction, apart from the comparison in the 'Other' race category.

For the subgroups of gender, exacerbation history, and number of CV risk factors, point estimates for the FF/UMEC/VI versus UMEC/VI rate ratio were all contained within the 95% CI of the comparison within the overall ITT Population. At least one of the point estimates for a category within the age, race, and geographical region subgroups fell outside the 95% CI of the comparison within the overall ITT Population. These results tended to occur in smaller subgroup categories and were not considered clinically relevant due to overlapping 95% CI with other categories within the respective subgroup.

Figure 9: Forest Plot of On-treatment Moderate/Severe Exacerbation Rate Ratio Overall and by Subgroup – FF/UMEC/VI vs UMEC/VI (Study CTT116855, ITT Population)



COPD Exacerbations by Eosinophil Subgroup

In CTT116855, the two secondary endpoints of model-estimated annual rate of on-treatment moderate/severe exacerbations and time to first on-treatment moderate/severe exacerbation, evaluated efficacy in the subgroup of subjects in the ITT Population with a baseline blood eosinophil count of ≥ 150 cells/µL. For these two endpoints, the key comparison was between the FF/UMEC/VI and UMEC/VI groups, although the FF/UMEC/VI and FF/VI groups were also compared, and treatment comparisons were also made in the subgroup of subjects with a baseline blood eosinophil count of <150 cells/µL.

Annual Rate of On-treatment Moderate/Severe Exacerbations by Eosinophil Subgroup

Regardless of baseline blood eosinophil count subgroup, treatment with FF/UMEC/VI resulted in a statistically significant reduction in the model-estimated annual rate of on treatment moderate/severe exacerbations at Week 52 compared with FF/VI (both p≤0.003) and compared with UMEC/VI (both p≤0.034). For the comparison between FF/UMEC/VI and FF/VI, the magnitude of the reduction was greater for the subgroup of subjects with baseline blood eosinophil count of <150 cells/µL (rate reduction: 20%; rate ratio: 0.80; 95% CI: 0.73, 0.88; p<0.001) than in the subgroup of subjects with baseline blood eosinophil count of ≥ 150 cells/µL (rate reduction: 12%; rate ratio: 0.88; 95% CI: 0.81, 0.96; p=0.003). For the comparison between FF/UMEC/VI and UMEC/VI, the magnitude of the reduction was greater for the subgroup of subjects with baseline blood eosinophil count of ≥ 150 cells/µL (rate reduction: 32%; rate ratio: 0.68; 95% CI: 0.62, 0.75; p<0.001) than in the subgroup of subjects with baseline blood eosinophil count of <150 cells/µL (rate reduction: 12%; rate ratio: 0.88; 95% CI: 0.78, 0.99; p=0.034).

Time to First Moderate/Severe Exacerbation by Eosinophil Subgroup

Based on the time to first analysis, treatment with FF/UMEC/VI in subjects with a baseline blood eosinophil count of ≥ 150 cells/µL resulted in a statistically significant reduction in the risk of a moderate/severe exacerbation by 15.0% compared with FF/VI (HR: 0.85; 95% CI: 7.8%, 21.7%; p<0.001) and by 23.2% compared with UMEC/VI (HR: 0.77; 95% CI: 15.4%, 30.4%; p<0.001). In subjects with a baseline blood eosinophil count of <150 cells/µL, treatment with FF/UMEC/VI resulted in a statistically significant reduction in the risk of a moderate/severe exacerbation by 14.6% compared with FF/VI (HR: 0.85; 95% CI: 6.1%, 22.3%; p<0.001). The reduction in risk compared with UMEC/VI was not statistically significant (4.0%; HR: 0.96; 95% CI: -8.2%, 14.8%; p=0.503).

Summary of main study (CTT116855)

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

Table 22 Summary of main study

Title: A phase III, 52 weeks, randomised, 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 (Study Number: CTT116855, Eudra-CT Number: 2013-003075-35).			
Study identifier	Study Number: CTT116855, Eudra-CT Number: 2013-003075-35		
Design	Phase III, randomised, double blind, 3 arm parallel group, multicentre, multinational		
	Duration of main phase: Duration of Run-in phase: Duration of Follow-up phase:		52 weeks 2 weeks 1 weeks
Hypothesis	Superiority		
Treatments groups	FF/UMEC/VI		FF/UMEC/VI 1 puff once in the morning (100/62.5/25 mcg per day), 52 weeks, n=4151, randomized
	FF/VI		FF/VI 1 puff once in the morning (100/25 mcg per day), 52 weeks, n=4134, randomized
	UMEC/VI		UMEC/VI 1 puff once in the morning (62.5/25 mcg per day), 52 weeks, n=2070, randomized
Endpoints and definitions	Primary endpoint	COPD exacerbation rate	Annual rate of moderate/severe COPD exacerbations (on-treatment)
	Secondary endpoints	Time to first exacerbation	Time to first on-treatment moderate/severe exacerbation
		trough FEV1	Change from baseline in trough FEV1 at Week 52
		SGRQ	Change from baseline in SGRQ Total Score at Week 52
Database lock			
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	**Intent to treat, week 52, comparison FF/UMEC/VI vs. UMEC/VI**		
	Treatment groups	FF/UMEC/VI	UMEC/VI
	Annual rate of moderate/severe COPD exacerbations (on-treatment)		
Descriptive statistics and estimate variability	Number of subject	4145	2069
	Model-estimated Exacerbation Rate	0.91	1.21

Effect estimate per comparison	Adjusted mean difference (95% CI)	**0.75** (0.70; 0.81)	
	Time to First moderate/severe COPD exacerbations (on-treatment)		
Descriptive statistics and estimate variability	Number of subject	1959	1036
	Probably of exacerbation (%)	49.9	53.3
Effect estimate per comparison	Hazard ratio (95% CI)	**0.84** (0.78; 0.91)	
	Change from baseline in trough FEV1 at Week 52		
	Number of subject	3366	1490
Descriptive statistics and estimate variability	LS mean change from Baseline (SE) [L]	0.094 (0.0042)	0.040 (0.0063)
Effect estimate per comparison	Adjusted mean difference (95% CI) [L]	**0.054** (0.039; 0.069)	
	p-value	**<0.001**	
	Change from baseline in SGRQ Total Score at Week 52		
	Number of subject	3318	1470
Descriptive statistics and estimate variability	LS mean change from Baseline (SE) [L]	-5.5 (0.23)	-3.7 (0.35)
Effect estimate per comparison	Adjusted mean difference (95% CI) [L]	**-1.8** (-2.6; -1.0)	
	p-value	**<0.001**	
Analysis population and time point description	**Intent to treat, week 52, comparison FF/UMEC/VI vs. FF/VI**		
	Treatment groups	FF/UMEC/VI	FF/VI
	Annual rate of moderate/severe COPD exacerbations (on-treatment)		
Descriptive statistics and estimate variability	Number of subject	4145	4133
	Model-estimated Exacerbation Rate	0.91	1.07
Effect estimate per comparison	Adjusted mean difference (95% CI)	**0.85** (0.80; 0.90)	
	Time to First moderate/severe COPD exacerbations (on-treatment)		
Descriptive statistics and estimate variability	Number of subject	1959	2039
	Probably of exacerbation (%)	49.9	53.7
Effect estimate per comparison	Hazard ratio (95% CI)	**0.85** (0.80; 0.91)	
	Change from baseline in trough FEV1 at Week 52		
	Number of subject	3366	3060
Descriptive statistics and estimate variability	LS mean change from Baseline (SE) [L]	0.094 (0.0042)	-0.003 (0.0044)
Effect estimate per comparison	Adjusted mean difference (95% CI) [L]	**0.097** (0.085; 0.109)	
	p-value	**<0.001**	
	Change from baseline in SGRQ Total Score at Week 52		
	Number of subject	3318	3026
Descriptive statistics and estimate variability	LS mean change from Baseline (SE) [L]	-5.5 (0.23)	-3.7 (0.24)
Effect estimate per comparison	Adjusted mean difference (95% CI) [L]	**-1.8** (-2.4; -1.1)	
	p-value	**<0.001**	
Notes	FF/UMEC/VI significantly reduced the model-estimated annual rate of moderate/severe COPD exacerbations by 15% and 25% compared with FF/VI and UMEC/VI, respectively.		

b) Supportive Study -200812

Primary endpoint: Change from Baseline in Trough FEV1 at Week 24

In this study, the efficacy of Trelegy Ellipta has been compared to FF/VI (92/22 micrograms) + UMEC (55 micrograms), co-administered once daily as a multi-inhaler therapy, in a multicentre, randomised, double-blind 24-week study in patients with COPD with a history of moderate or severe exacerbations within the prior 12 months.

The study met its primary efficacy endpoint and demonstrated non-inferiority of Trelegy Ellipta to FF/VI+UMEC in the improvement from baseline in trough FEV1 at Week 24. The lower bound of the CI was greater than the pre specified non-inferiority margin of -50 mL.

