10 March 2020
EMA/198723/2020
Committee for Medicinal Products for Human Use (CHMP)

Type II variation assessment report

Procedure No. EMEA/H/C/WS1683

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/WS1683/0012
Trelegy Ellipta	fluticasone furoate / umeclidinium / vilanterol	EMEA/H/C/004363/WS1683/0010
Temybric Ellipta	fluticasone furoate / umeclidinium / vilanterol	EMEA/H/C/005254/WS1683/0001

Worksharing MAH (WSA): GlaxoSmithKline Trading Services Limited

Note

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

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	19 Aug 2019	19 Aug 2019	☐
☐	CHMP Rapporteur Assessment Report	23 Sep 2019	24 Sep 2019	☐
☐	CHMP members comments	07 Oct 2019	07 Oct 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	10 Oct 2019	10 Oct 2019	☐
☐	Request for supplementary information	17 Oct 2019	17 Oct 2019	☐
☐	Submission	12 Nov 2019	11 Nov 2019	☐
☐	Re-start	13 Nov 2019	13 Nov 2019	☐
☐	CHMP Rapporteur Assessment Report	27 Nov 2019	26 Nov 2019	☐
☐	CHMP members comments	02 Dec 2019	02 Dec 2019	☐
☐	Updated CHMP Rapporteur Assessment Report	05 Dec 2019	05 Dec 2019	☐
☐	Request for supplementary information	12 Dec 2019	12 Dec 2019	☐
☐	Submission	28 Jan 2020	28 Jan 2020	☐
☐	Re-start	29 Jan 2020	29 Jan 2020	☐
☐	CHMP Rapporteur Assessment Report	12 Feb 2020	12 Feb 2020	☐
☐	CHMP members comments	17 Feb 2020	17 Feb 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Feb 2020	19 and 20 Feb 2020	☐
☐	Oral Explanation/Opinion	25 Feb 2020	25 Feb 2020	☐
☒	Opinion	27 Feb 2020	27 Feb 2020	☐

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1. Background information on the procedure

Trelegy Ellipta, Elebrato Ellipta (Fluticasone furoate / umeclidinium / vilanterol FF/UMEC/VI) once-daily was approved in the European Union (EU) on 15 November 2017 and on 12 June 2019 for Temybric Ellipta (Fluticasone furoate / umeclidinium / vilanterol FF/UMEC/VI) .
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 (ICS) and long-acting beta2-adrenergic agonist (LABA) or by a LABA and long acting muscarinic antagonist (LAMA) combination. FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity, UMEC is a LAMA and VI is a selective LABA.

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, GlaxoSmithKline Trading Services Limited submitted to the European Medicines Agency on 22 July 2019 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of SmPC in order to add information in section 5.1 on survival data from the IMPACT study.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics.

Rationale for the proposed change

The purpose of this variation application is to update the license for Trelegy Ellipta, Elebrato Ellipta and Temybric Ellipta to provide information relating to the effect of FF/UMEC/VI on all-cause mortality in patients with COPD. Specific revisions to the SmPC are proposed for Section 5.1 Pharmacodynamic properties.

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. The majority of these data have previously been presented as part of related variation procedure, however the MAH has made additional efforts to gather data on the survival status for patients who withdrew from the study prior to Week 52. These efforts have resulted in 99.6% of the originally enrolled patients being represented in the current dataset.

Additional supportive data from related studies have also been presented, but these are considered to be only indicative and so will only be briefly discussed in this report.

GLP/GCP Inspections

No non-clinical/clinical study sites were inspected in connection to this variation. Any GCP queries for the relevant trials have been addressed during previous assessment procedures.

2. Scientific discussion

2.1. Introduction

Fluticasone furoate/umeclidinium bromide/vilanterol Inhalation Powder 100/62.5/25 micrograms (mcg)

(hereafter referred to as FF/UMEC/VI) is an inhaled corticosteroid (ICS), long-acting muscarinic receptor antagonist (LAMA), long-acting beta2-adrenergic receptor agonist (LABA) combination product for once-daily oral inhalation. Each single inhalation provides a delivered dose of FF 92mcg, UMEC 55mcg and VI 22mcg.

FF/UMEC/VI (Trelegy Ellipta, Elebrato Ellipta and Temybric 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.

GlaxoSmithKline (GSK) is submitting this application to update the marketing authorisation for both Trelegy, Elebrato and Temybric, based on additional data on censored patients from study CTT116855. 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.

Time to death from any cause was listed under 'other' efficacy endpoints (not listed under secondary endpoints) and was not included in the confirmatory testing strategy. Hospitalisation was listed as health outcome endpoint. At the time of the original conclusion of the study, a minority of patients (5.5%) had withdrawn from the study prior to the Week 52 cut-off, and as a result data regarding the survival status of these missing patients were not included in the original Clinical Sturdy Report. Since then, the MAH has made an effort to find out as best as possible the status of these patients, and as a result of these efforts survival status data at week 52 for 99.6% % of the subjects initially enrolled in the trial is now available for analysis.

2.2. Clinical aspects

The MAH's request for update of the product information is based on the updated CSR for study CTT116855. Supporting data on All-Cause Mortality (ACM) from 4 related trials have also been submitted.

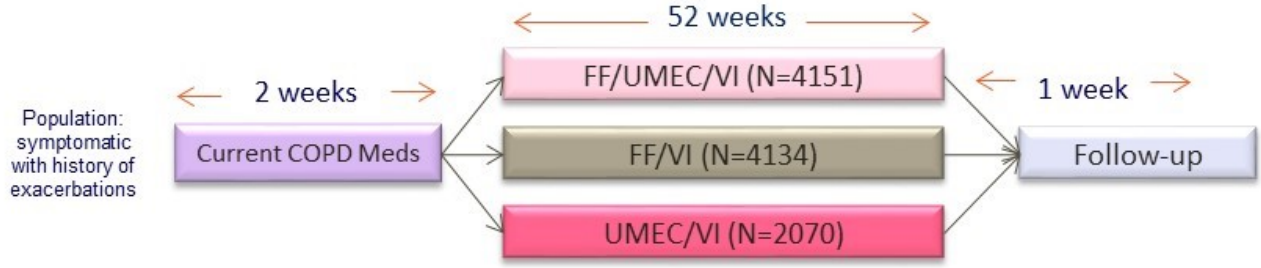
Study design

The IMPACT 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.

Study Schematic



Treatment with FF/UMEC/VI resulted in a statistically significant 42.1% reduction in the risk of on-treatment ACM compared with UMEC/VI. Similar statistically significant findings, though of smaller magnitude, were observed when off- treatment data were also included in the analysis (28.6% reduction in risk). The MAH acknowledged that caution was warranted in interpretation of the analysis of ACM that included on- and off-treatment data as reported in the main CSR given the proportion of subjects with missing vital status data at nominal Week 52 (n=574; 5.5% of overall population) that were censored in the analysis.

In order to confirm the robustness of the ACM findings, the MAH performed a retrospective collection of the missing vital status data and post-hoc analyses of time to ACM using a more complete dataset where survival status at nominal Week 52 was obtained for 99.6% of the Intent-to-Treat (ITT) Population (i.e., n= 42, 0.4% of vital status data remain missing at Week 52). No safety assessments were performed, and no safety data were collected as part of this initiative.

Dose Selection

The FF/UMEC/VI dose of 100/62.5/25 mcg used in Study CTT116855 was selected based on the doses of UMEC (62.5 mcg), UMEC/VI (62.5/25 mcg), and FF/VI (100/25 mcg) that have been approved for COPD in the US, EU, and other countries worldwide. These doses correspond to single inhalation delivered doses of FF 92 mcg, UMEC 55 mcg and VI 22 mcg.

Study population

Study CTT116855 was designed to assess benefit on exacerbations, and so 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, and 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.

Outcomes/endpoints

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.

Secondary endpoints included changes in FEV1 and SGRQ at week 52, and rate of and time to exacerbations of various severity. All-cause mortality at week 52 was also assessed, but as a minority of patients were withdrawn prior to week 52 the MAH thought that these missing data could undermine the reliability of this assessment.

Safety endpoints were appropriate for the condition and the interventions.

Table 1 Overview of Study CTT116855

An overview of the study is contained in the table below;

Study	Treatment Details (mcg)	Study Design/ Duration	Population	Endpoints
CTT116855	FF/UMEC/VI 100/62.5/25, FF/VI 100/25, UMEC/VI 62.5/25 2:2:1 randomization Once-daily dosing	R, DB, PG, MC, AC 2 week run-in on existing maintenance COPD medications, followed by 52-week treatment period Subjects who discontinued study treatment could remain in the study for the collection of key efficacy and safety data ITT Population = 10,355	COPD diagnosis ≥ 40 years of age ≥ 10 pack-year history of cigarette smoking Post bronchodilator FEV_1/FVC ratio <0.70 Post bronchodilator FEV_1 <50% predicted normal and a documented history of ≥ 1 moderate or severe COPD exacerbation in the previous 12 months ***or*** post bronchodilator FEV_1 ≥50% to <80% predicted normal and ≥2 moderate exacerbations or ≥1 severe (hospitalized) exacerbation in past 12 months Daily maintenance treatment for COPD for at least 3 months Score ≥10 on the CAT	Primary Efficacy Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI and FF/VI Key secondary efficacy endpoints (included in testing hierarchy) Change from baseline trough FEV_1 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 Other secondary efficacy endpoints (not included in testing hierarchy) 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 ≥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 ≥ 150 cells/µl Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI Other relevant efficacy endpoints (not included in testing hierarchy) **Time to ACM (on-treatment)** **Time to ACM (on- and off-treatment)** **Time to first on-treatment severe exacerbation** Safety AEs, AESI, ECGs, vital signs, clinical laboratory assessments

AC=active-controlled; ACM=all-cause mortality; AE=adverse event; AESI=adverse event of special interest; CAT=COPD Assessment Test; COPD=chronic obstructive pulmonary disease; DB=double-blind; ECG=electrocardiograms; FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC=forced vital capacity; ITT=Intent-To-Treat; MC=multicenter; PG=parallel group; R=randomized; SGRQ=St. George's Respiratory Questionnaire; TDI=Transition Dyspea Index; UMEC=umeclidinium; VI=vilanterol

Populations for Analysis of ACM

The following ITT Populations are considered to be of relevance:

1. The pre-specified ITT data for on-treatment only, designated "ITT"
2. The pre-specified ITT data plus vital status (VS) data including off-treatment data covering 94.5% of the randomized population at nominal Week 52 as presented in the original CSR, designated "ITT+VS."

3. The ITT+VS plus the vital status follow-up data from retrospective collection (VSFU) (on- and off-treatment) covering 99.6% of the randomized population at nominal Week 52, designated "ITT+VS+VSFU."

Table 2 Analysis Populations and Nomenclature for Post-Hoc Evaluations of ACM

Definition/Criteria	Analyses Evaluated	Analysis Nomenclature	Rationale for Population
Intent-to-Treat Population			
As defined for the CTT116855 main CSR: Comprised of all randomized subjects, excluding those who were randomized in error who did not receive a dose of study medication. A subject who was recorded as a screen or run-in failure and also randomized, but did not receive a dose of study treatment, was considered to be randomized in error. Any other subject who received a randomization number was considered to have been randomized.	On-treatment and on- and off-treatment ACM and severe exacerbations Sensitivity for ACM, on- and off-treatment including additional vital status collected	On-treatment: ITT On- and off-treatment: ITT+VS On- and off treatment, including additional vital status follow- up: ITT+VS+VSFU	To confirm the findings from the ITT data reported in the main CSR

Statistical Considerations for Efficacy Analyses

The main treatment comparisons of interest were FF/UMEC/VI compared with FF/VI and FF/UMEC/VI compared with UMEC/VI; however, the treatment comparison of UMEC/VI compared with FF/VI and the reverse comparison of FF/VI with UMEC/VI were also performed.

For ACM, the following efficacy analyses were pre-specified in CTT116855

- Time to on-treatment ACM (ITT)
- Time to ACM including on- and off-treatment data (ITT+VS)

Sub-group analyses were also performed for gender, race, region and BMI.Post-hoc analyses for ACM included;

- Time to ACM including on- and off-treatment data (ITT+VS+VSFU)
- Subgroup analyses of time to ACM on the basis of triple therapy use at Screening (yes/no) and ICS-containing medication use at Screening (yes/no) for ITT, ITT+VS, and ITT+VS+VSFU.
- Subgroup summaries of time to ACM by age, gender, and race (ITT+VS+VSFU)
- Additional missing data sensitivity analyses including imputation under MAR and tipping point analyses.

A Cox proportional hazards (PH) model was used for the primary analysis of time to ACM, with covariates of gender and age at Screening. Kaplan-Meier figures showing cumulative incidence of the proportion of subjects with an event over time for each treatment group were also presented.

Adjudication Committee

The protocol had an adjudication committee which was established to independently review and categorize the cause of each Serious Adverse Event (including deaths). The committee members remained blinded to treatment. The adjudication plan was described in the charter.

Baseline Characteristics

Baseline demographic characteristics were similar across the treatment groups and between the ITT and the Intention to Treat – Efficacy (ITT-E) analysis populations. The ITT-E population was based on the ITT population but excluded subjects recruited in Germany, Poland, Spain, Russian Federation, Republic of Korea, Japan, New Zealand, and Canada where ≥1 subject withdrew from participating in the study as well as withdrew consent to further collection of health information and did not reconsent for follow-up vital status collection. The results for the ITT-E population were consistent with those displayed for the ITT Population and are not discussed further in this report.

Table 3 Demographics (Study CTT116855, ITT and ITT-E Populations)

	ITT Population				ITT-E Population
Demographic Characteristic	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	Total N=10,009
Gender, n (%)					
n	4151	4134	2070	10,355	10,009
Male	2766 (67)	2748 (66)	1356 (66)	6870 (66)	6612 (66)
Female	1385 (33)	1386 (34)	714 (34)	3485 (34)	3397 (34)
Age[1], years					
n	4151	4134	2070	10,355	10,009
Mean	65.3	65.3	65.2	65.3	65.3
SD	8.24	8.30	8.26	8.27	8.29
Median	65.0	66.0	65.0	65.0	65.0
Min, Max	40, 90	40, 91	40, 94	40, 94	40, 94
Age Group (years), n (%)					
≤64[2]	1886 (45)	1876 (45)	962 (46)	4724 (46)	4556 (46)
65-74	1700 (41)	1693 (41)	832 (40)	4225 (41)	4079 (41)
75-84	530 (13)	537 (13)	261 (13)	1328 (13)	1299 (13)
≥85	35 (<1)	28 (<1)	15 (<1)	78 (<1)	75 (<1)
Race, n (%)					
n	4151	4133	2070	10,354	10,008
American Indian or Alaska Native	87 (2)	86 (2)	45 (2)	218 (2)	217 (2)
Asian – Central/South Asian	6 (<1)	3 (<1)	1 (<1)	10 (<1)	10 (<1)
Asian – East Asian	362 (9)	374 (9)	177 (9)	913 (9)	870 (9)
Asian – Japanese	151 (4)	152 (4)	82 (4)	385 (4)	382 (4)
Asian – South East Asian	149 (4)	147 (4)	75 (4)	371 (4)	371 (4)
Black or African American	122 (3)	99 (2)	43 (2)	264 (3)	264 (3)
Native Hawaiian or other Pacific Islander	2 (<1)	3 (<1)	2 (<1)	7 (<1)	7 (<1)
White – Arabic/North African	31 (<1)	45 (1)	24 (1)	100 (<1)	97 (<1)
White – White/Caucasian/ European	3200 (77)	3179 (77)	1604 (77)	7983 (77)	7687 (77)
Mixed Asian	0	0	0	0	0
Mixed White	0	0	0	0	0
Multiple	41 (<1)	45 (1)	17 (<1)	103 (<1)	103 (1)
Ethnicity, n (%)					
n	4151	4133	2070	10,354	10,008
Not Hispanic/Latino	3490 (84)	3471 (84)	1732 (84)	8693 (84)	8347 (83)
Hispanic/Latino	661 (16)	662 (16)	338 (16)	1661 (16)	1661 (17)
BMI, kg/m²					
n	4148	4134	2070	10,352	10,006
Mean	26.61	26.66	26.58	26.62	26.62
SD	6.216	6.081	5.873	6.094	6.103
Median	25.79	25.98	25.86	25.88	25.86
Min, Max	12.4, 66.0	12.6, 59.3	13.9, 52.1	12.4, 66.0	12.4, 66.0

Source: CTT116855 supplementary CSR ACM SRAP Table 1.02 and CTT116855 main CSR RAP Table 1.13

1. Only year of birth was collected. Age was derived at the date of the Pre-Screening Visit. Day and month of birth were imputed as 30 June.
2. Subjects in this age group had to be at least 40 years old.