Table 23: Analysis of Change from Baseline in Trough FEV_1 at Week 24 (modified Per Protocol Population)

	Trelegy Ellipta (n=478)	FF/VI+UMEC (n=478)	Trelegy Ellipta vs FF/VI+UMEC
Trough FEV_1 (L) at Week 24			
LS Mean Change from Baseline (SE) (95% CI)	0.113 (0.0112) (0.091, 0.135)	0.095 (0.0116) (0.072, 0.117)	
Treatment Difference (95% CI)			0.018 (-0.013, 0.050)

2.5.1. Discussion on clinical efficacy

Design and conduct of clinical studies

Common efficacy endpoints in Studies CTT116855 and 200812 include time to first moderate/severe COPD exacerbation, trough FEV1, and results for the SGRQ and TDI scores with responder analyses. Additional efficacy endpoints that were included only in Study CTT116855 include the primary endpoint of moderate/severe exacerbations of COPD, the annual rate of severe exacerbations, all-cause mortality, rescue medication use, and night-time awakenings.

Efficacy data and additional analyses

Key findings from Study CTT116855 are:

- FF/UMEC/VI demonstrated a statistically significant and clinically meaningful reduction in the annual rate of on-treatment moderate/severe COPD exacerbations compared with FF/VI (15% reduction, p<0.001) and UMEC/VI (25% reduction, p<0.001).
- In a sensitivity analysis, FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on- and off-treatment moderate/severe COPD exacerbations compared with FF/VI (11% reduction, p<0.001) and UMEC/VI (20% reduction, p<0.001).
- FF/UMEC/VI demonstrated a statistically significant decreased risk of an on-treatment moderate/severe COPD exacerbation compared with FF/VI (hazard ratio [HR] of 0.85, p<0.001) and UMEC/VI (HR of 0.84, p<0.001), corresponding to risk reductions of 14.8% and 16.0%, respectively (based on analysis of time to first event) with similar results including both on- and off-treatment data (risk reductions 12.8% and 14.5%, respectively, p<0.001).

- FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on-treatment severe COPD exacerbations (i.e., resulting in hospitalisation or death) compared with UMEC/VI (34% reduction, p<0.001). The reduction in the on-treatment annual rate of on-treatment severe COPD exacerbations for FF/UMEC/VI compared with FF/VI was not statistically significant (13% reduction, p=0.064).
- Regardless of baseline blood eosinophil count subgroup (i.e., <150 cells/µL and ⩾150 cells/µL) treatment with FF/UMEC/VI resulted in a statistically significant reduction in the annual rate of on treatment moderate/severe exacerbations compared with FF/VI (both p≤0.003) and compared with UMEC/VI (both p≤0.034).
- FF/UMEC/VI demonstrated a statistically significant reduction in the risk of on-treatment all-cause mortality compared with UMEC/VI (HR: 0.58; 95% CI: 0.38, 0.88; p=0.011, corresponding to a risk reduction of 42.1%). For the comparison of FF/UMEC/VI and FF/VI, the risk of on treatment all-cause mortality was similar (HR: 0.95; 95% CI: 0.64, 1.40, p=0.780, corresponding to a risk reduction of 5.5%). When both on-and off treatment mortality data were included in the analysis, the significant risk reduction in all-cause mortality was maintained for FF/UMEC/VI compared with UMEC/VI.
- FF/UMEC/VI demonstrated a statistically significant improvement in trough FEV1 at Week 52 compared with FF/VI (mean treatment difference of 97mL, p<0.001) and UMEC/VI (mean treatment difference of 54mL, p<0.001).
- FF/UMEC/VI demonstrated a statistically significant improvement of -5.5 points from baseline in SGRQ Total Score at Week 52 compared with FF/VI (mean treatment difference of -1.8 units, p<0.001) and UMEC/VI (mean treatment difference of -1.8 units, p<0.001).
- FF/UMEC/VI demonstrated statistically significant greater odds of being a responder vs. non-responder based on SGRQ Total Score (response defined as a decrease in score from baseline of 4 or more) at Week 52 compared with FF/VI (odds ratio 1.41, p<0.001) and UMEC/VI (odds ratio 1.41, p<0.001).
- FF/UMEC/VI demonstrated a statistically significant reduction in subject-recorded daily use of rescue albuterol compared with FF/VI and UMEC/VI when evaluated as both the mean number of occasions of rescue use per day and the percentage of rescue-free days (p<0.001 for both comparisons).
- FF/UMEC/VI demonstrated a statistically significant reduction in the mean number of night-time awakenings per night compared with UMEC/VI (p<0.001 for all four weekly analysis periods over 52 weeks) and FF/VI (p≤0.021 for all analysis periods, except for Weeks 1-4 and Weeks 33-36 which were not statistically significant different).

The supporting Study 200812 demonstrated the non-inferiority of FF/UMEC/VI to FF/VI+UMEC multiple inhaler triple therapy for the improvement in lung function based on the primary endpoint of trough FEV1 at Week 24. Additionally, the comparability of both treatments was supported by results for the SGRQ and TDI scores and the proportion of subjects who reported an on treatment moderate/severe COPD exacerbation.

While the MAH has indeed demonstrated the superiority of the triple combination over the dual components, and the non-inferiority of the triple combination over the components administered

separately but coincidentally, this in itself does not support the broadening of the indication for use as a first-line therapy. The use of the triple combination is currently recommended only as a step-up from dual therapy. However it is agreed that the step up from the dual therapy LABA/LAMA is considered sufficiently demonstrated and this is introduced in the section 4.1.

It is agreed that information on the effect of the product on exacerbations is clinically useful, and so this information is included in section 5.1, with a cross-reference to that section included in section 4.1.

2.5.2. Conclusions on the clinical efficacy

Based on the assessment of the clinical data, the SmPC is updated to reflect the changes above discussed. (Please refer also to the section update of PI later in the report).

2.6. Clinical safety

Introduction

This section focuses on the safety data from the pivotal study CTT116855 due to the volume of data (10355 subjects for 1 year). Safety data from the supportive study 200812 (1055 subjects for 6 months) are briefly summarized at the end of this Section.

Knowledge on the safety profile

There are known pharmacological effects of ICS, LAMAs, and LABAs. For ICS, these include hypothalamic–pituitary–adrenal-axis effects, local oropharyngeal effects, and ocular effects. In addition, in patients with COPD, treatment with ICS has been associated with bone disorders (specifically, disorders associated with decreased bone mineral density and fractures) and pneumonia. For LAMAs, these include CV effects, ocular disorders, urinary retention, gastrointestinal disorders, along with anticholinergic effects (e.g., dry mouth, cough) and for LABAs, these include CV and neuromuscular effects. The potential for treatment with FF/UMEC/VI to result in these effects was evaluated in the clinical trials.

Patient exposure

Subject exposure data were summarised for the ITT Population.

a) CTT116855

A total of 10,355 subjects were randomised and included in the CTT116855 ITT Population; 4151 subjects to the FF/UMEC/VI group, 4134 subjects to the FF/VI group, and 2070 subjects to the UMEC/VI group.

Mean duration of treatment exposure was higher in the FF/UMEC/VI group (325.9 days) compared with the FF/VI (304.5 days) and UMEC/VI (298.7 days) groups. A total of 76%, 69%, and 68% of subjects in the FF/UMEC/VI, FF/VI, and UMEC/VI groups, respectively, were exposed to treatment for 51 to 53 weeks. The proportion of subjects exposed to treatment in each duration category was higher in the FF/UMEC/VI group than in the FF/VI or the UMEC/VI group throughout the 52 weeks of the study. The reduction in the exposure rate during the last week of the study, Week 52, ranging from 53% to 59 % across groups, was a result of the study visit window.

b) 200812

Mean duration of treatment exposure was the same in both treatment groups (162.1 days in FF/UMEC/VI and 162.1 days in FF/VI+UMEC). Greater than 90% of subjects in both treatments groups were exposed to treatment for 23 to 25 weeks, and 94% and 95% of subjects were exposed to treatment for ≥20 weeks in the FF/UMEC/VI and FF/VI+UMEC groups, respectively. The proportion of subjects exposed to treatment in each duration category was similar between the treatment groups throughout the study.

Adverse Events

a) CTT116855

The most frequently reported on-treatment AEs were viral URTI and COPD. The incidence and exposure-adjusted rate of viral URTI were similar across treatment groups. The incidence of COPD was 11% in the FF/UMEC/VI and FF/VI groups and 13% in the UMEC/VI group, with a lower exposure adjusted rate in the FF/UMEC/VI group (152.9) compared with the FF/VI (172.1) and UMEC/VI (207.3) groups. Pneumonia and oral candidiasis had higher incidences and exposure-adjusted rates in the ICS-containing groups (i.e., FF/UMEC/VI and FF/VI) compared with the UMEC/VI group.

Table 24: The 10 Most Frequent On-treatment Adverse Events in Each Treatment Group (Study CTT116855, ITT Population)

Adverse Event (Preferred Term)	FF/UMEC/VI N=4151		FF/VI N=4134		UMEC/VI N=2070	
	n (%)	Rate [#][1]	n (%)	Rate [#][1]	n (%)	Rate [#][1]
Total duration at risk (subject-years)	3714.9		3457.9		1698.3	
Viral URTI	521 (13)	191.9 [713]	479 (12)	190.3 [658]	223 (11)	186.7 [317]
COPD	455 (11)	152.9 [568]	472 (11)	172.1 [595]	279 (13)	207.3 [352]
URTI	299 (7)	108.5 [403]	283 (7)	111.0 [384]	117 (6)	95.4 [162]
Pneumonia	298 (7)	88.6 [329]	264 (6)	86.8 [300]	93 (4)	57.7 [98]
Headache	233 (6)	103.6 [385]	198 (5)	96.3 [333]	103 (5)	83.0 [141]
Back pain	148 (4)	49.0 [182]	140 (3)	48.0 [166]	83 (4)	59.5 [101]
Bronchitis	152 (4)	47.1 [175]	130 (3)	47.1 [163]	73 (4)	50.6 [86]
Oral candidiasis	161 (4)	54.6 [203]	146 (4)	50.9 [176]	41 (2)	29.4 [50]
Cough	145 (3)	45.2 [168]	117 (3)	37.0 [128]	58 (3)	44.2 [75]
Arthralgia	122 (3)	36.6 [136]	86 (2)	27.8 [96]	46 (2)	34.2 [58]
Sinusitis	104 (3)	32.0 [119]	98 (2)	33.3 [115]	45 (2)	27.7 [47]
Dyspnoea	82 (2)	26.6 [99]	95 (2)	31.8 [110]	52 (3)	37.1 [63]
Pharyngitis	82 (2)	29.1 [108]	81 (2)	25.7 [89]	48 (2)	34.7 [59]

b) 200812

The most frequently reported AEs in the FF/UMEC/VI and FF/VI+UMEC groups were viral URTI (11% and 10%, respectively), headache (6% in both), and COPD (4% and 6%, respectively). The remaining most frequent AEs were reported for ≤5% of subjects in either treatment group and with a similar incidence in both treatment groups.

Table 25: The 10 Most Frequent[1] On-Treatment AEs in Each Treatment Group (ITT Population, Study 200812)

Preferred Term	FF/UMEC/VI (N=527)		FF/VI+UMEC (N=528)	
	n (%)	Rate2 [#Events]	n (%)	Rate2 [# Events]
Viral URTI	56 (11)	295.1 [69]	52 (10)	260.3 [61]
Headache	32 (6)	239.5 [56]	33 (6)	230.4 [54]
COPD	23 (4)	119.7 [28]	31 (6)	153.6 [36]
URTI	18 (3)	81.2 [19]	24 (5)	123.8 [29]
Influenza	17 (3)	77.0 [18]	18 (3)	76.8 [18]
Pneumonia	14 (3)	72.0 [17]	18 (3)	76.8 [18]
Pharyngitis	12 (2)	51.3 [12]	16 (3)	76.8 [18]
Back Pain	13 (2)	55.6 [13]	8 (2)	42.7 [10]
Bronchitis	9 (2)	42.8 [10]	7 (1)	34.1 [8]
Hypertension	8 (2)	38.5 [9]	11 (2)	55.5 [13]
Cough	5 (<1)	25.7 [6]	8 (2)	42.7 [10]

Serious adverse event/deaths/other significant events

On-Treatment Fatal Adverse Events

a) CTT116855

On-treatment fatal SAEs were reported for 68 (2%), 76 (2%), and 49 (2%) subjects in the FF/UMEC/VI, FF/VI, and UMEC/VI groups, respectively, with respective exposure-adjusted rates of 26.4, 27.8, and 38.3. COPD was the most frequently reported fatal SAE in each treatment group, reported with an incidence of <1% in each treatment group.

The events in the SOC of Cardiac disorders were reported with an incidence of <1% in each treatment group.

Pneumonia was also reported with an incidence of <1% in each treatment group.

b) 200812

A total of 10 on treatment fatal SAEs were reported for 8 subjects (4 subjects [<1%] in each treatment group). The most commonly reported on treatment fatal SAEs (PTs) were of 'pneumonia' (reported for 1 subject in the FF/UMEC/VI group and 2 subjects in the FF/VI+UMEC group), 'COPD' (reported for 1 subject in each treatment group), and 'acute MI' (reported for 1 subject in each treatment group).

Non-Fatal Serious Adverse Events

a) CTT116855

The incidence of on-treatment non-fatal SAEs was similar across treatment groups (19% to 21% across groups) with exposure-adjusted rates of 405.4, 395.9, and 405.1 in the FF/UMEC/VI, FF/VI, and UMEC/VI groups, respectively. The most common non-fatal on treatment SAEs were COPD (10% to 13% across groups) and pneumonia (2% to 4% across groups). The exposure-adjusted rate of COPD was lower for the FF/UMEC/VI (145.6) and FF/VI (158.2) groups compared with the UMEC/VI group (192.0). The exposure-adjusted rate of pneumonia was higher for ICS-containing groups (i.e., FF/UMEC/VI [50.6] and FF/VI [46.3]) compared with the UMEC/VI group (30.6).

Table 26: On-treatment Non-fatal SAEs Occurring in ≥1% Subjects in Any Treatment Group (Study CTT116855, ITT Population)

Non-fatal SAE System Organ Class Preferred Term	FF/UMEC/VI N=4151		FF/VI N=4134		UMEC/VI N=2070	
	n (%)	Rate [#][1]	n (%)	Rate [#][1]	n (%)	Rate [#][1]
Total duration at risk (subject-years)	3714.9		3457.9		1698.3	
Any Non-fatal SAE	847 (20)	405.4 [1506]	801 (19)	395.9 [1369]	433 (21)	405.1 [688]
Respiratory, thoracic, and mediastinal disorders	465 (11)	172.6 [641]	469 (11)	182.5 [631]	277 (13)	214.9 [365]
COPD	431 (10)	145.6 [541]	435 (11)	158.2 [547]	261 (13)	192.0 [326]
Infections and infestations	253 (6)	84.3 [313]	245 (6)	85.3 [295]	91 (4)	62.4 [106]
Pneumonia	175 (4)	50.6 [188]	147 (4)	46.3 [160]	51 (2)	30.6 [52]
Cardiac disorders	99 (2)	36.3 [135]	81 (2)	25.2 [87]	49 (2)	34.7 [59]
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	57 (1)	16.7 [62]	50 (1)	15.3 [53]	21 (1)	13.0 [22]
Gastrointestinal disorders	51 (1)	15.9 [59]	52 (1)	16.8 [58]	17 (<1)	10.0 [17]
Injury, poisoning, and procedural complications	49 (1)	15.9 [59]	40 (<1)	13.9 [48]	14 (<1)	9.4 [16]
Nervous system disorders	47 (1)	14.3 [53]	28 (<1)	8.4 [29]	13 (<1)	7.7 [13]

b) 200812

The incidence of on treatment non-fatal SAEs was similar between the treatment groups. There were 69 on treatment non-fatal SAEs reported for 50 subjects (9%) in the FF/UMEC/VI group and 86 on treatment non-fatal SAEs for 54 subjects (10%) in the FF/VI+UMEC group. 'COPD' was the most frequently reported SAE in both treatment groups.

Other Significant Adverse Events

Adverse Events Leading to Permanent Discontinuation of Investigational Product or Withdrawal.

a) CTT116855

The incidence of on-treatment AEs that led to permanent discontinuation or withdrawal was 6% to 9% across treatment groups with lower exposure-adjusted rates in the FF/UMEC/VI (92.1) group compared with the FF/VI (128.7) and UMEC/VI (144.3) groups.

Table 27: On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study in ≥1% of Subjects in Any Treatment Group (Study CTT116855, ITT Population)

Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from the Study System Organ Class Preferred Term	FF/UMEC/VI 100/62.5/25 N=4151		FF/VI 100/25 N=4134		UMEC/VI 62.5/25 N=2070	
	n (%)	Rate [#][1]	n (%)	Rate [#][1]	n (%)	Rate [#][1]
Any Adverse event leading to discontinuation of treatment or withdrawal from study	252 (6)	92.1 [342]	327 (8)	128.7 [445]	187 (9)	144.3 [245]
Respiratory, thoracic, and mediastinal disorders	109 (3)	32.0 [119]	109 (3)	32.0 [119]	104 (5)	68.9 [117]
COPD	65 (2)	17.5 [65]	93 (2)	26.9 [93]	72 (3)	42.4 [72]

b) 200812

The incidence of on treatment AEs that led to withdrawal from the study were similar between the treatment groups. Three percent of subjects in the FF/UMEC/VI group and 2% of subject in the FF/VI+UMEC group experienced of on treatment AEs that led to withdrawal from the study, the most common of which was 'COPD'.

Adverse Events of Special Interest

Adverse events of special interest for Studies CTT116855 and 200812 have been defined as AEs which have specified areas of interest for FF, UMEC, or VI or for the COPD population, given their known mechanisms of action.

For study CTT116855, the incidence and exposure-adjusted rates in other AESI groups were generally similar across treatment groups, including those associated with ICS-containing groups (e.g., Ocular effects and Decreased bone mineral density and associated fractures).

Of the AESI groups, CV effects was most frequently reported, with similar incidences and exposure-adjusted rates of any event in that group reported across treatment groups (10% to 11% and 157.0 to 167.2, respectively). Local steroid effects and Pneumonia were the next most frequently reported groups, and were reported at a similar incidence in the ICS-containing FF/UMEC/VI (337 subjects [8%] and 317 subjects [8%], respectively) and FF/VI (301 subjects [7%] and 292 subjects [7%], respectively) groups and more frequently compared with the UMEC/VI group (108 subjects [5%] and 97 subjects [5%], respectively).