BMI=body mass index; FF=fluticasone furoate; ITT-Intent-to-Treat; ITT-E=Intent-to-Treat – Efficacy; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium; VI=vilanterol

COPD exacerbation history at Screening was similar across treatment groups. A total of 55% of subjects had ≥2 moderate or severe COPD exacerbations in the prior year, and 22% had 1 severe COPD exacerbation in the prior year. Few subjects (4%) had ≥2 severe COPD exacerbations in the prior year.

Table 4 COPD Exacerbation History at Screening (Study CTT116855, ITT and ITT-E Populations)

COPD Exacerbations reported in the 12 months prior to Screening	ITT Population, n (%)				ITT-E Population Total N=10,009
	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	
Moderate COPD exacerbations, n	4151	4134	2070	10,355	10,009
0	766 (18)	792 (19)	378 (18)	1936 (19)	1864 (19)
1	1418 (34)	1421 (34)	703 (34)	3542 (34)	3416 (34)
2	1622 (39)	1584 (38)	795 (38)	4001 (39)	3870 (39)
≥3	345 (8)	337 (8)	194 (9)	876 (8)	859 (9)
≥2	1967 (47)	1921 (46)	989 (48)	4877 (47)	4729 (47)
Severe COPD exacerbations, n	4151	4134	2070	10,355	10,009
0	3064 (74)	3065 (74)	1555 (75)	7684 (74)	7425 (74)
1	940 (23)	921 (22)	439 (21)	2300 (22)	2230 (22)
2	112 (3)	121 (3)	66 (3)	299 (3)	285 (3)
≥3	35 (<1)	27 (<1)	10 (<1)	72 (<1)	69 (<1)
≥2	147 (4)	148 (4)	76 (4)	371 (4)	354 (4)
Total Moderate/Severe exacerbations, n	4151	4134	2070	10,355	10,009
0	2 (<1)	5 (<1)	2 (<1)	9 (<1)	9 (<1)
1	1853 (45)	1907 (46)	931 (45)	4691 (45)	4519 (45)
2	1829 (44)	1768 (43)	890 (43)	4487 (43)	4338 (43)
≥3	467 (11)	454 (11)	247 (12)	1168 (11)	1143 (11)
≥2	2296 (55)	2222 (54)	1137 (55)	5655 (55)	5481 (55)

Source: CTT116855 supplementary CSR ACM SRAP Table 1.05 and CTT116855 main CSR RAP Table 1.44
Note: Moderate COPD exacerbation: required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization); Severe COPD exacerbation: required hospitalization.
COPD=chronic obstructive pulmonary disease; FF=fluticasone furoate; ITT=Intent-to-Treat; ITT-E=Intent-to-Treat – Efficacy; UMEC=umeclidinium; VI=vilanterol

Smoking status and history were similar across treatment groups. A total of 65 % were former smokers. The total population had a mean of 46.6 pack-years with a range of 5 to 271 pack-years.

Table 5 Smoking History at Screening (Study CTT116855, ITT and ITT-E Populations)

Smoking History	ITT Population				ITT-E Population
	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	Total N=10,009
Smoking status, n (%)					
n	4151	4134	2070	10,355	10,009
Current smoker	1436 (35)	1423 (34)	728 (35)	3587 (35)	3444 (34)
Former smoker	2715 (65)	2711 (66)	1342 (65)	6768 (65)	6565 (66)
Years smoked					
n	4151	4134	2070	10,355	10,009
Mean	38.8	38.9	38.8	38.8	38.8
SD	10.96	10.82	10.81	10.87	10.90
Median	40.0	40.0	40.0	40.0	40.0
Min, Max	5, 71	8, 70	6, 70	5, 71	5, 71
Number of pack years [1]					
n	4151	4134	2070	10,355	10,009
Mean	46.7	46.4	47.0	46.6	46.6
SD	26.73	26.15	27.41	26.64	26.73
Median	40.0	40.0	41.0	40.0	40.0
Min, Max	10, 271	5, 240	10, 250	5, 271	5, 271

Source: CTT116855 supplementary CSR ACM SRAP Table 1.03 and ACM SRAP Table 1.04; CTT116855 main CSR RAP Table 1.34 and RAP Table 1.37

Note: Former smokers were defined as subjects who had not smoked for >6 months prior to the visit.

1. Pack years= (Number of cigarettes smoked per day/20) x number of years smoked

FF=fluticasone furoate; ITT=Intent-to-Treat; ITT-E=Intent-to-Treat – Efficacy; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium; VI=vilanterol

Lung function at Screening was similar across treatment groups. The mean post-bronchodilator FEV1 was 1.272 L with a mean percent predicted post-bronchodilator FEV1 of 45.5%. A total of 82% of subjects were not reversible to salbutamol.

Table 6 Screening Lung Function Tests (Study CTT116855, ITT and ITT-E Populations)

Lung Function Measures	ITT Population				ITT-E Population
	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	Total N=10,009
Pre-bronchodilator					
FEV_1 (L), n	4146	4133	2069	10,348	10,002
Mean	1.170	1.163	1.167	1.166	1.162
SD	0.4680	0.4681	0.4643	0.4673	0.4667
Median	1.100	1.090	1.090	1.090	1.090
Min, Max	0.28, 3.24	0.23, 3.37	0.21, 3.36	0.21, 3.37	0.21, 3.37
FEV_1/FVC ratio, n	4146	4133	2069	10,348	10,002
Mean	0.462	0.461	0.464	0.462	0.462
SD	0.1188	0.1192	0.1213	0.1195	0.1198
Median	0.456	0.455	0.457	0.456	0.456
Min, Max	0.17, 1.00	0.11, 1.00	0.19, 0.94	0.11, 1.00	0.11, 1.00
% predicted FEV_1, n	4144	4133	2068	10,345	9999
Mean	41.9	41.6	41.8	41.8	41.7
SD	14.58	14.45	14.36	14.48	14.49
Median	40.4	40.1	40.4	40.3	40.2
Min, Max	10, 98	7, 100	11, 85	7, 100	7, 100
Post-bronchodilator					
FEV_1 (L), n	4145	4133	2069	10,347	10,001
Mean	1.275	1.272	1.268	1.272	1.269
SD	0.4881	0.4864	0.4812	0.4860	0.4857
Median	1.210	1.210	1.200	1.200	1.200
Min, Max	0.32, 3.24	0.29, 3.51	0.28, 3.42	0.28, 3.51	0.28, 3.51
FEV_1/FVC ratio, n	4145	4133	2069	10,347	10,001
Mean	0.470	0.469	0.472	0.470	0.470
SD	0.1189	0.1191	0.1221	0.1196	0.1199
Median	0.467	0.464	0.462	0.465	0.464
Min, Max	0.15, 0.89	0.14, 0.86	0.17, 0.95	0.14, 0.95	0.14, 0.95
% predicted FEV_1, n	4145	4133	2069	10,347	10,001
Mean	45.7	45.5	45.4	45.5	45.5
SD	14.98	14.78	14.68	14.84	14.85
Median	44.5	44.3	44.1	44.3	44.3
Min, Max	11, 98	10, 100	14, 83	10, 100	10, 100
% reversibility to salbutamol, n	4144	4133	2068	10,345	9999
Mean	10.36	10.81	9.89	10.44	10.48
SD	12.374	12.555	12.046	12.386	12.403
Median	8.14	8.70	7.80	8.33	8.33
Min, Max	-58.6, 119.6	-53.3, 124.8	-55.4, 121.0	-58.6, 124.8	-58.6, 124.8

Source: CTT116855 supplementary CSR ACM SRAP Table 1.06 and CTT116855 main CSR RAP Table 1.50

FEV_1=forced expiratory volume in 1 second; FF=fluticasone furoate; FVC= forced vital capacity; ITT=Intent-to-Treat; ITT-E=Intent-to-Treat – Efficacy; Max=maximum; Min=minimum; SD=standard deviation; UMEC=umeclidinium; VI=vilanterol

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%), hypercholesterolemia (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.

Table 7 Cardiovascular Risk Factors (Study CTT116855, ITT Population)

CV Risk Parameter	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
CV Risk Factors [1]				
Any CV Risk Factor				
n	4151	4134	2070	10,355
Yes	2786 (67)	2812 (68)	1414 (68)	7012 (68)
No	1365 (33)	1322 (32)	656 (32)	3343 (32)
No. of CV Risk Factors				
n	4151	4134	2070	10,355
0	1365 (33)	1322 (32)	656 (32)	3343 (32)
1	1147 (28)	1158 (28)	580 (28)	2885 (28)
≥2	1639 (39)	1654 (40)	834 (40)	4127 (40)
CV Risk Factor				
Hypertension	2132 (51)	2207 (53)	1107 (53)	5446 (53)
Hypercholesterolaemia	1354 (33)	1332 (32)	681 (33)	3367 (33)
Diabetes mellitus	641 (15)	645 (16)	313 (15)	1599 (15)
Coronary artery disease	510 (12)	488 (12)	254 (12)	1252 (12)
Arrhythmia	335 (8)	323 (8)	158 (8)	816 (8)
Angina pectoris	291 (7)	307 (7)	139 (7)	737 (7)
Myocardial infarction	270 (7)	274 (7)	137 (7)	681 (7)
Congestive heart failure	223 (5)	192 (5)	124 (6)	539 (5)
Cerebrovascular accident	199 (5)	165 (4)	94 (5)	458 (4)
Vascular disease [2]	133 (3)	148 (4)	61 (3)	342 (3)
Family History of CV Risk Factors [3]				
Premature CAD (premature = women <65 years, men <55 years)				
n	4151	4134	2070	10,355
Yes	432 (10)	430 (10)	234 (11)	1096 (11)
No	3160 (76)	3097 (75)	1529 (74)	7786 (75)
Unknown	559 (13)	607 (15)	307 (15)	1473 (14)
Myocardial Infarction				
n	4151	4134	2070	10,355
Yes	651 (16)	673 (16)	361 (17)	1685 (16)
No	3004 (72)	2954 (71)	1431 (69)	7389 (71)
Unknown	496 (12)	507 (12)	278 (13)	1281 (12)
Stroke				
n	4151	4134	2070	10,355
Yes	448 (11)	464 (11)	230 (11)	1142 (11)
No	3191 (77)	3150 (76)	1565 (76)	7906 (76)
Unknown	512 (12)	520 (13)	275 (13)	1307 (13)

Source: CTT116855 main CSR RAP Table 1.28 and RAP Table 1.31

1. Includes past or current medical conditions recorded at Screening.
2. Carotid or aorto-femoral
3. History in first degree relatives only (biological mother or father, brother or sister, son or daughter)

CAD=coronary artery disease; CV=cardiovascular; FF=fluticasone furoate; ITT=Intent-to-Treat;UMEC=umeclidinium; VI=vilanterol

The percentages of subjects taking each COPD medication class combination at Screening were similar across treatment groups. As expected, given the severity of the study population, the majority of subjects were using combination therapies that included an ICS, the most predominant being open-triple (38%) and ICS/LABA therapies (29%). Ten percent (10%) of subjects were not taking an ICS, LABA, or LAMA at Screening.

Table 8 Summary of Number of Subjects by COPD Medication Class at Screening (Study CTT116855, ITT Population)

Medication Combination	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
n	4151	4134	2070	10355
ICS + LABA + LAMA	1581 (38)	1563 (38)	826 (40)	3970 (38)
ICS + LABA without LAMA	1220 (29)	1177 (28)	576 (28)	2973 (29)
LAMA + LABA without ICS	361 (9)	331 (8)	187 (9)	879 (8)
ICS + LAMA without LABA	45 (1)	41 (<1)	19 (<1)	105 (1)
LAMA without LABA or ICS	288 (7)	346 (8)	146 (7)	780 (8)
ICS without LABA or LAMA	125 (3)	127 (3)	60 (3)	312 (3)
LABA without ICS or LAMA	109 (3)	111 (3)	48 (2)	268 (3)
No ICS, LABA, or LAMA	422 (10)	438 (11)	208 (10)	1068 (10)

Source: CTT116855 supplementary ACM CSR SRAP Table 1.10

COPD= chronic obstructive pulmonary disease; FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=Intent-to-Treat; LABA= long-acting beta$_2$-adrenergic receptor agonist ; LAMA=long-acting muscarinic receptor antagonist; UMEC=umeclidinium; VI=vilanterol

While there was no specific mention of other non-COPD medication in the CSR, the balanced nature of the other baseline characteristics provides some reassurance that the treatment groups were unlikely to be unbalanced with regards to this aspect such that it would have had a significant effect on the ACM analysis. However, this was not stratified for in this study.