The exposure adjusted rates of any event in the Local steroid effects and Pneumonia AESI groups were higher in the FF/UMEC/VI (114.4 and 95.8, respectively) and FF/VI (107.3 and 96.6, respectively) groups compared with the UMEC/VI group (80.1 and 61.2, respectively).

a) 200812

The incidence of AESIs was low in both treatment groups, with CV effects being the most frequently reported (6% in FF/UMEC/VI and 5% in FF/VI+UMEC). The next most common AESIs were lower respiratory tract infections (LRTIs) excluding pneumonia (3% in FF/UMEC/VI and 2% in FF/VI+UMEC) and pneumonia (3% in FF/UMEC/VI and 4% in FF/VI+UMEC).

Pneumonia

*a)*CTT116855

There was a higher incidence of any event in the Pneumonia AESI group in the ICS-containing FF/UMEC/VI (317 subjects [8%]) and FF/VI (292 subjects [7%]) groups compared with the UMEC/VI group (97 subjects [5%])). The proportion of pneumonia events resulting in hospitalisation was generally similar across treatment groups (207 of 346 events [60%] in the FF/UMEC/VI group, 177 of 319 events [55%] in the FF/VI group, and 58 of 101 events [57%] in the UMEC/VI group). The proportion of pneumonia events associated with infiltrates on X-ray/CT scan was 48% (166 of 346 events) in the FF/UMEC/VI group, 49% (156 of 319 events) in the FF/VI group, and 40% (40 of 101 events) in the UMEC/VI group.

Based on analysis of time to first event, the risk of any on-treatment event in the Pneumonia AESI group was similar for FF/UMEC/VI compared with FF/VI (HR: 1.02, 95% CI: 0.87, 1.19; p=0.848). The risk of

any on-treatment event in the Pneumonia AESI group was statistically significantly increased for FF/UMEC/VI compared with UMEC/VI (HR: 1.53, 95% CI: 1.22, 1.92; p<0.001).

Table 28: Summary of On-treatment Pneumonia Incidence (Study CTT116855, ITT Population)

Pneumonia Details	FF/UMEC/VI 100/62.5/25 N=4151		FF/VI 100/25 N=4134		UMEC/VI 62.5/25 N=2070	
	n (%)	Rate [#][1]	n (%)	Rate[#][1]	n (%)	Rate [#][1]
Total duration at risk (subject-years)	3714.9		3457.9		1698.3	
Subjects with pneumonia	312 (8%)	93.1 [346]	282 (7%)	92.3 [319]	95 (5%)	59.5 [101]
Supported by X-ray/CT scan	154 (4%)	44.7 [166]	147 (4%)	45.1 [156]	40 (2%)	23.6 [40]
Pneumonias/subject, n (%)						
0	3839 (92%)		3852 (93%)		1975 (95%)	
1	284 (7%)		250 (6%)		89 (4%)	
2	24 (<1%)		28 (<1%)		6 (<1%)	
≤3	4 (<1%)		4 (<1%)		0	

1. Event rate per 1000 subject-years calculated as the number of events x 1000, divided by the total duration at risk. Note: A chest X-ray/CT scan was associated with pneumonia if it was performed within the duration of the pneumonia or between -7 to +10 days (inclusive) of the date of onset.
Note: Pneumonia was supported by a chest X-ray/CT scan if there was an associated X-ray/CT scan that showed the presence of infiltrates.

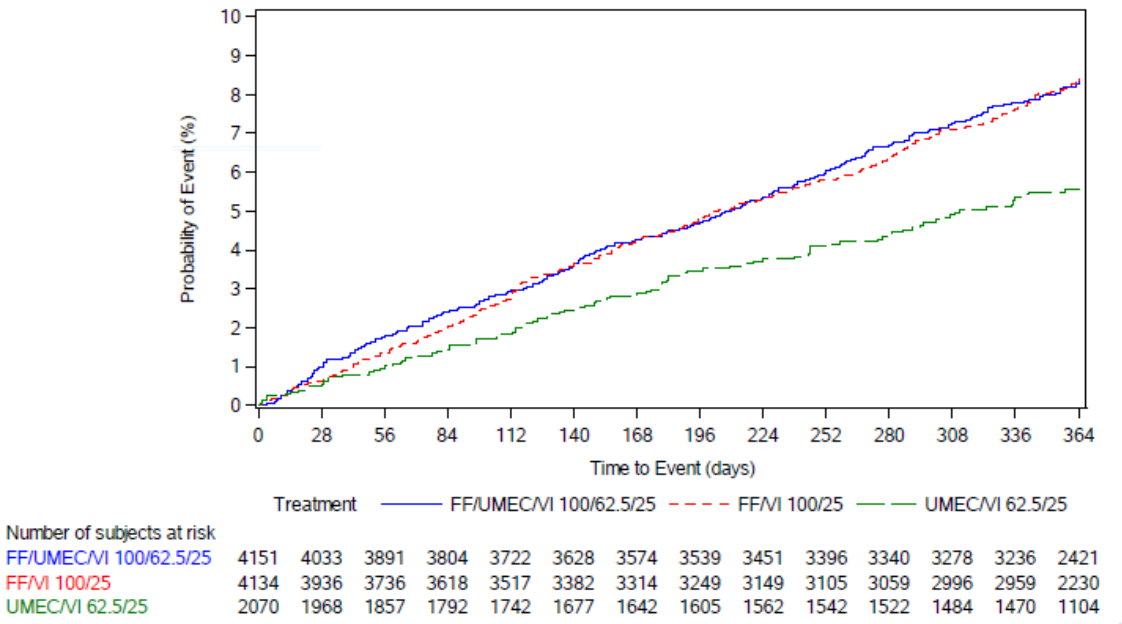


Figure 10: Kaplan-Meier Plot of Time to First On-treatment Event in the Pneumonia AESI Group (Study CTT116855, ITT Population)
b) 200812

There was a similar incidence of Pneumonia AESIs in the subjects in the FF/UMEC/VI (3%) and FF/VI+UMEC treatment groups (4%). The incidence of on treatment serious Pneumonia AESIs was

similar between the treatment groups, with 2% in the FF/UMEC/VI (all pneumonia) and 3% in the FF/VI+UMEC group.

Cardiovascular Events

a) CTT116855

CV effects was the most frequently reported AESI group and any event in that group occurred with a similar incidence across treatment groups (10% to 11% across groups). Overall, the exposure adjusted rates of these CV AESIs were similar across treatment groups.

The incidence of ischaemic heart disease (SMQ) was similar across treatment groups (1% to 2%). However, the exposure-adjusted rates for FF/UMEC/VI and UMEC/VI (26.1 and 30.6, respectively) were higher compared to FF/VI (18.5).

MACE analyses

Two analyses of MACE were performed, using broad and narrow MACE definitions. The broad-definition MACE included the ischaemic heart disease SMQ (MI SMQ and other ischaemic heart disease SMQ) excluding fatalities, the central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities, and adjudicated CV deaths. To investigate events relating specifically to MI rather than other cardiac ischaemic events, the narrow MACE definition included only the PTs of non-fatal MI and non-fatal acute myocardial in addition to central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities.

The incidence and exposure-adjusted rates for any on-treatment MACE events using the broad and narrow definitions were similar across treatment groups. A total of 80 subjects (2%) in the FF/UMEC/VI group, 60 subjects (1%) in the FF/VI group, and 37 subjects (2%) in the UMEC/VI group reported any MACE (narrow definition) with exposure-adjusted rates of 22.3, 18.8, and 22.4 for FF/UMEC/VI, FF/VI, and UMEC/VI, respectively. There were 20 (<1%) adjudicated CV deaths in the FF/UMEC/VI group, 27 (<1%) in the FF/VI group, and 16 (<1%) in the UMEC/VI group. The exposure-adjusted rate of adjudicated CV death was lower in the FF/UMEC/VI (5.4) group compared with the FF/VI (7.8) and UMEC/VI (9.4) groups. The exposure-adjusted rate of non-fatal central nervous system haemorrhages and cerebrovascular conditions was higher in the FF/UMEC/VI (10.8) group compared with the FF/VI (7.2) and UMEC/VI (5.9) groups. A total of 133 subjects (3%) in the FF/UMEC/VI group, 100 subjects (2%) in the FF/VI group, and 66 subjects (3%) in the UMEC/VI group reported any MACE (broad definition) with exposure-adjusted rates of 44.7, 35.3, and 44.8 for FF/UMEC/VI, FF/VI, and UMEC/VI, respectively.