Table 9 Categories for Assignment of Primary Cause of Serious Adverse Reports/Deaths

Primary Serious Adverse Report	Subcategory
Cardiovascular	Sudden death (deaths only) Myocardial infarction/ischemic heart disease Congestive heart failure Stroke Haemorrhagic Thromboembolic Indeterminate Other cardiovascular cause
Respiratory	COPD exacerbation With evidence of pneumonia Without evidence of pneumonia Pneumonia/respiratory tract infection without COPD exacerbation Asthma associated Pulmonary embolism Other respiratory cause
Cancer	Lung Breast Colorectal Unknown primary Other cancer cause
Other	Not applicable
Unknown	Inadequate information Indeterminate

Results

Table 10 Summary of Efficacy Results for Study CTT116855

Endpoint	Unit	FF/UMEC/VI vs. FF/VI	FF/UMEC/VI vs. UMEC/VI
Primary Endpoint			
Annual rate of on-treatment moderate/severe exacerbations	% rate reduction	15%	25%
Key Secondary Efficacy Endpoints and Treatment Comparisons			
Change from baseline in trough FEV_1 at Week 52 comparing FF/UMEC/VI with FF/VI	Litres	0.097	N/A
Change from baseline in SGRQ Total Score at Week 52 comparing FF/UMEC/VI with FF/VI	Units	-1.8	N/A
Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI	% risk reduction	14.8%	16.0%
Additional Secondary Endpoint			
Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI	% rate reduction	13%	34%
Other Efficacy Endpoints – Exacerbations			
Annual rate of all on-treatment exacerbations (mild, moderate, severe)	% rate reduction	16%	25%
Annual rate of on-treatment moderate exacerbations	% rate reduction	16%	23%
Annual rate of on-treatment moderate/severe exacerbations requiring systemic/oral corticosteroids	% rate reduction	17%	33%
Annual rate of on-treatment moderate/severe exacerbations requiring antibiotics	% rate reduction	13%	13%
Time to first on-treatment mild/moderate/severe exacerbation	% risk reduction	15.3%	15.5%
Time to first on-treatment moderate exacerbations	% risk reduction	14.9%	13.5%
Time to first on-treatment moderate/severe exacerbations requiring systemic/oral corticosteroids	% risk reduction	16.0%	21.4%
Time to first on-treatment moderate/severe exacerbations requiring antibiotics	% risk reduction	12.3%	7.6%
Time to first on-treatment severe exacerbation	% risk reduction	11.2%	25.1%
Time to each on-treatment moderate/severe exacerbation	% risk reduction	13.7%	20.5%
Time to each on-treatment severe exacerbation	% risk	12.0%	25.2%

Other Efficacy Endpoints - All Cause Mortality			
Time to death from any cause (on-treatment only)	% risk reduction	5.5%	42.1%
Time to death from any cause (on and off treatment; original analysis with 5.5% of data censored at Week 52)	% risk reduction	10.3%	28.6%
Other Efficacy Endpoints - Lung Function			
Change from baseline in trough FEV1 at Week 52 FF/UMEC/VI with UMEC/VI)	Litres	N/A	0.054
Percentage of subjects with an increase from baseline in trough FEV1 ≥100mL at Week 52	Odds	2.07	1.64
Change from baseline in post-bronchodilator FEV1 at Week 52	Litres	0.110	0.039
FEV1 reversibility at Week 52	mL	12.5	-9.3
Change from baseline in trough FVC at Week 52	Litres	0.164	0.032
Change from baseline in post-bronchodilator FVC at Week 52	Litres	0.176	0.023
Other Efficacy Endpoints - Quality of Life			
Change from baseline in SGRQ Total score at Week 52 (FF/UMEC/VI with UMEC/VI)	Units	N/A	-1.8
Proportion of responders according to the SGRQ Total score at Week 52	Odds	1.41	1.41
Change from baseline in CAT score at Week 52	Units	-0.5	-0.4
Proportion of responders according to the CAT score at Week 52	Odds	1.24	1.28
TDI focal score at Week 52	Units	0.27	0.09
Proportion of responders according to TDI at Week 52	Odds	1.36	1.33
Subject global rating of activity limitation and subject global impression of change in activity limitation at Week 52	Odds	1.15	1.06
Subject global rating of severity of COPD and change in COPD severity at Week 52	Odds	1.27	1.15
Other Efficacy Endpoints – Diary			
Change from baseline in Mean Number of Occasions of use of rescue albuterol/salbutamol (occasions/day) at Weeks 49-52	occasions	-0.28	-0.30
Change from baseline in percentage of rescue-free days at Weeks 49-52	% rescue free days	5.2	4.4

Change from baseline in mean number of night-time awakenings per night due to COPD symptoms at Weeks 49-52	number awakenings	-0.05	-0.10
Change from baseline in the percentage of days symptoms stopped usual activities	% days	-2.1	-1.9

Table 11 Summary and Analysis of Time to On-treatment ACM and Annual Rate and Time to First On-Treatment Severe Exacerbation (Study CTT116855, ITT Population)

	FF/UMEC/VI 100/62.5/25	**FF/VI 100/25**	**UMEC/VI 62.5/25**
Time to On-treatment ACM			
Number of subjects with event, n (%)	50 (1.20)	49 (1.19)	39 (1.88)
KM probability of having an event (%) 95% CI	1.320 (0.999, 1.743)	1.309 (0.978, 1.750)	2.165 (1.585, 2.956)
Number of subjects included in the Cox proportional hazards model	4151	4134	2070
FF/UMEC/VI vs Column Hazard ratio [1] 95% CI Percentage reduction in risk [2] 95% CI p-value		0.95 (0.64, 1.40) 5.5% (-40.2%, 36.3%) 0.780	0.58 (0.38, 0.88) 42.1% (11.9%, 61.9%) 0.011
Annual Rate of On-treatment Severe Exacerbations			
Number of subjects Model-estimated exacerbation rate 95% CI	4145 0.13 (0.12, 0.14)	4133 0.15 (0.13, 0.16)	2069 0.19 (0.17, 0.22)
FF/UMEC/VI vs Column Rate ratio [3] 95% CI p-value Percentage reduction in rate [4] 95% CI		0.87 (0.76, 1.01) 0.064 13% (-1%, 24%)	0.66 (0.56, 0.78) <0.001 34% (22%, 44%)

Time to First On-treatment Severe Exacerbation			
Number of subjects with event (%)	447 (11)	461 (11)	272 (13)
Number of subjects without an event (censored) (%)	3704 (89)	3673 (89)	1798 (87)
KM probability of having event (%) 95% CI	11.7 (10.7, 12.8)	12.9 (11.8, 14.1)	14.8 (13.2, 16.5)
Number of subjects included in the Cox proportional hazards model	4145	4133	2069

All-cause mortality

Results of the pre-specified on-treatment analyses (ITT) and on- and off-treatment analyses (ITT+VS) of ACM-related endpoints (incidence of death and time to ACM) from the main CTT116855 CSR are presented for comparison with the results of the on- and off-treatment analyses including additional vital status follow-up data (ITT+VS+VSFU).

All of the on-treatment deaths in Study CTT116855 were previously identified and included in the pre-specified analyses of time to ACM for on-treatment data.

Pre-specified analyses from Study CTT116855 showed that treatment with FF/UMEC/VI provided reductions in the risk of on-treatment (42.1%; ITT) and on- and off-treatment (28.6%;

ITT+VS) ACM compared with UMEC/VI over 52 weeks; smaller reductions

were observed compared with FF/VI.

Post-hoc analyses based on 99.6% of missing vital status data reported that treatment with FF/UMEC/VI provided a reduction in the risk of on- and off-treatment ACM with additional vital status follow up (27.7%; ITT+VS+VSFU) compared with UMEC/VI; non-significant reductions were observed compared with FF/VI.

A 5.5% reduction in the risk of on-treatment ACM was observed for FF/UMEC/VI compared with FF/VI, though this difference was not statistically significant at the 5% level.

For all comparisons, the log rank p-value was consistent with the p-value from the Cox PH model.

Key findings from the analyses of time to ACM in Study CTT116855 are summarized for the ITT Population below.

Table 12 Summary of Key ACM Results (Study CTT116855, ITT Population)

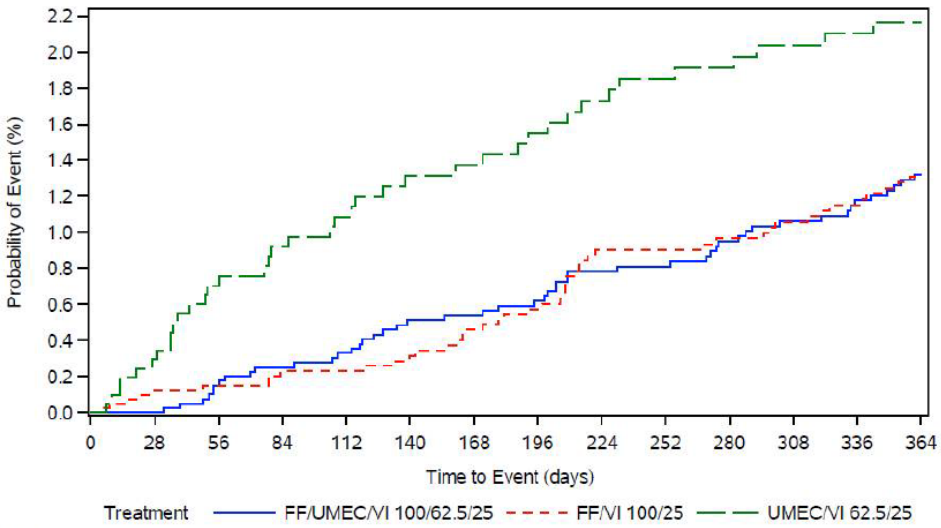
	FF/UMEC/VI 100/62.5/25 N=4151	FF/VI 100/25 N=4134	UMEC/VI 62.5/25 N=2070
On-treatment only[1] (ITT)			
Number of subjects included in the Cox proportional hazards model	**4151**	**4134**	**2070**
Number of subjects with event, n (%)	50 (1.20)	49 (1.19)	39 (1.88)
FF/UMEC/VI vs Column			
Hazard ratio (95% CI)[2]		0.95 (0.64, 1.40)	0.58 (0.38, 0.88)
p-value		0.780	0.011
Log-rank p-value		0.785	0.012
FF/VI vs UMEC/VI			
Hazard ratio (95% CI)[2]			0.61 (0.40, 0.93)
p-value			0.022
Log-rank p-value			0.023
On- and off-treatment (ITT+VS)[3]			
Number of subjects with event, n (%)	89 (2.14)	97 (2.35)	60 (2.90)
FF/UMEC/VI vs Column			
Hazard ratio (95% CI)[2]		0.90 (0.67, 1.20)	0.71 (0.51, 0.99)
p-value		0.458	0.043
Log-rank p-value		0.481	0.053
FF/VI vs UMEC/VI			
Hazard ratio (95% CI)[2]			0.80 (0.58, 1.10)
p-value			0.164
Log-rank p-value			0.175
On- and off-treatment (ITT+VS+VSFU)[4]			
Number of subjects with event, n (%)	98 (2.36)	109 (2.64)	66 (3.19)
FF/UMEC/VI vs Column			
Hazard ratio (95% CI)[2]		0.89 (0.67, 1.16)	0.72 (0.53, 0.99)
p-value		0.387	0.042
Log-rank p-value		0.405	0.048
FF/VI vs UMEC/VI			
Hazard ratio (95% CI)[2]			0.82 (0.60, 1.11)
p-value			0.190
Log-rank p-value			0.199

Source: CTT116855 supplementary CSR ACM SRAP Table 2.001, ACM SRAP Table 2.003, ACM SRAP Table 2.005, and ACM SRAP Table 2.007

1. On-treatment deaths are those which occurred between study treatment start date and 7 days after study treatment stop date, inclusive.
2. Hazard ratio and 95% CI are from a Cox proportional hazards model with covariates of treatment group, age, and sex.
3. On and off-treatment deaths are those which occurred between study treatment start date and 7 days after study treatment stop date (inclusive) for study treatment completers or up to the projected Week 52 date + 7 days for subjects that prematurely discontinued study treatment.
4. On and off-treatment deaths are those which occurred between study treatment start date and the latest of (study treatment stop date and the projected Week 52 date [based on treatment start date]) + 7 days, inclusive.

ACM=all-cause mortality; CI=confidence interval; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 1 Kaplan-Meier Plot of Time to On-treatment ACM (ITT) (Study CTT116855, ITT Population)



Incidence of Death (ITT Population)

The incidence of on-treatment deaths and on- and off-treatment deaths was lower in the FF/UMEC/VI and FF/VI groups compared with the UMEC/VI group. The ITT+VS+VSFU data set included a total of 27 additional off-treatment deaths that were identified in the collection of additional vital status information (9 in the FF/UMEC/VI group, 12 in the FF/VI group, and 6 in the UMEC/VI group). For the ITT+VS+VSFU comparisons, the risk of ACM was reduced for FF/UMEC/VI compared with UMEC/VI, corresponding to a 27.7% reduction. Smaller reductions in the risk of on- and off-treatment ACM were observed for FF/UMEC/VI compared with FF/VI and for FF/VI compared with UMEC/VI, with risk reductions corresponding to 11.3% and 18.5%, respectively; these differences were not statistically significant at the 5% level. For all ITT+VS+VSFU comparisons, the log rank p-value was consistent with the p-value from the Cox PH model.

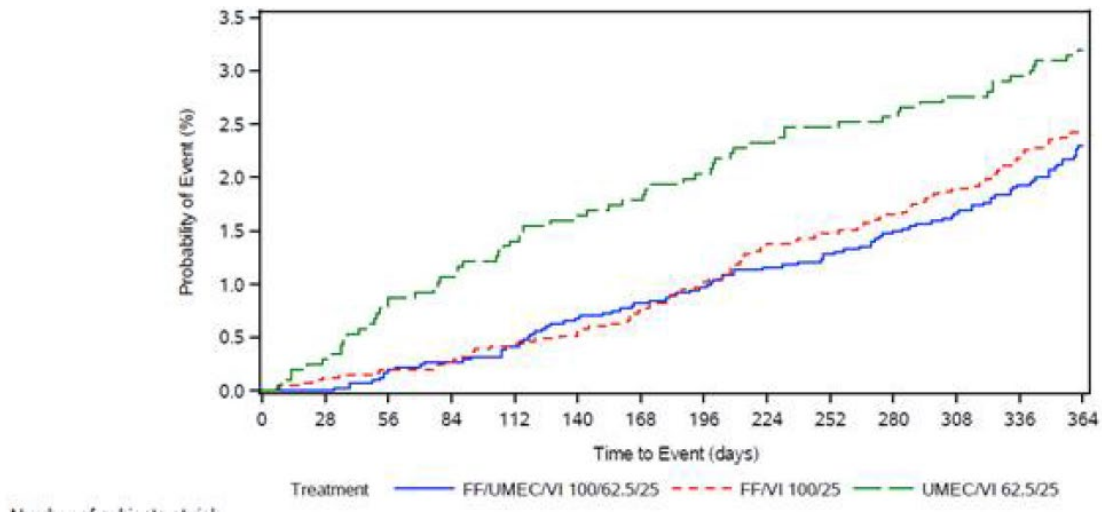
Table 13 Number (%) of Deaths from any Cause – On-Treatment Only, and On- and Off-Treatment (Study CTT116855, ITT Population)

	FF/UMEC/VI 100/62.5/25	FF/VI 100/25	UMEC/VI 62.5/25
	n (%)	n (%)	n (%)
ITT Population, N	4151	4134	2070
On-treatment Deaths (ITT)			
Number of subjects with event	50 (1.20)	49 (1.19)	39 (1.88)
On- and Off-treatment Deaths (ITT+VS)			
Number of subjects with event	89 (2.14)	97 (2.35)	60 (2.90)
On- and Off-treatment Deaths (ITT+VS+VSFU)			
Number of subjects with event	98 (2.36)	109 (2.64)	66 (3.19)

Source: CTT116855 supplementary CSR ACM SRAP Table 2.001, ACM SRAP Table 2.003, and ACM SRAP Table 2.005.

FF=fluticasone furoate; ITT=Intent-to-Treat; ITT=Intent-to-Treat – Efficacy; UMEC=umeclidinium; VI=vilanterol

Figure 2 Kaplan-Meier Plot of Time to ACM Including On- and Off Treatment Data (ITT+VS+VSFU) (Study CTT116855, ITT Population)



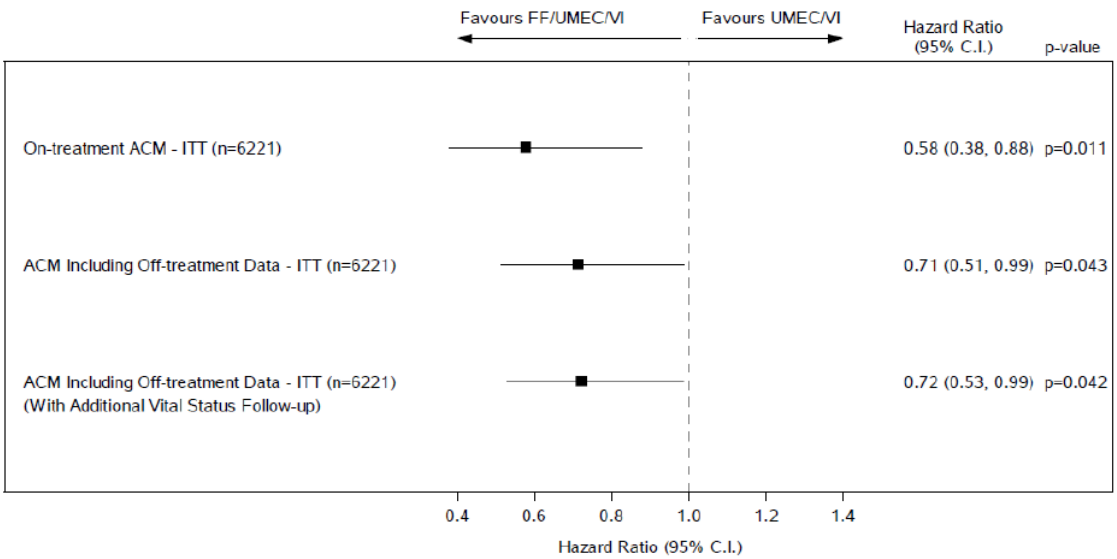
Summary of Analyses of Time to ACM

The populations analysed are described below : The pre-specified ITT data for on-treatment only, designated "ITT"

1. The pre-specified ITT data plus vital status (VS) data including off-treatment data covering 94.5% of the randomized population at nominal Week 52 as presented in the original CSR, designated "ITT+VS."
2. The ITT+VS plus the vital status follow-up data from retrospective collection (VSFU) (on- and off-treatment) covering 99.6% of the randomized population at nominal Week 52, designated "ITT+VS+VSFU."

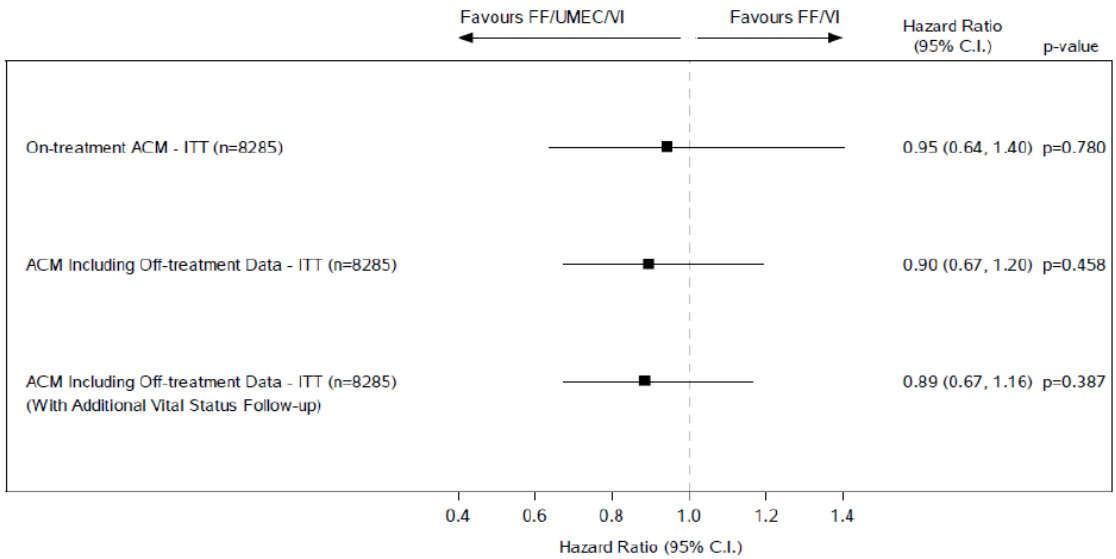
For the comparison of FF/UMEC/VI with UMEC/VI, the risk reductions in the risk of ACM observed in on- and off-treatment data with additional vital status follow-up ITT+VS+VSFU analyses were consistent with the results for on- treatment ACM (ITT) and on- and off-treatment ACM (ITT+VS).

Figure 3 Forest Plot Comparing ACM Results for FF/UMEC/VI with UMEC/VI (Study CTT116855, ITT Population)



Source: CTT116855 supplemental CSR ACM SRAP Figure 2.93
Note: n is the number of subjects in the analysis for the two treatment groups of interest.
Note: Analyses performed using a Cox proportional hazards model with covariates of treatment group, age, and sex.
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 4 Forest Plot Comparing ACM Results for FF/UMEC/VI with FF/VI (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.95
Note: n is the number of subjects in the analysis for the two treatment groups of interest.
Note: Analyses performed using a Cox proportional hazards model with covariates of treatment group, age and sex.
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 5 Forest Plot of On- and Off-treatment ACM (ITT+VS+VSFU) Results

Comparing Primary and Tipping Point Analyses for FF/UMEC/VI with UMEC/VI (Study CTT116855, ITT Population)

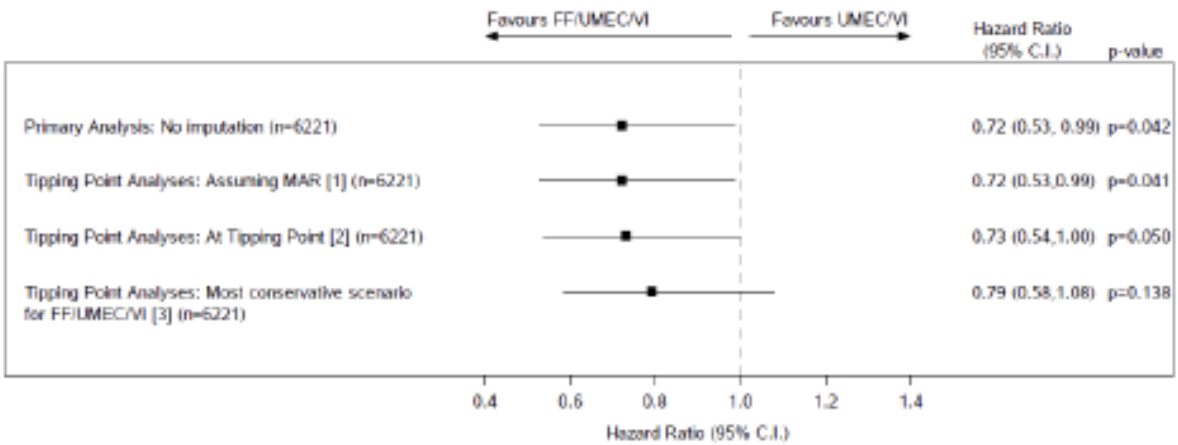


Table 14 Summary of On-treatment Adjudicated Cause of Death

	FF/UMEC/VI 100/62.5/25 (N=4151) n (%) Rate [#]	FF/VI 100/25 (N=4134) n (%) Rate [#]	UMEC/VI 62.5/25 (N=2070) n (%) Rate [#]
Total duration at risk (subject-years)	3780.6	3523.3	1730.9
Primary Cause of Death [1]			
Total	50 (1%) 13.2 [50]	49 (1%) 13.9 [49]	39 (2%) 22.5 [39]
Cardiovascular	16 (<1%) 4.2 [16]	21 (<1%) 6.0 [21]	15 (<1%) 8.7 [15]
Respiratory	15 (<1%) 4.0 [15]	12 (<1%) 3.4 [12]	9 (<1%) 5.2 [9]
Cancer	4 (<1%) 1.1 [4]	4 (<1%) 1.1 [4]	2 (<1%) 1.2 [2]
Unknown	11 (<1%) 2.9 [11]	8 (<1%) 2.3 [8]	11 (<1%) 6.4 [11]
Other	4 (<1%) 1.1 [4]	4 (<1%) 1.1 [4]	2 (<1%) 1.2 [2]
Death Associated with COPD			
Yes	18 (<1%) 4.8 [18]	14 (<1%) 4.0 [14]	15 (<1%) 8.7 [15]
No	20 (<1%) 5.3 [20]	24 (<1%) 6.8 [24]	11 (<1%) 6.4 [11]
Inadequate Information	7 (<1%) 1.9 [7]	6 (<1%) 1.7 [6]	9 (<1%) 5.2 [9]
Indeterminate	5 (<1%) 1.3 [5]	5 (<1%) 1.4 [5]	4 (<1%) 2.3 [4]
Cardiovascular			
Any Event	16 (<1%) 4.2 [16]	21 (<1%) 6.0 [21]	15 (<1%) 8.7 [15]
Sudden Death	12 (<1%) 3.2 [12]	15 (<1%) 4.3 [15]	11 (<1%) 6.4 [11]
Myocardial Infarction/Ischemic Heart Disease	0	2 (<1%) 0.6 [2]	0
Congestive Heart Failure	0	1 (<1%) 0.3 [1]	1 (<1%) 0.6 [1]
Stroke	2 (<1%) 0.5 [2]	3 (<1%) 0.9 [3]	1 (<1%) 0.6 [1]
Haemorrhagic	0	1 (<1%) 0.3 [1]	0
Thromboembolic	0	0	0
Indeterminate	2 (<1%) 0.5 [2]	2 (<1%) 0.6 [2]	1 (<1%) 0.6 [1]
Other Cardiovascular Cause	2 (<1%) 0.5 [2]	0	2 (<1%) 1.2 [2]
Respiratory			
Any Event	15 (<1%) 4.0 [15]	12 (<1%) 3.4 [12]	9 (<1%) 5.2 [9]
COPD Exacerbation	12 (<1%) 3.2 [12]	10 (<1%) 2.8 [10]	9 (<1%) 5.2 [9]
With Evidence of Pneumonia	5 (<1%) 1.3 [5]	2 (<1%) 0.6 [2]	4 (<1%) 2.3 [4]
Without Evidence of Pneumonia	7 (<1%) 1.9 [7]	8 (<1%) 2.3 [8]	5 (<1%) 2.9 [5]
Pneumonia/Respiratory Tract Infection without COPD Exacerbation	2 (<1%) 0.5 [2]	0	0

	FF/UMEC/VI 100/62.5/25 (N=4151)	FF/VI 100/25 (N=4134)	UMEC/VI 62.5/25 (N=2070)
Asthma Associated	0	0	0
Pulmonary Embolism	0	0	0
Other Respiratory Cause	1 (<1%) 0.3 [1]	2 (<1%) 0.6 [2]	0
Cancer			
Any Event	4 (<1%) 1.1 [4]	4 (<1%) 1.1 [4]	2 (<1%) 1.2 [2]
Lung	1 (<1%) 0.3 [1]	1 (<1%) 0.3 [1]	0
Breast	0	0	0
Colorectal	0	0	1 (<1%) 0.6 [1]
Unknown Primary	0	1 (<1%) 0.3 [1]	0
Other Cancer Cause	3 (<1%) 0.8 [3]	2 (<1%) 0.6 [2]	1 (<1%) 0.6 [1]
Unknown			
Any Event	11 (<1%) 2.9 [11]	8 (<1%) 2.3 [8]	11 (<1%) 6.4 [11]
Inadequate Information	9 (<1%) 2.4 [9]	5 (<1%) 1.4 [5]	7 (<1%) 4.0 [7]
Indeterminate	2 (<1%) 0.5 [2]	3 (<1%) 0.9 [3]	4 (<1%) 2.3 [4]

Table 15 Summary of Adjudicated Cause of Death Including Off-treatment Data

	FF/UMEC/VI 100/62.5/25 (N=4151)	**FF/VI 100/25 (N=4134)**	**UMEC/VI 62.5/25 (N=2070)**
		n (%) Rate [#]	**n (%) Rate [#]**
Total duration at risk (subject-years)	4088.3	4030.1	1999.3
Primary Cause of Death [1]			
Total	88 (2%) 21.5 [88]	92 (2%) 22.8 [92]	58 (3%) 29.0 [58]
Cardiovascular	26 (<1%) 6.4 [26]	31 (<1%) 7.7 [31]	20 (<1%) 10.0 [20]

Respiratory	25 (<1%) 6.1 [25]	26 (<1%) 6.5 [26]	18 (<1%) 9.0 [18]
Cancer	13 (<1%) 3.2 [13]	7 (<1%) 1.7 [7]	6 (<1%) 3.0 [6]
Unknown	14 (<1%) 3.4 [14]	14 (<1%) 3.5 [14]	11 (<1%) 5.5 [11]

Table 16 Summary of On-treatment ACM (ITT) Within 30 Days by Adjudicated Cause of Death (Study CTT116855, ITT Population)

Primary cause of death/Event type	**FF/UMEC/VI 100/62.5/25**	**FF/VI 100/25**	**UMEC/VI 62.5/25**
Within first 30 days			
Total	0	5 (0.12)	7 (0.34)
Cardiovascular Sudden death	0	2 (0.05)	5 (0.24)
Stroke/Indeterminate cause	0	1 (0.02)	3 (0.14)
Other cardiovascular cause	0	1 (0.02)	1
Respiratory	0	0	0
COPD exacerbation with evidence of pneumonia	0	0	2 (0.10)
Death associated with COPD	0	0	

Table 17 All-cause mortality endpoint in IMPACT

Treatment	**N**	***Number of deaths (%)***	**Hazard Ratio vs. Comparator (95% CI)**	**Reduction in Risk (95% CI)**	**p value**
Trelegy Ellipta	4,151	*98 (2.36)*			
UMEC/VI	2,070	*66 (3.19)*	0.72 (0.53, 0.99)	27.7% (1.2, 47.1)	0.042
FF/VI	4,134	*109 (2.64)*	0.89 (0.67, 1.16)	11.3%	0.387

Analyses of on-treatment all-cause mortality were also conducted, and results were consistent with the above results. Trelegy Ellipta significantly reduced the risk of on- treatment all-cause mortality by 42.1% (95% CI: 11.9, 61.9; p=0.011) compared with UMEC/VI. The reduction in risk of all-cause mortality was 5.5% (95% CI: -40.2, 36.3) with Trelegy Ellipta compared with FF/VI; however, this result was not statistically significant.

Subgroup analyses

The study transferred subjects from their previous maintenance therapy for COPD via randomization (2:2:1) to FF/UMEC/VI, FF/VI, or UMEC/VI. This design provides the opportunity to evaluate the impact of step down in therapy on the ACM findings using subgroup analysis for subjects switched from prior triple therapy to the FF/VI or UMEC/VI treatment groups, and for evaluation of the impact of abrupt withdrawal of ICS therapy using subgroup analysis of subjects switched from prior ICS therapy (used primarily in a combination with a LABA and/or LAMA) to the UMEC/VI treatment group.

Demographic and Baseline Characteristics by Triple and ICS Subgroups

A higher percentage of subjects (62%) were not on triple therapy at Screening than those who were on triple therapy at Screening (38%), while a higher percentage of subjects were taking ICS at Screening (71%) vs those who were not (29%).