Table 29: Major Adverse Cardiac Events (Study CTT116855, ITT Population)

MACE	FF/UMEC/VI 100/62.5/25 N=4151		FF/VI 100/25 N=4134		UMEC/VI 62.5/25 N=2070	
	n (%)	Rate [#] [1]	n (%)	Rate [#] [1]	n (%)	Rate [#] [1]
Narrow Definition						
Any MACE	80 (2)	22.3 [83]	60 (1)	18.8 [65]	37 (2)	22.4 [38]
Adjudicated CV death	20 (<1)	5.4 [20]	27 (<1)	7.8 [27]	16 (<1)	9.4 [16]
Non-fatal CNS haemorrhages & cerebrovascular conditions (SMQ)	38 (<1)	10.8 [40]	21 (<1)	7.2 [25]	10 (<1)	5.9 [10]
Non-fatal MI (PT)	9 (<1)	2.4 [9]	6 (<1)	1.7 [6]	5 (<1)	2.9 [5]
Non-fatal acute MI (PT)	13 (<1)	3.8 [14]	7 (<1)	2.0 [7]	7 (<1)	4.1 [7]
Broad Definition						
Any MACE	133 (3)	44.7 [166]	100 (2)	35.3 [122]	66 (3)	44.8 [76]
Adjudicated CV death	20 (<1)	5.4 [20]	27 (<1)	7.8 [27]	16 (<1)	9.4 [16]
Non-fatal CNS haemorrhages & cerebrovascular conditions	38 (<1)	10.8 [40]	21 (<1)	7.2 [25]	10 (<1)	5.9 [10]
Non-fatal MI (SMQ)	49 (1)	14.0 [52]	29 (<1)	9.3 [32]	24 (1)	14.7 [25]
Non-fatal other ischaemic heart disease (SMQ)	41 (<1)	14.5 [54]	32 (<1)	11.0 [38]	25 (1)	14.7 [25]

Sources: CSR CTT116855 RAP Table 3.046 and CSR CTT116855 RAP Table 3.047

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

CV=cardiovascular; CNS=central nervous system; MACE=Major Adverse Cardiac Event; MI=myocardial infarction; PT=Preferred Term; SMQ=Standardised MedDRA Query; RAP=Reporting and Analysis Plan

ECG Findings

For the ITT Population, 12-lead ECGs were obtained at baseline (Screening) and 15 to 45 minutes post-dose after 4, 28, and 52 weeks of treatment. In addition, a subset of subjects performed a pre-dose ECG in addition to the post-dose ECG at the Week 4 Visit (Pre-dose ECG Population).

ITT Population: At baseline, the proportion of subjects with abnormal ECG findings was similar across treatment groups (31% to 32% across groups). At any visit post-baseline, abnormal findings were reported for 1783 subjects (44%) in the FF/UMEC/VI group, 1757 subjects (44%) in the FF/VI group, and 860 subjects (44%) in the UMEC/VI group. For subjects with normal ECG findings at baseline, a worst case post-baseline shift to abnormal was reported for 584 subjects (14%) in the FF/UMEC/VI group, 602 subjects (15%) in the FF/VI group, and 297 subjects (15%) in the UMEC/VI group.

Table 30: ECG Abnormalities Occurring in ⩾3% of Subjects in Any Treatment Group (Study CTT116855, ITT Population)

ECG Abnormality	FF/UMEC/VI 100/62.5/25 N=4151		FF/VI 100/25 N=4134		UMEC/VI 62.5/25 N=2070	
	n (%)	Rate [#] [1]	n (%)	Rate [#] [1]	n (%)	Rate [#] [1]
Baseline [2]						
n	4148		4133		2068	
Any abnormal ECG finding	1583 (38)		1555 (38)		789 (38)	
Left anterior fascicular block	321 (8)		210 (5)		96 (5)	
First degree AV block (PR interval > 200msec)	261 (6)		290 (7)		166 (8)	
Right bundle branch block	242 (6)		151 (4)		53 (3)	
Ectopic supraventricular rhythm	223 (5)		147 (4)		79 (4)	
T waves flat	177 (4)		194 (5)		121 (6)	
T wave inversion	151 (4)		197 (5)		107 (5)	
Ectopic ventricular rhythm	141 (3)		278 (7)		134 (6)	
St depression	131 (3)		163 (4)		75 (4)	
Any time post-baseline						
n	4066		3962		1974	
Any abnormal ECG finding	2201 (54)	2030.8 [7544]	2139 (54)	2057.0 [7113]	1059 (54)	2003.8 [3403]
Ectopic supraventricular rhythm	452 (11)	178.5 [663]	441 (11)	181.9 [629]	238 (12)	197.8 [336]
T waves flat	421 (10)	187.9 [698]	431 (11)	196.4 [679]	210 (11)	190.2 [323]
First degree AV block (PR interval > 200msec)	405 (10)	213.7 [794]	415 (10)	235.4 [814]	180 (9)	210.8 [358]
Left anterior fascicular block	389 (10)	267.6 [994]	368 (9)	261.4 [904]	186 (9)	276.8 [470]
Ectopic ventricular rhythm	370 (9)	138.6 [515]	329 (8)	126.1 [436]	158 (8)	124.8 [212]
T wave inversion	297 (7)	150.5 [559]	312 (8)	166.9 [577]	140 (7)	148.4 [252]
Right bundle branch block	284 (7)	213.7 [794]	246 (6)	183.9 [636]	113 (6)	176.1 [299]
St depression	262 (6)	129.2 [480]	294 (7)	150.7 [521]	129 (7)	127.8 [217]
Sinus tachycardia (rate >100 beats/min)	205 (5)	73.2 [272]	215 (5)	84.7 [293]	110 (6)	81.3 [138]
Other conduction	132 (3)	59.2 [220]	166 (4)	83.9 [290]	81 (4)	79.5 [135]
Atrial fibrillation	126 (3)	83.2 [309]	113 (3)	78.1 [270]	51 (3)	71.8 [122]

Sources: CSR CTT116855 RAP Table 3.081 and CSR CTT116855 RAP Table 3.083

1. Rate is event rate per 1000 subject-years, calculated as the number of reports of abnormal finding x 1000, divided by the total duration at risk.
2. Baseline abnormalities are abnormalities from the most recent ECG performed prior to first dose of study treatment.

ECG=electrocardiogram; RAP=Reporting and Analysis Plan

Pre-dose ECG Population: At baseline, abnormal ECG findings were reported for 138 subjects (38%) in the FF/UMEC/VI group, 118 subjects (36%) in the FF/VI group, and 66 subjects (42%) in the UMEC/VI group. At any visit post-baseline, abnormal findings were reported for 190 subjects (52%) in the FF/UMEC/VI group, 155 subjects (47%) in the FF/VI group, and 73 subjects (46%) in the UMEC/VI group. For subjects with normal ECG findings at baseline, a worst case post-baseline shift to abnormal was reported for 57 subjects (16%) in the FF/UMEC/VI group, 44 subjects (13%) in the FF/VI group, and 12 subjects (8%) in the UMEC/VI group.

a) 200812

CV AESIs were the most frequently reported AESI group and occurred with a similar incidence in the FF/UMEC/VI and FF/VI+UMEC groups (6% and 5%, respectively). All of the CV AESI subgroups occurred at a similar incidence in both treatment groups.

Safety in special populations

Safety in Subgroups

Study CTT116855 specified safety subgroup summaries and analyses by gender, age, race, geographical region (including a US/Non-US sites subgroup for summaries only), exacerbation history, and CV risk. Additional subgroups were evaluated for pneumonia evaluation and fatalities, and included smoking status, BMI, and pneumonia history. Subgroup analyses were not specified for Study 200812.

The safety subgroup analyses for Study CTT116855 are summarized as follows:

- Overall, no notable, clinically relevant, or unexpected differences between subgroups were observed. Where differences were observed, these were mainly due to a relatively low number of subjects and/or a low number of events.
- Female subjects reported a higher rate of any on-treatment AE and male subjects reported a higher rate of any on-treatment SAEs and fatal SAEs (including adjudicated serious adverse reports) for all treatment groups and AEs leading to premature discontinuation of study treatment or withdrawal from the study for FF/UMEC/VI and sFF/VI.
- Subjects in the ≤64 years of age subgroup had lower rates of AEs, SAEs and fatal SAEs (including adjudicated serious adverse reports) and AEs leading to permanent discontinuation of study treatment or withdrawal from the study, while subjects within the 65 to 74 years of age subgroup had similar to higher rates of events, and subjects within the 75 to 84 years of age subgroup had higher rates of events, with the exception of the 75 to 84 years of age subgroup in the UMEC/VI group, which had a similar or lower rate of events compared with the ITT Population. The UMEC/VI group had the smallest number of subjects in the 75 to 84 years of age subgroup compared with the other age subgroups; therefore, any differences found in the UMEC/VI group may be due to smaller total duration at risk. Interpretation of findings the ≥85 years of age subgroup were limited due to the relatively low number of subjects (<1% of the population in each treatment group).
- The rate of any on-treatment AEs, fatal SAEs and SAEs (including adjudicated serious adverse reports and adjudicated non-fatal serious adverse reports) was higher in Asian subjects compared with the overall ITT Population, with the exception of any on-treatment AEs and fatal SAEs within the FF/UMEC/VI group. Within each treatment group, the rate of adjudicated fatal serious adverse reports and AEs leading to permanent discontinuation of study treatment or withdrawal from the study was similar or lower in Asian subjects compared with the overall ITT Population.
- From the five geographical subgroups (Western Europe, Asia, North America, and South America), subjects in South America had the lowest rate of AEs, SAEs (including adjudicated serious adverse reports) and AEs leading to treatment/study discontinuation compared with the ITT Population. The highest rates of AEs, SAEs (including adjudicated serious adverse reports) and AEs leading to treatment/study discontinuation compared with the ITT Population were in

subjects in North America (FF/UMEC/VI and UMEC/VI groups) or in Asia (FF/VI). Overall, within each treatment group, subjects in Western Europe had a lower rate of any on-treatment fatal SAEs.