Evaluation of baseline characteristics indicate greater disease severity for subjects on triple or ICS therapy vs those not on the corresponding therapy at Screening. Specifically, when comparing subjects on triple therapy vs not on triple therapy at Screening, those on triple therapy had a lower mean percent-predicted post- bronchodilator FEV1 (42.8% vs 47.3%), a higher percentage of subjects with GOLD grade 3 (52% vs 46%) and GOLD grade 4 (19% vs 14%), and a higher percentage of subjects with $\geq$1 severe exacerbation in the prior year (31% vs 23%). Similar results were shown for subjects on ICS vs those not on ICS at Screening.

Table 18 Baseline Characteristics by Subgroup (Study CTT116855, ITT Population)

Baseline Characteristic	N=10,355			
	On Triple Therapy at Screening	No Triple Therapy at Screening	ICS Use at Screening	No ICS Use at Screening
Number (%) of subjects at Screening	3970 (38)	6385 (62)	7360 (71)	2995 (29)
Age (years) [1], n	3970	6385	7360	2995
Mean (SD)	65.6 (8.11)	65.1 (8.36)	65.3 (8.23)	65.2 (8.36)
Gender, n	3970	6385	7360	2995
Male, n (%)	2598 (65)	4272 (67)	4813 (65)	2057 (69)
Smoking status, n	3970	6385	7360	2995
Current smoker, n (%)	1231 (31)	2356 (37)	2408 (33)	1179 (39)
Post-bronchodilator % predicted FEV_1, n	3969	6378	7355	2992
Mean (SD)	42.8 (13.99)	47.3 (15.09)	44.7 (14.66)	47.7 (15.06)
GOLD Grade, n	3969	6385	7355	2992
GOLD 1, n (%)	2 (<1)	20 (<1)	9 (<1)	13 (<1)
GOLD 2, n (%)	1132 (29)	2587 (41)	2485 (34)	1234 (41)
GOLD 3, n (%)	2080 (52)	2902 (46)	3630 (49)	1352 (45)
GOLD 4, n (%)	755 (19)	869 (14)	1231 (17)	393 (13)
Exacerbation history, n	3970	6385	7360	2995
<2 moderate and no severe exacerbations in the past year, n (%)	1194 (30)	1862 (29)	2141 (29)	915 (31)
≥2 moderate or ≥1 severe exacerbations in the past year, n (%)	2776 (70)	4523 (71)	5219 (71)	2080 (69)
≥1 severe exacerbation	1226 (31)	1445 (23)	2017 (27)	654 (22)

Source: CTT116855 ACM CSR SRAP Table 1.11, Table 1.12, Table 1.15, Table 1.16, Table 1.17, Table 1.18, Table 1.19, Table 1.20

Note: Moderate COPD exacerbation: required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization); Severe COPD exacerbation: required hospitalization.

1. Only year of birth was collected. Age was derived at the date of the Pre-Screening Visit. Day and month of birth were imputed as 30 June.

FF=fluticasone furoate; ICS=inhaled corticosteroid; ITT=Intent-to-Treat; SD=standard deviation; UMEC=umeclidinium; VI=vilanterol

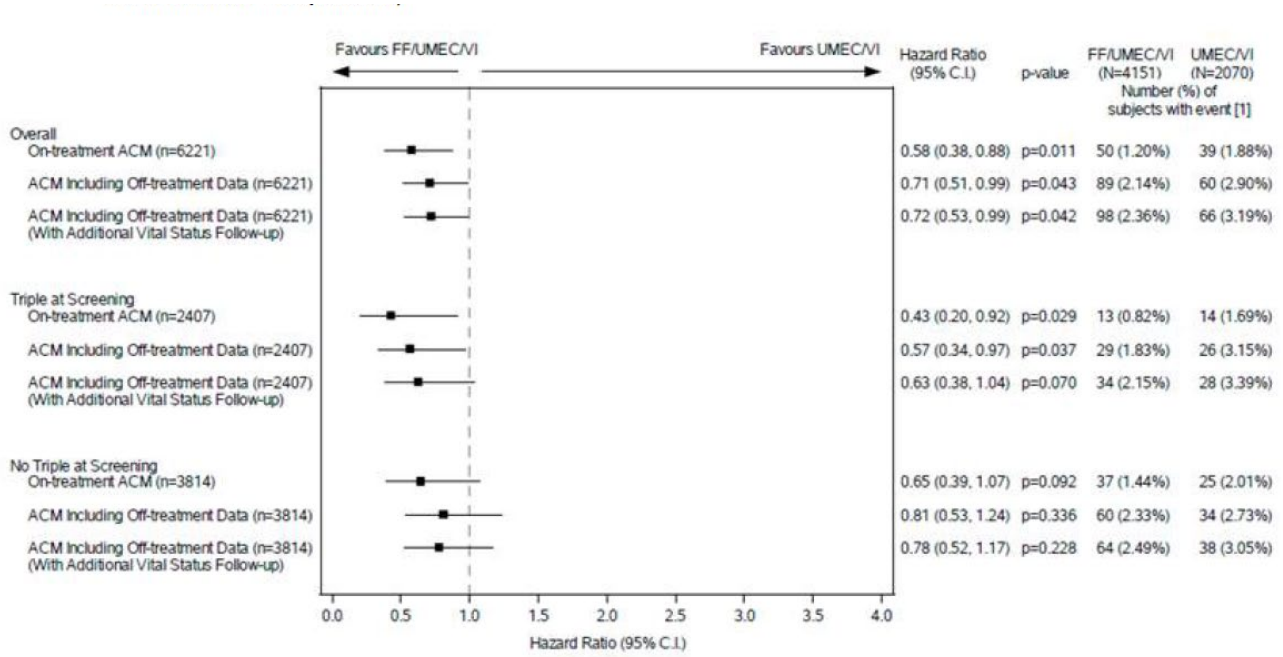
COPD Exacerbations reported in the 12 months prior to Screening	ITT Population, n (%)				ITT-E Population Total N=10,009
	FF/UMEC/VI 100/62.5/25 N=4151	FF/VI 100/25 N=4134	UMEC/VI 62.5/25 N=2070	Total N=10,355	
Moderate COPD exacerbations, n	4151	4134	2070	10,355	10,009
0	766 (18)	792 (19)	378 (18)	1936 (19)	1864 (19)
1	1418 (34)	1421 (34)	703 (34)	3542 (34)	3416 (34)
2	1622 (39)	1584 (38)	795 (38)	4001 (39)	3870 (39)
≥3	345 (8)	337 (8)	194 (9)	876 (8)	859 (9)
≥2	1967 (47)	1921 (46)	989 (48)	4877 (47)	4729 (47)
Severe COPD exacerbations, n	4151	4134	2070	10,355	10,009
0	3064 (74)	3065 (74)	1555 (75)	7684 (74)	7425 (74)
1	940 (23)	921 (22)	439 (21)	2300 (22)	2230 (22)
2	112 (3)	121 (3)	66 (3)	299 (3)	285 (3)
≥3	35 (<1)	27 (<1)	10 (<1)	72 (<1)	69 (<1)
≥2	147 (4)	148 (4)	76 (4)	371 (4)	354 (4)
Total Moderate/Severe exacerbations, n	4151	4134	2070	10,355	10,009
0	2 (<1)	5 (<1)	2 (<1)	9 (<1)	9 (<1)
1	1853 (45)	1907 (46)	931 (45)	4691 (45)	4519 (45)
2	1829 (44)	1768 (43)	890 (43)	4487 (43)	4338 (43)
≥3	467 (11)	454 (11)	247 (12)	1168 (11)	1143 (11)
≥2	2296 (55)	2222 (54)	1137 (55)	5655 (55)	5481 (55)

Triple Therapy at Screening

While the classes of medications used in the triple therapy subgroup are uniform, those used in the non-triple subgroup are not and include a variety of LAMA, LABA, and ICS class combinations and monotherapies. The most common non-triple combinations were ICS/LABA (29%), LAMA/LABA (8%), and LAMA alone (8%). The lack of uniformity of prior therapy in the non-triple subgroup provides an additional factor that may confound interpretation of the results for the subgroup analyses by triple therapy at Screening.

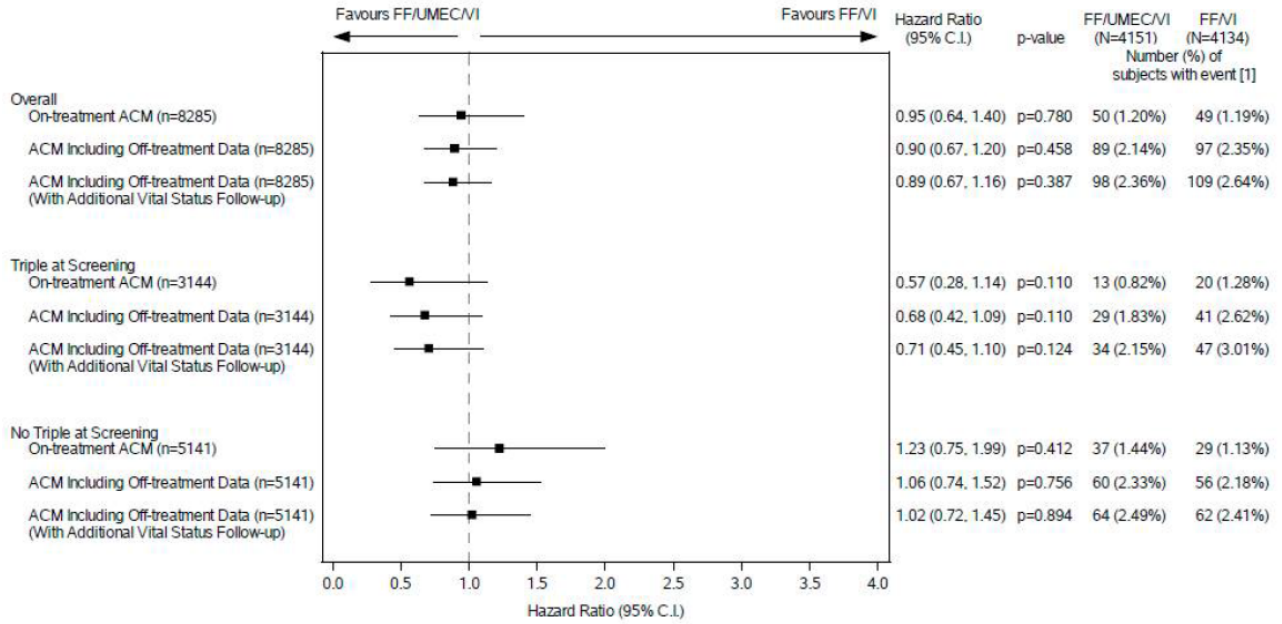
Of the 38% of subjects taking triple therapy at Screening, approximately 60% of these subjects were randomization to the FF/VI (40%) and UMEC/VI (20%) groups, whereas the remaining 40% were randomized to FF/UMEC/VI. The percentage of subjects who stepped down from triple therapy to FF/VI and UMEC/VI, respectively, were 38% and 40% within each treatment group, which represents 15% and 8% of the overall population. The percentage of subjects who stepped across from triple therapy at Screening to FF/UMEC/VI was 38% within the treatment group, which represents 15% of the overall population.

Figure 6 Forest Plot of ACM Overall and by Triple Therapy Use at Screening for FF/UMEC/VI vs UMEC/VI (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.39.
Note: n is the number of subjects in the analysis for the two treatment groups of interest. Analysis performed using a Cox proportional hazards model with covariates of treatment group, age, and sex.
[1] % is calculated out of the number of subjects in the subgroup
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 7 Forest Plot of ACM Overall and by Triple Therapy Use at Screening for FF/UMEC/VI vs FF/VI (Study CTT116855, ITT Population)



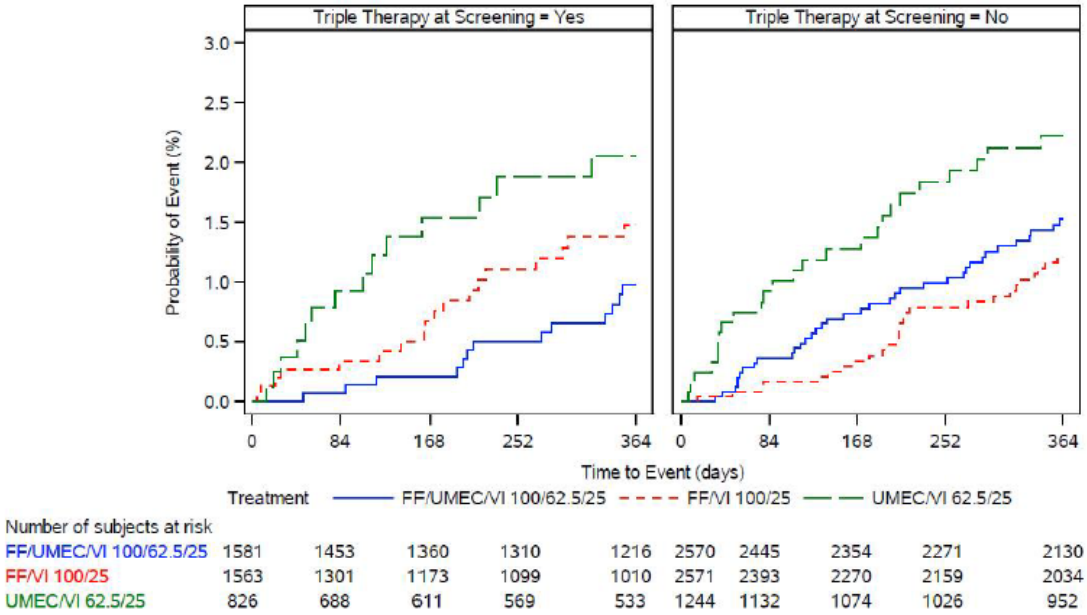
Source: CTT116855 supplementary CSR ACM SRAP Figure 2.40

Note: n is the number of subjects in the analysis for the two treatment groups of interest. Analysis performed using a Cox proportional hazards model with covariates of treatment group, age, and sex.

[1] % is calculated out of the number of subjects in the subgroup.

ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

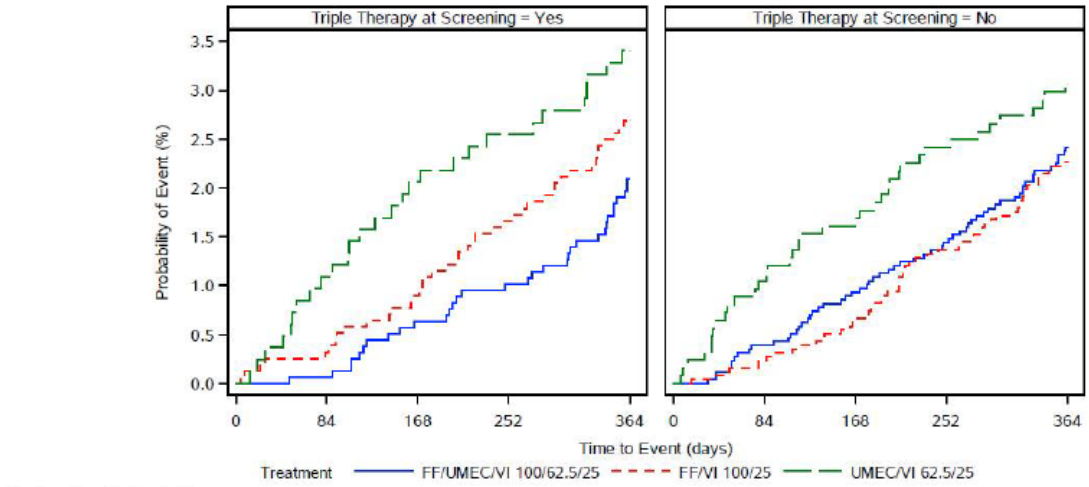
Figure 8 Kaplan-Meier Plot of Time to On-treatment ACM (ITT) By Triple Therapy Use at Screening (Study CTT116855, ITT Population)



Number of subjects at risk										
FF/UMEC/VI 100/62.5/25	1581	1453	1360	1310	1216	2570	2445	2354	2271	2130
FF/VI 100/25	1563	1301	1173	1099	1010	2571	2393	2270	2159	2034
UMEC/VI 62.5/25	826	688	611	569	533	1244	1132	1074	1026	952

Source: CTT116855 supplementary CSR ACM SRAP Figure 2.05
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 9 Kaplan-Meier Plot of Time to On- and Off-treatment ACM with Additional Vital Status Follow-up (ITT+VS+VSFU) By Triple Therapy Use at Screening (Study CTT116855, ITT Population)



Number of subjects at risk

FF/UMEC/VI 100/62.5/25	1581	1577	1567	1560	1487	2570	2560	2546	2532	2432
FF/VI 100/25	1563	1558	1548	1536	1431	2571	2560	2547	2524	2417
UMEC/VI 62.5/25	826	816	806	797	755	1244	1229	1221	1211	1159

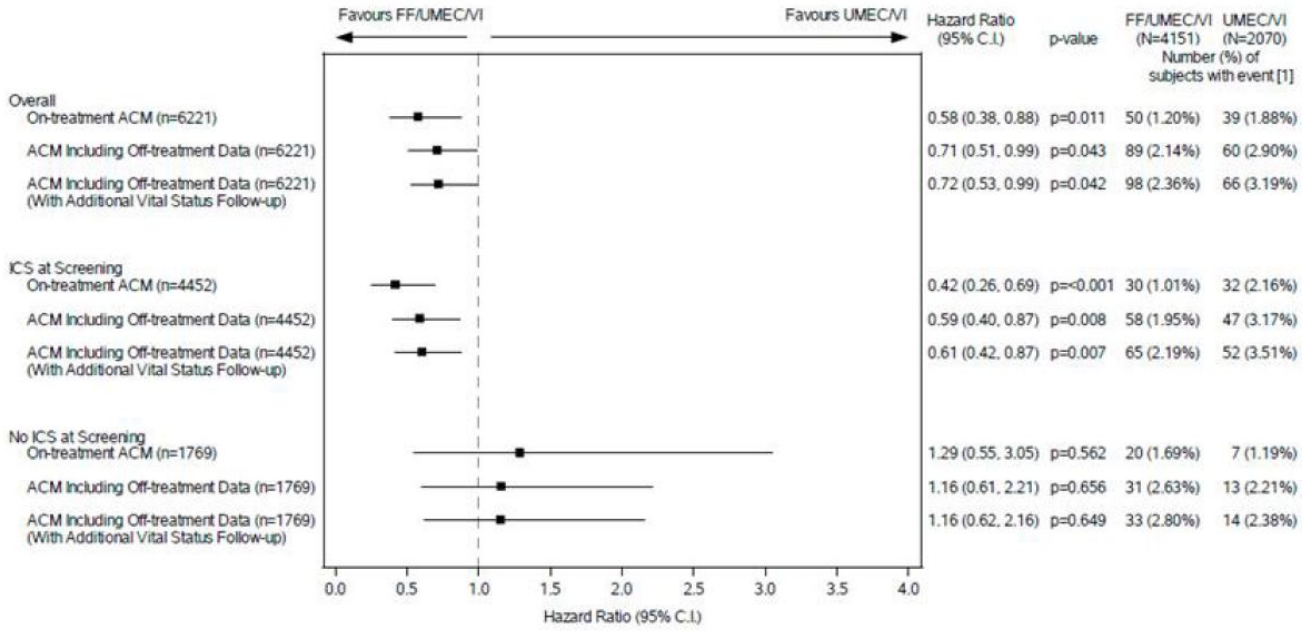
Source: CTT116855 supplementary CSR ACM SRAP Figure 2.07
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

ICS Use at Screening

Overall, 71% of subjects were taking ICS at Screening (which included mono-, dual, or triple therapy) and 29% of subjects were not taking ICS at Screening. The percentage of subjects on various ICS therapies was similar across treatment groups.

In subjects taking ICS at Screening, treatment with FF/UMEC/VI statistically significantly reduced the risk of ACM compared with subjects withdrawn from ICS through randomization to the UMEC/VI group.

Figure 10 Forest Plot of ACM By ICS Use at Screening for FF/UMEC/VI vs UMEC/VI (Study CTT116855, ITT Population)



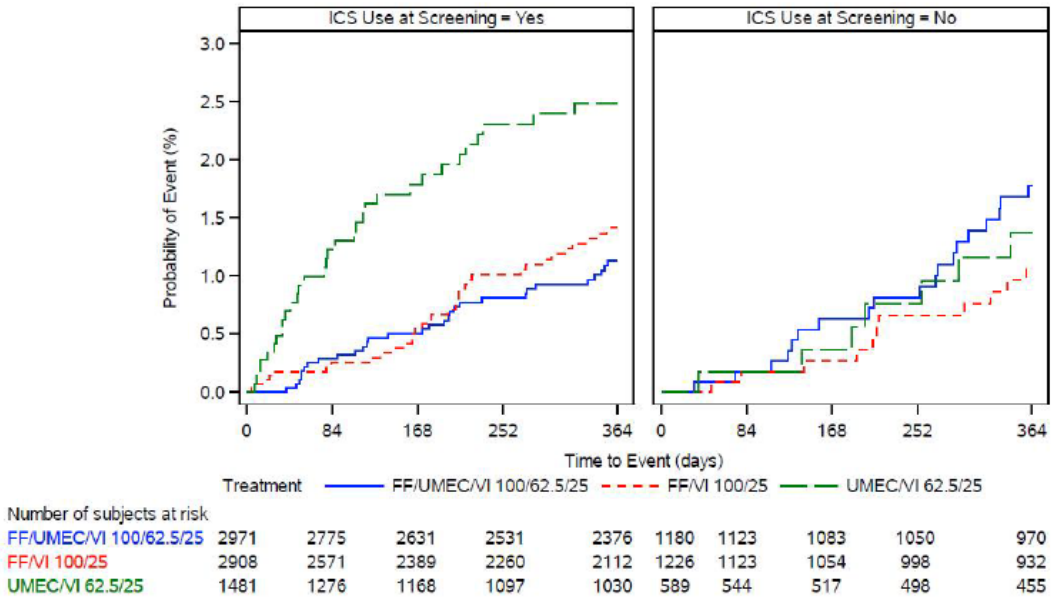
Source: CTT116855 supplementary CSR ACM SRAP Figure 2.42

[1] % is calculated out of the number of subjects in the subgroup.

Note: n is the number of subjects in the analysis for the two treatment groups of interest. Analysis performed using a Cox proportional hazards model with covariates of treatment group, age, and gender.

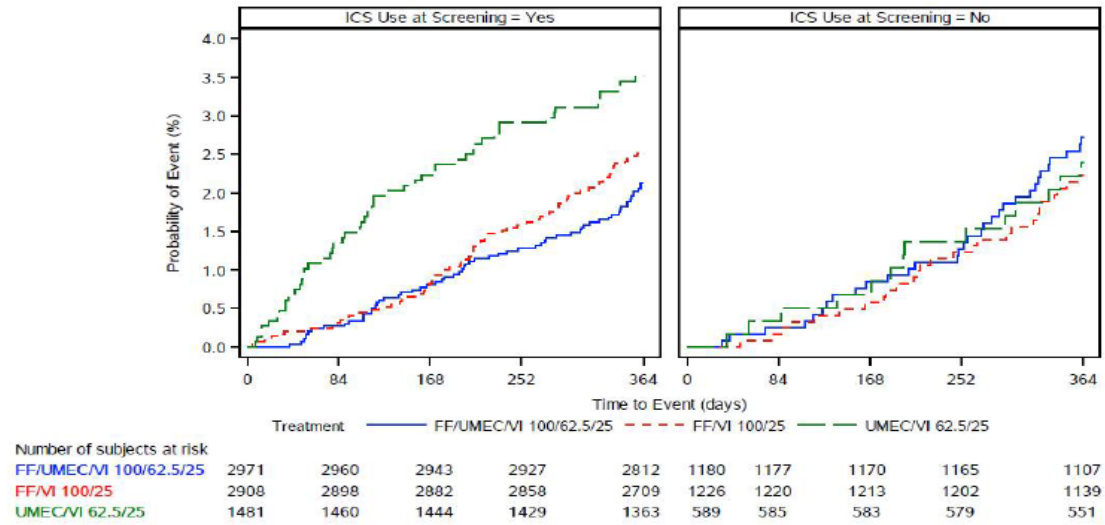
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 11 Kaplan-Meier Plot of Time to On-treatment ACM (ITT) By ICS Use at Screening (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.08
ACM=all-cause mortality; FF=fluticasone furoate; ICS=inhaled corticosteroids; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 12 Kaplan-Meier Plot of Time to On- and Off-treatment ACM with Additional Vital Status Follow-up (ITT+VS+VSFU) By ICS Use at Screening (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.10
ACM=all-cause mortality; FF=fluticasone furoate; ICS=inhaled corticosteroids; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

ACM by Time Intervals

Deaths occurred throughout the study period in all treatment groups whether on-treatment (ITT), on- and off-treatment (ITT+VS), or on-and off-treatment with additional vital status follow-up (ITT+VS+VSFU). The Kaplan-Meier probabilities of death continued to increase within the first 30, 60, or 180 days for each treatment group and were not concentrated early in the study period. The percentage of deaths in the UMEC/VI group was higher than the ICS-containing FF/UMEC/VI and FF/VI groups within 30, 60, and 180 days.

The primary causes of death as determined by the independent adjudicators for these time periods were primarily non-respiratory in nature (i.e., CV, other, or unknown). Of those subjects randomized to a non-ICS containing regimen (UMEC/VI), 7 on-treatment deaths occurred in the UMEC/VI group within the first 30 days, 2 of which were respiratory in nature. Five deaths occurred in the FF/VI group in the first 30 days while no deaths occurred in the FF/UMEC/VI group in the first 30 days.

Based on relatively small numbers of patients in this category, it is agreed that the differences seen in ACM, between patients taking ICS and those not were not (FF/UMEC/VI versus UMEC/VI) is not as a result from acute withdrawal of ICS. However, a contributory factor cannot be entirely out ruled in those individual patients.

Time Interval Analysis by Triple Therapy Use at Screening

On- and off-treatment deaths with additional vital status follow-up (ITT+VS+VSFU) occurred throughout the study period in all treatment groups and both triple therapy at Screening subgroups (yes/no), with the exception that no deaths occurred in the FF/UMEC/VI group during the first 30 days. The incidence of on- and off-treatment deaths (ITT+VS+VSFU) generally increased within the first 30, 60, and 180 days for each treatment group and triple therapy at screening subgroup category. These findings were consistent with those for the ITT and ITT+VS evaluations.

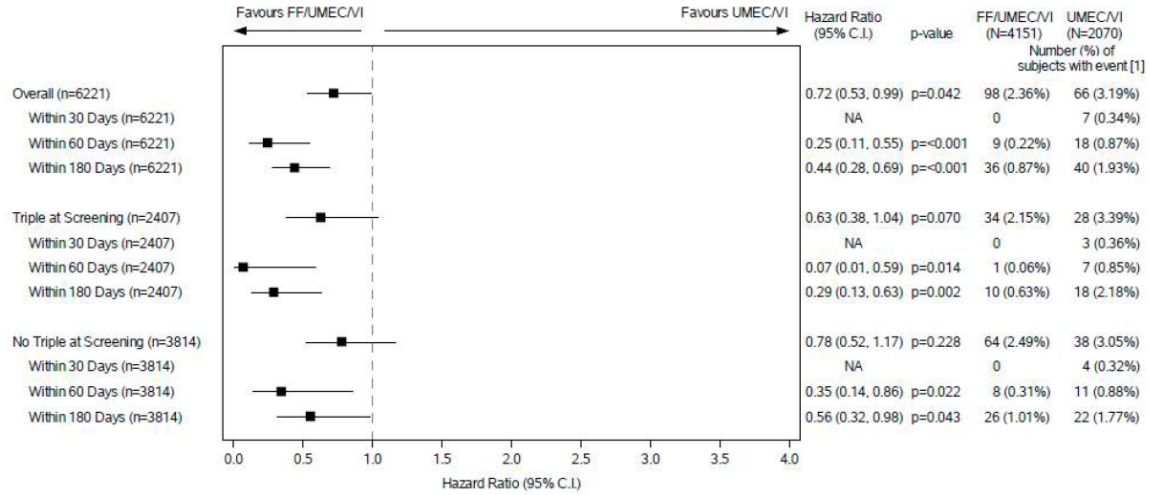
In subjects on triple therapy at Screening who were then randomized to either dual therapy, on-treatment deaths (ITT) occurred within 30 days after stepping down from triple therapy to FF/VI (4 subjects [0.26%]) and UMEC/VI (3 subjects [0.36%], with additional deaths observed in each treatment group within 60 and 180 days. No additional on- or off-treatment deaths occurred within 30 days for either step down in treatment group (ITT+VS+VSFU).

Reductions in the risk of on- and off-treatment ACM were observed for the comparisons of FF/UMEC/VI versus UMEC/VI within 60 and 180 days regardless of triple therapy use at Screening.

In the subgroup of subjects taking triple therapy at Screening who stepped down to dual therapy by randomization to UMEC/VI or FF/VI, the risk of on- and off-treatment ACM was comparable within both 60 and 180 days for each comparison. Together these results suggest withdrawal of therapy did not affect the overall interpretation of the findings for ACM.

Figure 13 Forest Plot of On- and Off-treatment ACM with Additional Vital Status Follow-up (ITT+VS+VSFU) By Triple Therapy Use at Screening and Time Interval for FF/UMEC/VI vs UMEC/VI (Study CTT116855, ITT Population)

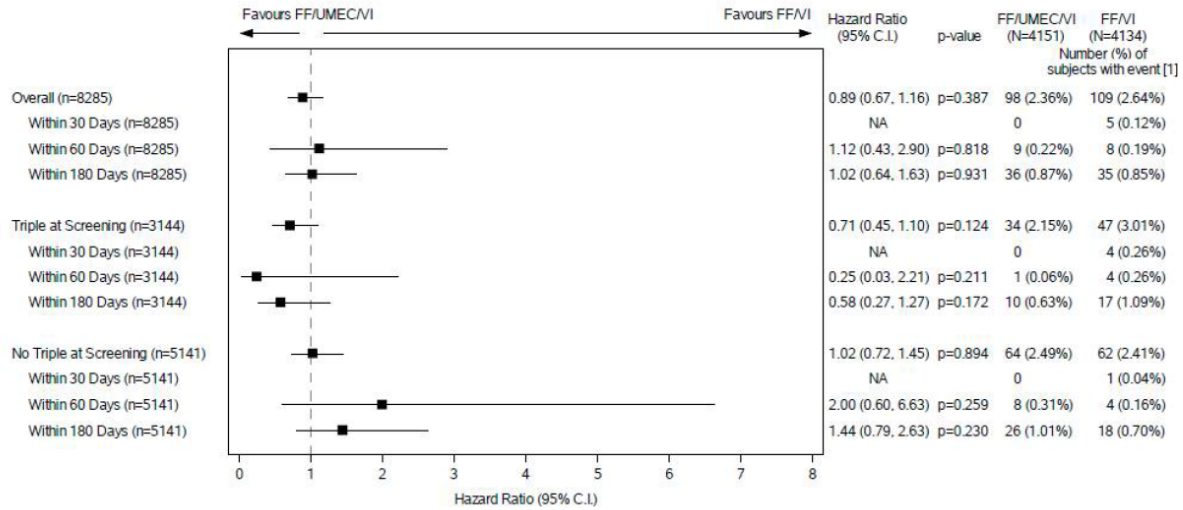
Figure 15 Forest Plot of On- and Off-treatment ACM with Additional Vital Status Follow-up (ITT+VS+VSFU) By Triple Therapy Use at Screening and Time Interval for FF/UMEC/VI vs UMEC/VI (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.54
[1] % is calculated out of the number of subjects in the subgroup.
Note: n is the number of subjects in the analysis for the two treatment groups of interest. Analysis performed using a Cox proportional hazards model with covariates of treatment group, age, and sex. Analysis was not performed if there were zero events in one or more of the three treatment arms (FF/UMEC/VI, FF/VI or UMEC/VI).
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Figure 14 Forest Plot of On- and Off-treatment ACM with Additional Vital Status Follow-up (ITT+VS+VSFU) By Triple Therapy Use at Screening and Time Interval for FF/UMEC/VI vs UMEC/VI (Study CTT116855, ITT Population)

Figure 16 Forest Plot of On- and Off-treatment ACM with Additional Vital Status Follow-up (ITT+VS+VSFU) By Triple Therapy Use at Screening and Time Interval for FF/UMEC/VI vs FF/VI (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.55
Note: n is the number of subjects in the analysis for the two treatment groups of interest. Analysis performed using a Cox proportional hazards model with covariates of treatment group, age, and sex. Analysis was not performed if there were zero events in one or more of the three treatment arms (FF/UMEC/VI, FF/VI or UMEC/VI).
[1] % is calculated out of the number of subjects in the subgroup.
ACM=all-cause mortality; FF=fluticasone furoate; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Time Interval Analysis by ICS Use at Screening

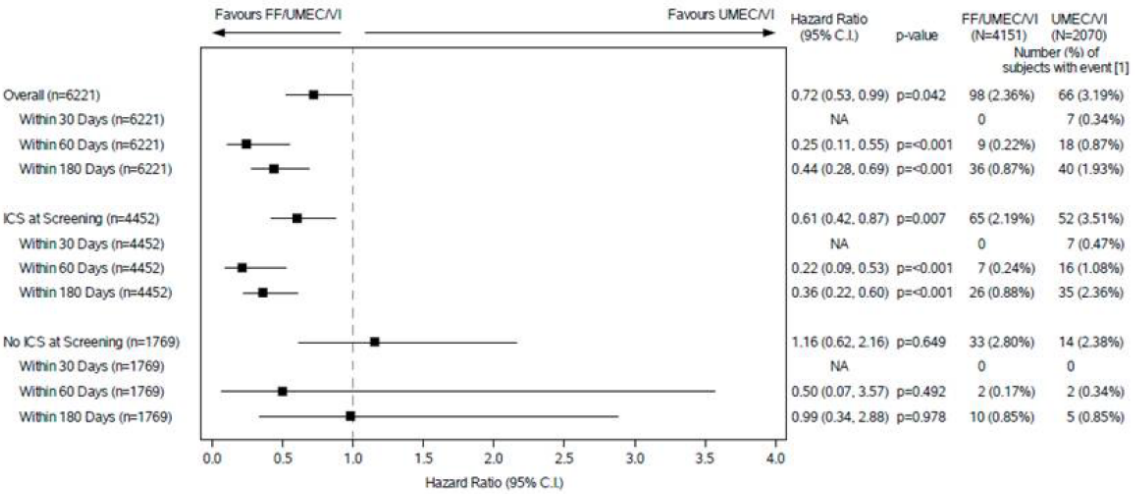
In subjects taking ICS at Screening, on- and off-treatment deaths with additional vital status follow-up (ITT+VS+VSFU) occurred throughout the study period in all treatment groups, with the exception that no deaths occurred in the FF/UMEC/VI group during the first 30 days. In subjects not taking ICS at Screening, no deaths occurred in the first 30 days in any treatment group. The incidence of on- and off-treatment death generally increased within the first 30, 60, and 180 days for each treatment group and ICS use at screening subgroup category. These findings were consistent with those for the ITT and ITT+VS evaluations.

In subjects switched from an ICS-containing medication at Screening by randomization to UMEC/VI, 7 on-treatment deaths (0.47%) occurred within 30 days. In subjects taking ICS-containing medications at screening who were randomized to the FF/VI group, 5 deaths (0.17%) occurred within the first 30 days. Additional deaths generally occurred within 60 and 180 days in both treatment groups. When off-treatment deaths were included (ITT+VS and ITT+VS+VSFU), results were consistent with the on-treatment ITT set.

Reductions in the risk of on- and off-treatment ACM (ITT+VS+VSFU) were observed for the comparisons of FF/UMEC/VI versus UMEC/VI overall and within 60 and 180 days for those subjects taking ICS use at Screening. In the subgroup of subjects not taking ICS at Screening, the number of events within 60 and 180 days were too small to make meaningful comparisons across treatment groups.

As above, the fact that acute withdrawal of patients from baseline ICS did not seem to result in insignificant increase in early ACM deaths does not change the fact that there was a significant overall difference in ACM between patients randomised to take ICS-containing medications versus those randomised not to do so if those patients had been taking an ICS at baseline, while there was no benefit to ICS in patients who had not required ICS at baseline.

Figure 15 Forest Plot of On- and Off-treatment ACM By ICS Use and Time Interval for FF/UMEC/VI vs UMEC/VI (ITT+VS+VSFU) (Study CTT116855, ITT Population)



Source: CTT116855 supplementary CSR ACM SRAP Figure 2.63
[1] % is calculated out of the number of subjects in the subgroup.
Note: n is the number of subjects in the analysis for the two treatment groups of interest. Analysis performed using a Cox proportional hazards model with covariates of treatment group, age, and gender. Analysis was not performed if there were zero events in one or more of the three treatment arms (FF/UMEC/VI, FF/VI or UMEC/VI).
ACM=all-cause mortality; FF=fluticasone furoate; ICS=inhaled corticosteriod; ITT=Intent-to-Treat; UMEC=umeclidinium; VI=vilanterol

Data from supportive studies

The MAH also included information on other studies which have evaluated the effect of an ICS treatment or LAMA treatment in patients with COPD. These studies show reductions in ACM that numerically favoured the ICS/LABA containing arms compared with placebo and LABA monotherapy arms.

Table 19 Overview of Prior Randomized Clinical Trials for FF/VI and FP/SALM that Evaluated ACM in Subjects with COPD

Study Identifier	Study Design	Treatment Details (mcg)	N (ITT)	ACM Related Study Endpoint(s)
SUMMIT (HZC113782)[1]	MC, R, DB, PG, PC, event-driven Up to 4 years	FF/VI ELLIPTA 100/25 QD FF ELLIPTA 100 QD VI ELLIPTA 25 QD Placebo ELLIPTA QD	4121 4135 4118 4111 Total: 16,485	Time to death from any cause, regardless of maintenance of study medication (Primary Efficacy)
TORCH (SCO30003)[2]	MC, R, DB, PG, PC 3 years	FP/SALM DISKUS 500/50 BID FP DISKUS 500 BID SALM DISKUS 50 BID Placebo DISKUS BID	1533 1534 1521 1524 Total: 6112	Time to death from any cause by 3 years (Primary Efficacy)
INSPIRE SCO40036[3]	MC, R, DB, DD, AC, PG 2 years	FP/SALM DISKUS 500/50 BID TIO HandiHaler 18 QD	658 665 Total: 1323	Incidence of deaths (safety) Time to death on-treatment (efficacy *post-hoc)*

Notes:
1. Vestbo, 2016
2. Calverley, 2007
3. Wedzicha, 2008

AC=active control; ACM=All-cause mortality; BID=twice-daily; DB=double-blind; DD=double-dummy; FF=fluticasone furoate; FP=fluticasone propionate; ITT=Intent-to-Treat; MC=multicenter; PC=placebo controlled; PG=parallel group; QD=once-daily; R=randomized; SALM=salmeterol; TIO=tiotropium; VI=vilanterol

Description of Studies

SUMMIT

SUMMIT was a randomized (1:1:1:1), double-blind, placebo-controlled, parallel group study that evaluated the long-term (up to 4 years) efficacy and safety of FF/VI 100/25 mcg once daily (FF/VI 100/25), FF 100 mcg once daily (FF 100), and VI 25 mcg once daily (VI 25) in subjects with moderate COPD. The study employed an event-driven design and was to conclude when approximately 1,000 reports of the primary outcome event of death were received. A total of 16,485 randomized subjects were included in the analysis population. While the primary comparison in SUMMIT was FF/VI compared with placebo, the component arms were included to demonstrate the contributions of each component to the overall. As this study was an event-driven mortality trial, the amount of missing data for vital status was considerably lower than that observed for Study CTT116855.

SUMMIT enrolled male and female subjects 40 to 80 years of age with an established history of COPD, a Screening FEV1 between 50% to 70% of the predicted values, a FEV1/FVC of ≤0.70, and symptomatic COPD based on a score of ≥2 on the modified Medical Research Council (mMRC) dyspnoea scale. Subjects 40 to <60 years of age were required to have established CV disease and subjects >60 years of age were required to have either established CV disease or to have been treated for 2 or more CV disease risk factors.

The primary efficacy endpoint was time to death (including on- and off-treatment data) from any cause.

TORCH

TORCH was a 3-year, multicentre, randomised (1:1:1:1), double-blind, controlled trial that evaluated the efficacy and safety of FF/SALM 500/50 mcg twice-daily (N=1,533) compared with FP DISKUS 500 mcg twice-daily (N=1,534), SALM DISKUS 50 mcg twice-daily (N=1,521), and placebo DISKUS twice-daily (N=1,524) on survival in 6,112 subjects with moderate to severe COPD. During the trial, subjects were permitted usual COPD therapy with the exception of other ICS and long-acting bronchodilators. The subjects were aged 40 to 80 years with a smoking history of >10 pack-years, an established history of COPD, a pre-bronchodilator FEV1 <60% of predicted at trial entry, and <10% of predicted reversibility. Each subject who withdrew from double-blind treatment for any reason was followed for the full 3-year trial period to determine survival status. The primary efficacy endpoint was ACM. As this study was a mortality trial, the amount of missing data for vital status was considerably lower than that observed for Study CTT116855.

INSPIRE

INSPIRE was a 2-year, multicentre, randomised (1:1), double-blind, double-dummy controlled trial that evaluated the efficacy and safety of FP/SALM 500/50 mcg twice-daily (N=658) compared with TIO 18 mg once-daily via HandiHaler (N=665) in 1,323 subjects with moderate to severe COPD. Eligible subjects entered a 2-week run-in period during which they discontinued all existing COPD maintenance medications and received oral prednisolone 30 mg/day and inhaled SALM 50 mcg twice-daily to standardize their clinical condition before randomization. The subjects were 40 to 80 years of age, with a smoking history of >0 pack-years, a clinical history of COPD exacerbations, a post-bronchodilator FEV1 <50% predicted, reversibility to 400 mcg albuterol (salbutamol) 10% or less of predicted FEV1, and a score of ≥2 on the mMRC dyspnea scale. Subjects with any respiratory disorders other than COPD or who required daily long-term oxygen therapy (>12 hours/day) were excluded. All-cause mortality was a pre-specified safety endpoint.

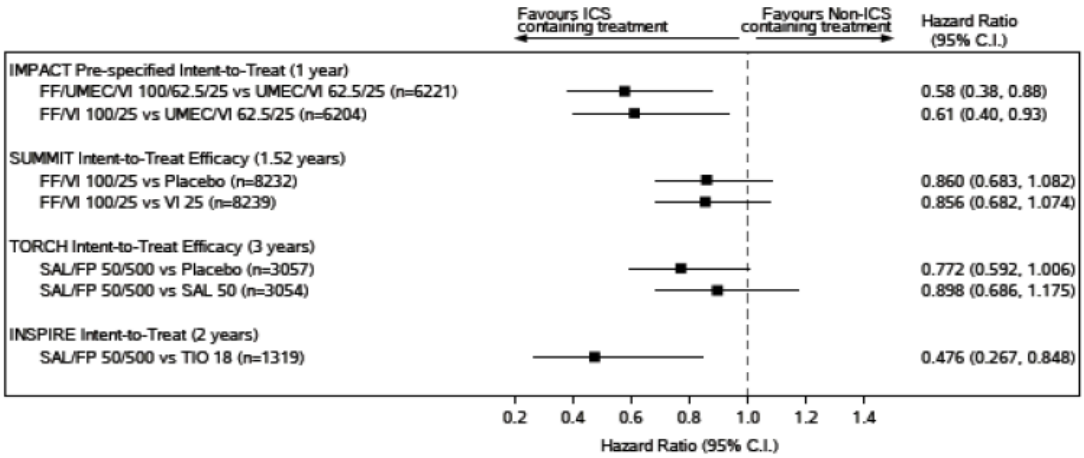
The a priori comparison of the total number of reported deaths in each treatment group was done with the Fisher's exact test. Additional post-hoc analyses were performed for time to death on treatment (including deaths up to 2 weeks post–treatment cessation) using the Cox PH model with covariates of smoking status at baseline, percent predicted FEV1 at baseline, age, gender, and country.

Comparison of Results for Mortality across Trials

For SUMMIT and TORCH, selected results for the ICS/LABA vs placebo and ICS/LABA vs LABA comparisons are shown to highlight reductions in the risk of ACM across studies for ICS-containing combinations with non-ICS containing treatment arms. While these results are consistent with the data shown for IMPACT in showing a contribution of ICS on reduction of ACM, both studies formally failed to show an effect on mortality.

The comparison of ICS vs placebo is not shown since ICS alone is not a treatment for COPD.

Figure 16 Forest Plot of On-Treatment Analysis of ACM for IMPACT (ITT), SUMMIT, TORCH, and INSPIRE Studies



Source: Clinical Overview Supporting Figure 2.03
Note: n is the number of subjects in the analysis for the 2 treatment groups of interest.
Note: SUMMIT was an event driven study. The median treatment exposure (up to the common end date) is shown.
Note: SUMMIT and IMPACT use a Cox proportional hazards model with covariates of treatment group, age and sex.
Note: TORCH used a Log rank analysis stratified by smoking status. INSPIRE used a Cox proportional hazards model with covariates of treatment group, smoking status, age, sex, baseline disease severity and country (post-hoc analysis).
ACM=all-cause mortality; CI=confidence interval; FF=fluticasone furoate; FP=fluticasone propionate; ICS=inhaled corticosteroid; SAL=salmeterol; TIO=tiotropium; UMEC=umeclidium; VI=vilanterol

In the INSPIRE trial, post-hoc analysis showed that subjects treated with FP/SALM 500/50 mcg twice-daily demonstrated a 52% reduction in the risk of ACM compared with subjects treated with TIO (p=0.012). Together, these prior studies are supportive of the ACM findings in CTT116855 by demonstrating consistent findings for a numerical (but again non-significant) reduction in the risk of ACM when an ICS (either FF or FP) is used in combination with a LABA in patients with COPD.