- For subjects with a history in the prior year of <2 moderate/severe exacerbations and subjects with a history ≥2 moderate/severe exacerbations, no notable differences were seen within each treatment group in the rate of AEs, SAEs and fatal SAEs (including adjudicated serious adverse reports) and AEs leading to permanent discontinuation of study treatment or withdrawal from the study compared with the ITT Population.
- Of those subjects with no, 1, or >= to 2 CV risk factors, subjects with >= to 2CV risk factors reported a higher rate of AEs, SAEs and fatal SAEs (including adjudicated serious adverse reports) and AEs leading to permanent discontinuation of study treatment or withdrawal from the study when compared with the ITT Population.
- No notable differences were observed in the incidence and rate of fatal SAEs and adjudicated fatal serious adverse reports for current and former smokers compared with the ITT Population.
- The rate of on-treatment fatal SAEs was higher for subjects with a BMI <25 kg/m2 and subjects with a BMI ≤21 kg/m2 compared with the ITT Population. Similar findings were seen for on treatment adjudicated fatal serious adverse reports; however, the differences between the rates were generally less pronounced. The rate of on-treatment fatal SAEs and on treatment adjudicated fatal serious adverse reports was lower for subjects with a BMI <25 kg/m2 and subjects with a BMI >21 kg/m2 compared with the ITT Population.
- No notable differences were observed in the rate of any on-treatment fatal SAEs and adjudicated fatal serious adverse reports for subjects with a past history of pneumonia and subjects with no past history of pneumonia compared with the ITT Population.

Discontinuation due to adverse events

The incidence of on-treatment AEs that led to permanent discontinuation of study treatment or withdrawal from the study was 6% to 9% across treatment groups with lower exposure-adjusted rates in the FF/UMEC/VI (92.1) group compared with the FF/VI (128.7) and UMEC/VI (144.3) groups.

Table 31: On-treatment Adverse Events Leading to Permanent Discontinuation of Study Treatment or Withdrawal from the Study in ⩾1% of Subjects in Any Treatment Group (Study CTT116855, ITT Population).

Adverse Events Leading to Discontinuation of Study Treatment or Withdrawal from the Study System Organ Class Preferred Term	FF/UMEC/VI 100/62.5/25 N=4151		FF/VI 100/25 N=4134		UMEC/VI 62.5/25 N=2070	
	n (%)	Rate [#] [1]	n (%)	Rate [#] [1]	n (%)	Rate [#] [1]
Any Adverse event leading to discontinuation of treatment or withdrawal from study	252 (6)	92.1 [342]	327 (8)	128.7 [445]	187 (9)	144.3 [245]
Respiratory, thoracic, and mediastinal disorders	109 (3)	32.0 [119]	109 (3)	32.0 [119]	104 (5)	68.9 [117]
COPD	65 (2)	17.5 [65]	93 (2)	26.9 [93]	72 (3)	42.4 [72]

Source: CSR CTT116855 RAP Table 3.011

1. Rate was event rate per 1000 subject-years, calculated as the number of events x 1000, divided by the total duration at risk. #=number of event

RAP=Reporting and Analysis Plan

2.6.1. Discussion on clinical safety

The safety population supporting the extension of indication comprised a total of 10355 subjects treated with the closed triple combination FF/UMEC/VI 100/62.5/25 for 1 year in Study CTT116855. Different to prior studies, patients with significant cardiovascular (CV) disease were included in order to allow an assessment of safety that was more representative of the 'real world' population (e.g. subjects with a past history of previous myocardial infarction [>6 months prior to Screening], New York Heart Association Class 1–3 heart failure, and unstable or life-threatening cardiac arrhythmia requiring intervention [>3 months prior to Screening] were eligible).

The incidence of CV risk factors was similar across treatment groups. Sixty-eight percent of subjects reported any CV risk factor, with 40% of subjects reporting ≥ 2 CV risk factors. The most frequently reported CV risk factors were hypertension (53%), hypercholesterolaemia (33%), diabetes mellitus (15%), and coronary artery disease (12%). The percentage of subjects reporting a family history (first degree relatives only) of premature coronary artery disease, myocardial infarction, or stroke was 11% to 16% overall and was similar across treatment groups.

The most frequently reported on-treatment AEs were viral upper respiratory tract infection (URTI) and COPD. The incidence and exposure-adjusted rate of viral URTI were similar across treatment groups (11% to 13% and 186.7 to 191.9, respectively). The incidence of COPD was 11% in the FF/UMEC/VI and FF/VI groups and 13% in the UMEC/VI group, with a lower exposure-adjusted rate in the FF/UMEC/VI group (152.9) compared with the FF/VI (172.1) and UMEC/VI (207.3) groups. Pneumonia and oral candidiasis had higher incidences and exposure-adjusted rates in the ICS-containing groups (i.e., FF/UMEC/VI and FF/VI) compared with the UMEC/VI group.

ICS-containing treatments are known to increase the risk of pneumonia in COPD patients. This signal was first identified in the TORCH study (Calverley et al 2007). This was a large clinical study of 3 years treatment duration comparing the fluticasone propionate/salmeterol combination with its component parts and placebo in COPD patients. This study was considered in a 2010 review of the risk of pneumonia in COPD patients by the CHMP Pharmacovigilance Working Party that concluded that the treatment with an ICS, either alone or in combination with a LABA, increases the risk of pneumonia in COPD patients. On

27 April 2015 the European Commission triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the benefit-risk balance of ICS containing medicinal products indicated in the treatment of COPD. The review confirmed the risk of pneumonia with these products. The review, however, did not find any conclusive evidence of differences in this risk for different products.

In study CTT116855, as expected there was a higher incidence of pneumonia in the FF/UMEC/VI group (298 subjects [7%]) and in the FF/VI group (264 subjects [6%]) compared with the UMEC/VI group (93 subjects [4%]). The pneumonia event rate per 1000 subjects were 88.6 in the FF/UMEC/VI group and 86.8 in the FF/VI group compared to 57.7 in the UMEC/VI group. The higher risk of pneumonia of about 35% comparing FF/UMEC/VI with UMEC/VI has to be taken into account when balancing the benefit against the risk.

When comparing the FF/UMEC/VI and FF/VI groups, the AEs with higher incidences (viral URTI, COPD, URTI, and pneumonia) had a similar risk for FF/UMEC/VI and FF/VI groups. When comparing the FF/UMEC/VI and UMEC/VI groups, the risk of COPD was lower for FF/UMEC/VI group while the risk of pneumonia and oral candidiasis was lower for UMEC/VI, as expected based on ICS class effects. While it seems evident that the triple combination was generally well tolerated when compared with the dual therapies, the difference in the rates of pneumonia between the ICS- and non ICS-containing arms was evident. This reflects the known adverse event profile of ICS medications, and has an impact on the substitution potential of the triple therapy versus the LAMA/LABA combinations. Therefore, a paragraph describing the above data on pneumonia is included in section 4.8 of the SmPC.

A total of 244 subjects were reported to have had a fatal SAE (on-treatment and post-treatment). One hundred ninety-three subjects were reported to have had an on-treatment fatal SAE.

On-treatment fatal SAEs were reported with an incidence of 2% in each treatment group and with exposure-adjusted rates of 26.4, 27.8, and 38.3 in the FF/UMEC/VI, FF/VI, and UMEC/VI groups, respectively. COPD was the most frequently reported fatal SAE in each treatment group, reported with an incidence of <1% in each treatment group and with exposure-adjusted rates of 3.5, 6.4, and 6.5 in the FF/UMEC/VI, FF/VI, and UMEC/VI groups, respectively. The events in the SOC of Cardiac disorders were reported with an incidence of <1% in each treatment group; a lower exposure-adjusted rate was observed in the FF/UMEC/VI (4.8) and FF/VI (4.6) groups compared with the UMEC/VI (7.7) group. Nevertheless, no consistent patterns or imbalances were noted across treatment groups when examining the primary causes of death. Cardiac disorders and COPD exacerbation are categories expected in patients with severe and very severe COPD.

The incidence of on-treatment SAEs (fatal and non-fatal) was similar across treatment groups (21 % to 23% across groups). The most common on-treatment SAEs (fatal and non-fatal) were COPD (11% to 13% across groups) and pneumonia (3% to 4% across groups). The exposure-adjusted rate of COPD was lower for the FF/UMEC/VI (149.1) and FF/VI (164.5) groups compared with the UMEC/VI group (198.4). The exposure-adjusted rate of pneumonia was higher for the FF/UMEC/VI (53.3) and FF/VI (47.7) groups compared with the UMEC/VI group (32.4) as expected.