UPLIFT

UPLIFT was a randomised, double-blind, parallel-group study over 4 years that compared TIO via the Handihaler with placebo in subjects with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs. Subjects were at least 40 years of age, with a FEV1 of 70% or less after bronchodilation and a FEV1/FVC of ≤0.70. Co-primary endpoints were the rate of decline in the mean FEV1 before and after bronchodilation beginning on Day 30. Secondary endpoints included measures of FVC, changes in response on SGRQ, and exacerbations of COPD. Mortality was evaluated as a protocol-defined endpoint.

Table 20 Summary of UPLIFT Trial

Study Identifier	Study Design	Treatment Details (mcg)	N (ITT)	All-Cause Mortality-Related Study Endpoint(s)
UPLIFT (205.235)[1]	MC, R, DB, PG, PC 4 Years	TIO 18 Handihaler QD Placebo Handihaler QD	3006 2987 Total: 5993	Time to death from any cause

Notes:
1. Tashkin, 2008
ACM=All-cause mortality; DB=double-blind; ITT=Intent-to-Treat; MC=multicenter; PC=placebo controlled; PG=parallel group; QD=once-daily; R=randomized; TIO=tiotropiuml

In UPLIFT, a lower risk of on-treatment time to ACM was seen in the TIO group (hazard ratio, 0.84; 95% CI, 0.73–0.97). Statistical significance was observed at the end of the protocol-defined treatment period (p=0.034) but not 30 days thereafter (p=0.086). While this study was not specifically designed to evaluate the effect of TIO on ACM, the results indicate that the LAMA class may have a beneficial effect on ACM in COPD That being said, the numbers of patients treated in this trial make the interpretation of the ACM finding difficult, especially in the context of the comments in IMPACT as previously described.

2.3. Discussion

The MAH has already presented results from Study CTT116855 to support previous variation applications. At that time, however, the MAH did not seek additional product information text related to ACM, as there was a significant proportion of patients whose data had been censored prior to Week 52 and, in their opinion, this might have led to questions regarding the reliability of the analysis. As such, the MAH made efforts to gather as much of this missing data as possible, with the result that 99.6% of patient survival data at Week 52 are present in this application for review.

Study CTT116855, was a 1-year, randomised trial in subjects with symptomatic COPD and a history of exacerbations, demonstrated a reduction in the risk of ACM for the comparison of FF/UMEC/VI with UMEC/VI, in the UMEC/VI group. The MAH has suggested that these results are clinically relevant and so merit inclusion in section 5.1 of the SmPC despite this endpoint not being included in the confirmatory testing strategy for the trial.

During the assessment, the MAH amended its initial proposed text in section 5.1 of the SmPC as follows for consideration by CHMP.

Survival
In IMPACT, over 52 weeks Trelegy Ellipta significantly reduced the risk of all-cause mortality, including on- and off-treatment data, by 27.7% compared with UMEC/VI (vital status confirmed in 99.6% of patients at Week 52) (see Table 3). The risk reduction of all-cause mortality was 11.3% with Trelegy Ellipta compared with FF/VI; however, this result was not statistically significant.

Table 21 All-cause mortality endpoint in IMPACT over 12 months in symptomatic patients with COPD at risk of exacerbations

Treatment	***N***	***Hazard Ratio vs. Comparator (95% CI)***	***Reduction in Risk (95% CI)***	***p value***
Trelegy Ellipta	*4,151*			
UMEC/VI	*2,070*	*0.72 (0.53, 0.99)*	*27.7% (1.2, 47.1)*	*0.042*
FF/VI	*4,134*	*0.89 (0.67, 1.16)*	*11.3% (-16.5, 32.5)*	*0.387*

CI=confidence interval

Analyses of on-treatment all-cause mortality were also conducted, and results were consistent with the above results. Trelegy Ellipta significantly reduced the risk of on-treatment all-cause mortality by 42.1% (95% CI: 11.9, 61.9; p=0.011) compared with UMEC/VI. The reduction in risk of all-cause mortality was 5.5% (95% CI: -40.2, 36.3) with Trelegy Ellipta compared with FF/VI; however, this result was not statistically significant.

According to the MAH, the reduction in the risk of ACM shown for the comparison of FF/UMEC/VI with UMEC/VI was primarily driven by the FF component of FF/UMEC/VI.

The difference demonstrated in relation to FF/VI was not statistically different at the 5% level and is not considered to be clinically relevant.

It was seen in the subgroup analysis related to ICS use at screening suggested that patients who had been taking an ICS at screening did better when maintained on therapy containing an ICS than if randomised to a non-ICS containing arm. In contrast, patients who had not been taking an ICS at screening did not gain any survival benefit from being randomised to an ICS containing arm. The applicant has acknowledged that the number of patients who had not been taking an ICS at screening, as well as the number of mortality events in this subgroup were too small to allow a fully powered analysis if ACM.

In subjects not taking ICS at Screening, there was no evidence of a difference in the risk of ACM for FF/UMEC/VI compared with UMEC/VI as per figure 12 above. However, any definitive conclusion related to ICS withdrawal effects is limited by the small number of subjects and mortality events in the non-ICS subgroup, resulting in less robust analysis of ACM as evidenced by the wider CIs shown for the non-ICS subgroup compared with the ICS-users subgroup.

Patients who were not taking an ICS at screening derived no ACM benefit from the addition of a steroid in this trial, although as the applicant has pointed out the number of patients in that subgroup is too small for a robust analysis to occur.

The IMPACT study was not primarily designed to assess mortality between the treatment arms in COPD patients. All-cause mortality ('on-treatment only' and 'on-and off-treatment') was one of a large number of pre-defined 'other' or tertiary efficacy endpoints not included in the confirmatory testing strategy and without correction for multiplicity. The MAH argued that since all tests within the predefined statistical testing hierarchy for the primary and key secondary endpoints in IMPACT achieved statistical significance (with $p<0.001$), it was therefore acceptable to evaluate treatment comparisons for 'Other' endpoints and to draw inferences for statistical significance using a 5% reference level. However, the high number of tertiary endpoints does not rule out the possibility of post hoc selection based on having observed a favourable result. This methodological issue creates uncertainty in relation to the statistical robustness of the results.

The hazard ratio estimate for the UMEC/VI comparison based on both on- and off-treatment data was substantially smaller in magnitude than the best-case estimate based on on-treatment data only and had an uncorrected p-value of 0.042. The final results are based on analyses on-treatment and on- and off-treatment data that included retrospectively collected, off-trial, 52-week vital status data on 5.1% of trial participants.

The magnitude of the absolute treatment effect (on- and off-treatment data) estimated as less than 1% in absolute terms comparing UMEC/VI/FF versus UMEC/VI and taken together that it was not included in the confirmatory testing strategy also lead to uncertainties regarding robustness of the results.

In addition, the IMPACT STUDY was only of 12 months' duration and therefore the magnitude of benefit beyond 12 months remains to be demonstrated.

Supportive information included by the MAH

The MAH included information on previous randomized controlled trials (SUMMIT, TORCH, and INSPIRE and UPLIFT), which demonstrated a numerical reduction in the risk of ACM for ICS (FF or FP) + LABA combinations compared with LABA or LAMA alone or with placebo. The SUMMIT and TORCH studies were large studies conducted over a long duration. Both enrolled a large number of subjects to provide sufficient powering for all-cause mortality. In particular, in the SUMMIT study enrolled approx. 16,500 patients with a history, or be at increased risk, of cardiovascular disease were randomised. The primary efficacy outcome was the time to death from any cause, regardless of maintenance of study medication (follow-up continued until at least 1000 deaths had occurred). Compared with placebo, all-cause mortality was unaffected by FF/VI therapy (hazard ratio [HR] 0·88 [95% CI 0·74–1·04]; 12% relative reduction; p=0·137) or the components (FF, HR 0·91 [0·77–1·08]; p=0·284; VI, 0·96 [0·81–1·14]; p=0·655).

In UPLIFT, a lower risk of on-treatment time to ACM was seen in the TIO group (hazard ratio, 0.84; 95% CI, 0.73–0.97). Statistical significance was observed at the end of the protocol-defined treatment period (p=0.034) but not 30 days thereafter (p=0.086).

Although it is acknowledged that IMPACT had differences in patient population or risk of exacerbations to other clinical trials examining ACM, SUMMIT and TORCH studies did not show significant benefit of LABA/ICS compared to LAMA alone.

Inclusion of non-primary endpoints in the SmPC

The EU Commission Guideline on the Summary of Product Characteristics, Revision 2 (2009) states that, for Section 5.1, "in the exceptional cases when clinically relevant information from subgroup or post-hoc analyses is presented, it should be identified as such in a balanced manner reflecting the limited robustness of both positive and negative secondary observations."

During the assessment of this procedure, two Requests for Supplementary Information (RSI) with major objections were raised, in view of the uncertainties regarding the effect on Trelegy on ACM:

Major objection raised in the first RSI;

The difference in ACM between the arms could be primarily due to the effect of the removal of ICS in patients who had been taking ICS-containing medications at screening. A positive effect of adding ICS to patients who had not previously been taking ICS was not demonstrated. In addition, the evidence does not support the proposed biological plausibility for the expected difference. It has been asserted that the improvement in COPD in terms of lung function and reduction in exacerbation as the reason for the improvement in ACM, however there is little or no difference between FF/VI/UMEC vs FF/VI in terms of ACM despite a meaningful difference in lung function and reduction in exacerbation which points to a lack

of internal consistency. The MAH should justify the information submitted or re-analyse the data taking this into account.

Major objection raised in the second RSI

a) Statistical grounds: The IMPACT study was not designed to assess mortality between the treatment arms in COPD patients. Although it is acknowledged that patients were followed up for outcomes in the study, this was an exploratory analysis of a tertiary endpoint without correction for multiplicity. Furthermore, the hazard ratio estimate for the UMEC/VI comparison based on both on- and off-treatment data was substantially smaller in magnitude than the best-case estimate based on on-treatment data only and had a p-value of 0.042. Therefore, the effect has not been demonstrated with sufficient robustness to warrant inclusion in Section 5.1 of the SPC. The MAH is requested to further justify the robustness of the data.

b) Clinical utility: the applicability and use of the data for prescribers is questioned as it is limited to 12 months' treatment duration and the difference of ACM in patients on Triple therapy versus FF/VI on treatment is 0.7% and in data including off treatment is of the magnitude of 1.3%. In line with clinical practice the need for stepping patients up from dual therapy to triple is for patients 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 and not on perceived risk of mortality. The MAH is further requested to justify why this information is important for Healthcare professionals.

Following the Oral Explanation, the CHMP considered that no new elements were brought forward by the Applicant that could address satisfactorily the above major objections, which remained unsolved.
The above discussion reflects the argumentation from the MAH and the CHMP position in addressing the major objections.
In conclusion, the CHMP was of the view that the addition of further information in section 5.1 of the SmPC on survival data from the IMPACT study is not sufficiently justified and the variation to the terms of the marketing authorisation should be refused. The grounds for refusal adopted by the CHMP are detailed hereafter. (see Recommendation section).

2.4. Overall summary of the scientific evaluation

The current procedure concerned an update of section 5.1 of the SmPC in order to add information related to mortality based on a new analysis of study CTT116855 (IMPACT) previously submitted to support the initial approval of UMEC/VI/FF.

As some patients withdrew prior to week 52 the MAH performed a retrospective collection of the missing vital status data and perform post-hoc analyses of time to ACM using a more complete dataset where survival status at nominal Week 52 was obtained for 99.6% of the Intent-to-Treat (ITT) Population (i.e., n= 42, 0.4% of vital status data remain missing at Week 52).

The primary efficacy endpoint of study CTT116855 was the annual rate of moderate/severe exacerbations on patients treated with UMEC/VI/FF compared with both VI/FF and UMEC/VI.

Secondary endpoints included changes in FEV1 and SGRQ at week 52, and rate of and time to exacerbations of various severity. All-cause mortality at week 52 was also assessed.

The conclusion of the MAH was that in subjects with symptomatic COPD and a history of exacerbations, a reduction in the risk of All-cause-mortality (ACM) was robustly demonstrated for the comparison of UMEC/VI/FF with UMEC/VI, based on results over one year duration from study CTT116855.

The reduction in the risk of ACM shown for the comparison of UMEC/VI/FF with UMEC/VI was primarily driven by the FF component of UMEC/VI/FF. There was no significant ACM benefit for UMEC/VI/FF compared to the VI/FF dual inhaler.

The MAH has suggested that these results are clinically relevant and so merit inclusion in section 5.1 of the SmPC despite this endpoint not being included in the confirmatory testing strategy for the trial. The MAH considered that since all tests within the predefined statistical testing hierarchy for the primary and key secondary endpoints in IMPACT achieved statistical significance (with $p<0.001$), it was therefore acceptable to evaluate treatment comparisons for 'Other' endpoints and to draw inferences for statistical significance using a 5% reference level.

All-cause mortality ('on-treatment only' and 'on-and off-treatment') was one of a large number of pre-defined 'other' or tertiary efficacy endpoints not included in the confirmatory testing strategy and without correction for multiplicity. The high number of tertiary endpoints does not rule out the possibility of post hoc selection based on having observed a favourable result. This methodological issue creates uncertainty in relation to the statistical robustness of the results. The magnitude of the absolute treatment effect (on- and off-treatment data) estimated as less than 1% in absolute terms comparing UMEC/VI/FF versus UMEC/VI and taken together that it was not included in the confirmatory testing strategy also lead to uncertainties regarding robustness of the results.

3. Changes to the Product Information,

The update of section 5.1 to include a paragraph on mortality cannot be agreed as a result of this assessment.

4. Overall conclusion and impact on the benefit/risk balance

The outcome of the variation application is negative and the proposed amendments are rejected. There is no change in the benefit risk balance as a result of this assessment.

The benefit-risk balance of Trelegy Ellipta, Temybric Ellipta, and Elebrato Ellipta remains positive in the approved indication.

5. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of section 5.1 of the SmPC to add a paragraph on mortality based on an updated analysis from the IMPACT study.

The IMPACT 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. It was the pivotal study supporting the initial marketing authorisation. 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.

☒ is refused.

Grounds for refusal:

Whereas

- All-cause mortality ('on-treatment only' and 'on-and off-treatment') was one of a large number of pre-defined 'other' or tertiary efficacy endpoints not included in the confirmatory testing strategy and without correction for multiplicity.
- The high number of tertiary endpoints does not rule out the possibility of post hoc selection based on having observed a favourable result.
- From a clinical perspective the data from both on and off treatment show that the true magnitude of the effect size is uncertain comparing UMEC/VI/FF versus UMEC/VI.
- No significant or clinically relevant difference was observed compared to the VI/FF dual inhaler.

On the basis of the above, the MAH has not provided robust data that warrant addition of a paragraph on mortality in section 5.1 of the SmPC, consequently the CHMP has refused of the variation to the terms of the marketing authorisation.

Amendments to the marketing authorisation

N/A

6. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion for Trelegy Ellipta, Elebrato Ellipta, Temybric Ellipta EMEA/H/C/WS1683