Two MACE analyses were performed, using broad and narrow MACE definitions. The broad-definition MACE included the ischaemic heart disease SMQ (myocardial infarction SMQ and other ischaemic heart disease SMQ) excluding fatalities, the central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities, and adjudicated CV deaths. To investigate events relating specifically to myocardial infarction rather than other cardiac ischaemic events, the narrow MACE definition included only the PTs of non-fatal myocardial infarction and non-fatal acute myocardial in addition to central nervous system haemorrhages and cerebrovascular conditions SMQ excluding fatalities.

Any MACEs (broad definition) were reported in 133 (3%) subjects in the FF/UMEC/VI group, in 100 subjects (2%) in the FF/VI group and in 66 subjects (3%) in the UMEC/VI group. The event rate per 1000 subject-year was 44.7 in the FF/UMEC/VI group, 35.3 in the FF/VI group and 44.8 in the UMEC/VI group. Any MACEs (narrow definition) were reported in 80 (2%) subjects in the FF/UMEC/VI group, in 60 subjects (1%) in the FF/VI group and in 37 subjects (2%) in the UMEC/VI group. The event rate per 1000 subject-year was 22.3 in the FF/UMEC/VI group, 18.8 in the FF/VI group and 22.4 in the UMEC/VI group.

Overall, although the rate of cardiac adverse events in all groups were low, particularly in the FF/UMEC/VI group, the results suggest an additive effect when LABA and LAMA are administered together. Reports of increased risk of such events in patients with COPD who are receiving long-acting bronchodilators are reported also in the literature (e.g. Wang MT et al. 2018 reported an approximate 1.5 fold increased severe CV risk within 30 days after LABA and LAMA initiation). However at this stage, the CHMP agreed that a specific warning for an additive effect is not warranted and the potential risk of CV effects with LAMA and LABA use is adequately covered by current class labelling for all age groups. Additionally, no RMP update is considered necessary, however, minor changes have been introduced to the RMP to bring it in line with the new template.

Based on the evaluation of AE data from study CTT116855 six additional ADRs are proposed for inclusion in the FF/UMEC/VI label: bronchitis, sinusitis, urinary tract infection (UTI), constipation, dysphonia, and dry mouth. In addition, changes in frequency are proposed for two existing ADRs in the FF/UMEC/VI label, based on the frequency reported in Study CTT116855: Candidiasis of mouth and throat from 'uncommon' to 'common' and Oropharyngeal pain from 'uncommon' to 'common', respectively. Accordingly, the update of the ADRs section is included in section 4.8 of the SmPC

In study 200812, the safety profile of FF/UMEC/VI in the treatment of COPD subjects was similar to that of FF/VI+UMEC and consistent with previous data for FF/UMEC/VI in a COPD population.

2.6.2. Conclusions on clinical safety

As described above, the SmPC is updated in order to reflect either new ADRs or changes in frequency of ADRs in section 4.8, as well as an update on incidence of pneumonia in the clinical studies based on the clinical safety data provided in this application. The changes were considered approvable by the CHMP.

2.6.3. PSUR cycle

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.

2.7. Risk management plan

Minor changes have been introduced to the RMP to bring it in line with the new template (rev. 2).

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

The PRAC considered that the risk management plan version 2.1 is acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Pneumonia
Important potential risks	Serious Cardiovascular Events
	Decreased bone mineral density and associated fractures
Missing information	None

Pharmacovigilance plan

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

Risk minimisation measures

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Pneumonia	**Routine risk minimisation measures:** Section 4.4 and section 4.8 of the SmPC (also Section 4 of Product Leaflet). **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Targeted Follow Up Questionnaire **Additional pharmacovigilance activities:** None
Serious Cardiovascular Events	**Routine risk minimisation measures:** Section 4.4 and section 4.8 of the SmPC (also Section 4 of Product Leaflet). **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Decreased Bone Mineral Density and Associated Fractures	**Routine risk minimisation measures:** Section 4.4 and section 4.8 of the SmPC (also Section 4 of Product Leaflet). **Additional risk minimisation measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** None **Additional pharmacovigilance activities:** None

2.8. Update of the Product information

Based on the clinical data provided from the clinical studies, several sections of the SmPC are updated. In the indication, the possibility to use Trelegy in patients not adequately treated with a combination of LAMA/ LABA. Additionally, the effect on exacerbations is adequately demonstrated and referent to section 5.1 results are inserted in the indication as mentioned below: (amendments are inserted in track changes)

Trelegy 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 ***or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist*** *(for effects on symptom control* ***and o****n* ***exacerbations*** *see section 5.1).*

An update of adverse reactions in section 4.8 in agreed upon to reflect new ADRs observed from the clinical data submitted. (see below)

System Organ Class	Adverse reactions	Frequency
Infections and infestations	Pneumonia Upper respiratory tract infection **Bronchitis** Pharyngitis Rhinitis **Sinusitis** Influenza Nasopharyngitis **Candidiasis of mouth and throat** **Urinary tract infection**	Common
	Viral respiratory tract infection	Uncommon
Nervous system disorders	Headache	Common
Eye disorders	Vision blurred (see section 4.4)	Not known
Cardiac disorders	Supraventricular tachyarrhythmia Tachycardia Atrial fibrillation	Uncommon
Respiratory, thoracic & mediastinal disorders	Cough **Oropharyngeal pain**	Common
	~~**Dysphonia**~~	Uncommon
Gastrointestinal disorders	**Constipation**	**Common**

Additionally the warning related pneumonia is updated to reflect the clinical data of the CTT116855. The following paragraph is inserted.

In a 52-week study, with a total of 10,355 patients with COPD and a history of moderate or severe exacerbations within the prior 12 months (mean post-bronchodilator screening FEV_1 46% of predicted, SD 15%) (study CTT116855), the incidence of pneumonia was 8% (317 patients) for Elebrato Ellipta (n = 4,151), 7% (292 subjects) for fluticasone furoate/vilanterol (n = 4,134), and 5% (97 subjects) for umeclidinium/vilanterol (n = 2,070). Fatal pneumonia occurred in 12 of 4,151 patients (3.5 per 1,000 patient-years) receiving Elebrato Ellipta, 5 of 4,134 patients (1.7 per 1,000 patient-years) receiving fluticasone furoate/vilanterol, and 5 of 2,070 patients (2.9 per 1,000 patient-years) receiving umeclidinium/vilanterol.

Finally the section 5.1 is completely updated with the results of the clinical studies described in this application and the results of the PK studies are also included in section 5.2 of the SmPC.

As a consequence of this extension of indication, sections 4.1, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.8.1. User consultation

The changes to the package leaflet are minimal and do not require user consultation with target patient groups. These changes are 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 objective of this extension of indication application is to amend the indication of Trelegy Ellipta from the currently approved "step-up" indication to a more general maintenance in moderate to severe COPD patients thus remove the step up indication. The other changes to the product information are ancillary to this main objective, and are based on the results of the three studies summarised in this report.
The main phase 3 clinical studies supporting this application are one pivotal study CTT116855 and one supportive study 200812. A population PK report is also provided (study 208059).

Study CTT116855 was a randomised, double-blind, parallel-group study that compared the efficacy and safety of FF/UMEC/VI with FF/VI and UMEC/VI for 52 weeks in subjects with COPD. This study was designed to evaluate the benefit of FF/UMEC/VI over the FF/VI and UMEC/VI dual component medications in subjects with advanced, symptomatic COPD and at risk of exacerbation using a primary endpoint of the annual rate of on-treatment moderate/severe COPD exacerbations.

Study 200812 was a randomised, double blind, parallel group study comparing FF/UMEC/VI administered in one Ellipta inhaler with FF/VI + UMEC administered in separate Ellipta inhalers over 24 weeks in subjects with COPD. This study was designed to demonstrate the non-inferiority of FF/UMEC/VI to FF/VI+UMEC using a primary endpoint of trough FEV1 at Week 24 with a margin of non-inferiority of 50 mL

The population PK analysis (Study 208059) evaluated combined data from a subset of COPD patients that participated in 3 phase IIIa/b studies (CTT116855, CTT116853, 200812) to characterise the PK of FF, UMEC and VI following administration of FF/UMEC/VI from a single Ellipta inhaler and to assess the effect of covariates on the PK of FF, UMEC and VI.

In Study CTT116855, for the primary endpoint FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of on-treatment moderate/severe exacerbations compared with FF/VI and UMEC/VI [0.91 (0.87-0.95) in FF/UMEC/VI group, 1.07 (1.02-1.12) in FF/VI group and 1.21 (1.14-1.29) in UMEC/VI group ($p<0.001$ for both comparisons)]. The effect of FF/UMEC/VI on the annual rate of moderate/severe COPD exacerbations was maintained when both on- and off-treatment data were included in the analysis. For this analysis, FF/UMEC/VI demonstrated a statistically significant reduction in the annual rate of moderate/severe COPD exacerbations compared with FF/VI (11% reduction, $p<0.001$) and UMEC/VI (20% reduction, $p<0.001$).

FF/UMEC/VI demonstrated a statistically significant reduction in the risk of on-treatment all-cause mortality compared with UMEC/VI (HR: 0.58; 95% CI: 0.38, 0.88; $p=0.011$, corresponding to a risk reduction of 42.1%). For the comparison of FF/UMEC/VI and FF/VI, the risk of on treatment all-cause mortality was similar (HR: 0.95; 95% CI: 0.64, 1.40, $p=0.780$, corresponding to a risk reduction of 5.5%). When both on-and off treatment mortality data were included in the analysis, the significant risk reduction in all-cause mortality was maintained for FF/UMEC/VI compared with UMEC/VI.

3.2. Favourable effects

The results of the pivotal trial show that treatment with FF/UMEC/VI results in a significant reduction in the number of moderate or severe exacerbations when compared to either FF/VI or UMEC/VI. There were also significant improvements in many of the other symptomatic and lung function indices studied in the trial as secondary endpoints.

Overall, the data provided by the MAH also support the inclusion of symptomatic and exacerbation-related text in the indication, and could be used to justify the use of triple therapy as a step-up from ICS-containing dual therapy in patients not controlled on dual therapy.

3.3. Uncertainties and limitations about favourable effects

Although the improvement in terms of exacerbations was statistically significantly higher for FF/UMEC/VI compared to the dual combinations (FF/VI and UMEC/VI) the effects were only slightly higher compared to FF/VI. The change compared to FF/VI was 0.16 (model estimated exacerbation rate) and for severe COPD exacerbations showed only a difference of 0.02 compared to FF/VI. The clinical significance of the differences seen for both moderate to severe and severe exacerbations is debatable. Considering the efficacy and safety, the MAH proposed amendment of the indication to remove the step-up indication is not supported at this time based on the submitted data. An alternative text has been proposed and accepted, maintaining the step up indication from dual therapies.

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.

Based on the evaluation of AE data from study CTT116855 six additional ADRs are proposed for inclusion in the FF/UMEC/VI label: bronchitis, sinusitis, urinary tract infection (UTI), constipation, dysphonia, and dry mouth. In addition, changes in frequency are proposed for two existing ADRs in the FF/UMEC/VI label, based on the frequency reported in Study CTT116855: Candidiasis of mouth and throat from 'uncommon' to 'common' and Oropharyngeal pain from 'uncommon' to 'common', respectively.

In study 200812, the safety profile of FF/UMEC/VI in the treatment of COPD subjects was similar to that of FF/VI+UMEC and consistent with previous data for FF/UMEC/VI in a COPD population.

Referring to MACE events, from the submitted clinical data there is no evidence of an additive effect when UMEC and VI are administered together.

In study CTT116855, as expected there was a higher incidence of pneumonia in the FF/UMEC/VI group (298 subjects [7%]) and in the FF/VI group (264 subjects [6%]) compared with the UMEC/VI group (93 subjects [4%]). The pneumonia event rate per 1000 subjects were 88.6 in the FF/UMEC/VI group and 86.8 in the FF/VI group compared to 57.7 in the UMEC/VI group. The higher risk of pneumonia of about 35% comparing FF/UMEC/VI with UMEC/VI has to be taken into account when balancing the benefit against the risk.

When comparing the FF/UMEC/VI and FF/VI groups, the AEs with higher incidences (viral URTI, COPD, URTI, and pneumonia) had a similar risk for FF/UMEC/VI and FF/VI groups. When comparing the FF/UMEC/VI and UMEC/VI groups, the risk of COPD was lower for FF/UMEC/VI group while the risk of pneumonia and oral candidiasis was lower for UMEC/VI, as expected based on ICS class effects. This reflects the known adverse event profile of ICS medications, and has an impact on the substitution potential of the triple therapy versus the LAMA/LABA combinations. The update on pneumonia is reflected in the SmPC and an updated paragraph is added in section 4.8.

3.5. Uncertainties and limitations about unfavourable effects

Not applicable.

3.6. Effects Table

Table 32. Effects Table for Trelegy Ellipta

Effect	Short description	Unit	FF/UMEC/VI	FF/VI UMEC/VI	Uncertainties / Strength of evidence	References
Favourable Effects						
Exacer-bations	Annual rate of mod/severe exacerbations	Rate	0.91	- 1.21		Study CTT116855
Trough FEV1	Change from baseline	LS Mean change	0.094	- 0.040		
SGRQ	Change from baseline	LS Mean change	-5.5	- -3.7		
Unfavourable Effects						
Pneumonia		n (%)	312 (8%)	282 (7%) 95 (5%)	ICS-containing treatments are known to increase the risk of pneumonia in COPD patients.	Study CTT116855
MACE		n (%)	80 (2%)	60 (1%) 37 (2%)	There is no evidence of an additive effect when UMEC and VI are administered together.	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

For patients at risk of COPD exacerbations, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategy document for the management of patients with COPD recommends an incremental approach to therapy, beginning with either a LAMA, LAMA/LABA, or ICS/LABA therapy [GOLD, 2017]. If patients develop further exacerbations, escalation of pharmacologic therapy is recommended. For example, patients on LAMA therapy can be switched to a LAMA/LABA or ICS/LABA with further escalation to triple ICS/LAMA/LABA therapy or those on a dual therapy can be switched to triple therapy if required.

This clearly states that triple therapy is currently thought to be best used as an escalation therapy for those incompletely controlled with dual therapy, either ICS/LABA or LABA/LAMA. It does not suggest that patients with moderate to severe COPD should be commenced on triple therapy. That being said, the current GOLD guidelines are open regarding the evidence base on which these recommendations are based. As such, the MAH intention that triple therapy could be used as a first line is not supported, however the data support amendment of the proposed indication to reflect that it should be used as a step up from LABA/LAMA dual therapy.

Overall, the data provided by the MAH support the inclusion of references to symptomatic and exacerbation-related text in the indication, and could be used to justify the use of triple therapy as a step-up from both non ICS- and ICS-containing dual therapy in appropriate patients. Although the improvement in terms of exacerbations was statistically significantly higher for FF/UMEC/VI compared to the dual combinations (FF/VI and UMEC/VI) the effects were only slightly higher compared to FF/VI. The change compared to FF/VI was 0.16 (model estimated exacerbation rate) and for severe COPD exacerbations showed only a difference of 0.02 compared to FF/VI. The clinical significance of the

differences seen for both moderate to severe and severe exacerbations can be debated. Considering the efficacy and safety the proposed amendment of the indication is not supported at this time. An alternative text has been agreed as follows: "*Trelegy 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* ***or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist*** *(for effects on symptom control* ***and <u>on</u> exacerbations*** *see section 5.1)."*

From a safety point of view, concerns regarding the long-term use of ICS medication are well established. These concerns have been reflected in the investigation of newer LABA/LAMA combinations over the recent past, and are further reflected in the GOLD guidelines. Amongst other things, pneumonia is associated with long-term ICS use, and this adverse event was also found in the clinical studies provided by the applicant to support this variation application. Of note, there were significant differences between the rates of pneumonia between the FF/UMEC/VI and UMEC/VI groups, whereas there was no difference between the FF/UMEC/VI and FF/VI groups. This finding suggests that, while there may be a benefit of FF/UMEC/VI over UMEC/VI in terms of the effect on exacerbations, this is offset to some degree by the increased risk of pneumonia in the former. There was no significant difference in the risk of pneumonia between the ICS-containing groups.

3.7.2. Balance of benefits and risks

Not applicable.

3.8. Conclusions

The overall B/R of Trelegy Ellipta is positive as in patients not adequately treated by a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist treatment. The indication is amended as follows: "*Trelegy 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* ***or a combination of a long-acting β2-agonist and a long-acting muscarinic antagonist*** *(for effects on symptom control* ***and <u>on</u> exacerbations*** *see section 5.1)."*

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

To modify the approved current COPD therapeutic indication to include the possibility to use Trelegy Ellipta and Elebrato Ellipta as maintenance treatment in patients not adequately treated by dual LABA/LAMA therapy. Additionally cross reference to the effects on symptoms is added. This is based on the results of study CTT116855 and study 200812 and the population PK report 208059.
As a consequence, the indication section (4.1), Undesirable effects section (4.8), Pharmacodynamic Properties section (5.1), Pharmacokinetic properties section (5.2) and Preclinical Safety data section (5.3) of the SmPC have been updated. The package leaflet and RMP (v2.1) has been updated accordingly.

The worksharing procedure leads to amendments to the Summary of Product Characteristics and Package Leaflet. A minor amendment in annex II is also introduced to bring it in line with the QRD template.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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

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

Risk management plan (RMP)

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

In addition, 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.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

To modify the approved current COPD therapeutic indication to include the possibility to use Trelegy Ellipta and Elebrato Ellipta as maintenance treatment in patients not adequately treated by dual LABA/LAMA therapy. Additionally cross reference to the effects on symptoms is added. This is based on the results of study CTT116855 and study 200812 and the population PK report 208059.
As a consequence, the indication section (4.1), Undesirable effects section (4.8), Pharmacodynamic

Properties section (5.1), Pharmacokinetic properties section (5.2) and Preclinical Safety data section (5.3) of the SmPC have been updated. The package leaflet has been updated accordingly.
A minor amendment in annex II is also introduced to bring it in line with the QRD template. Additionally, minor changes have been introduced to the RMP to bring it in line with the new template (revision 2).

Summary

Please refer to the published assessment report Elebrato Ellipta-Trelegy Ellipta-WS-1369: EPAR - Assessment Report – Variation.