Clinical trial results:
The Clinical Effectiveness of Fluticasone Furoate/Umeclidinium Bromide/Vilanterol in a Single Inhaler (TRELEGYTM ELLIPTATM) when Compared with Non-ELLIPTA Multiple Inhaler Triple Therapies in COPD Patients within a Usual Care Setting

Summary

EudraCT number	2017-004369-29
Trial protocol	SE GB NL ES
Global end of trial date	10 October 2019

Results information

Result version number	v1 (current)
This version publication date	04 September 2020
First version publication date	04 September 2020

Trial information

Trial identification

Sponsor protocol code	206854

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 8664357343, GSKClinicalSupportHD@gsk.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 December 2019

Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	10 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effectiveness of TRELEGY ELLIPTA with non-ELLIPTA MITT for the impact of COPD on wellbeing and daily life after 24 weeks treatment.

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 871
Country: Number of subjects enrolled	Netherlands: 638
Country: Number of subjects enrolled	Spain: 264
Country: Number of subjects enrolled	Sweden: 268
Country: Number of subjects enrolled	United Kingdom: 1300
Worldwide total number of subjects	3341
EEA total number of subjects	3341

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1148
From 65 to 84 years	2128
85 years and over	65

Subject disposition

Recruitment

Recruitment details:

This was a Phase IV, open-label, randomized study to evaluate the effectiveness of TRELEGY ELLIPTA relative to non-ELLIPTA multiple inhaler triple therapies (MITT) for chronic obstructive pulmonary disease (COPD) control within the usual clinical practice setting. TRELEGY and ELLIPTA are registered trademarks of GlaxoSmithKline group of companies.

Pre-assignment

Screening details:

A total of 3341 participants were screened and 3109 participants (Par.) were enrolled in this study. Of which, 3092 participants were randomized and received the study treatment. The remaining 17 participants were randomized in error (those who were recorded as screen failures and also randomized) and did not receive investigational product (IP).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI

Arm description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Arm type	Experimental
Investigational medicinal product name	Fluticasone furoate /Umeclidinium bromide/Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

A combination of fluticasone furoate blended with lactose in the first strip (100 microgram [mcg] per blister) and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler via inhalation route for a period of 24 weeks.

Arm title	Non-ELLIPTA MITT

Arm description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Arm type	Active comparator
Investigational medicinal product name	Non-ELLIPTA Multiple Inhaler Triple Therapies (MITT)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Inhaled corticosteroid/long-acting muscarinic receptor antagonist/long-acting beta agonist products twice daily as prescribed by the physician for a period of 24 weeks.

Number of subjects in period 1[1]	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI	Non-ELLIPTA MITT
Started	1545	1547
Randomized but did not start IP	1 [2]	0 [3]
Completed IP	1256 [4]	1359 [5]
Not Completed IP	288 [6]	188 [7]
Withdrew IP (WIP): Lost to follow-up	15 [8]	24 [9]
WIP: Protocol deviation	0 [10]	2 [11]
WIP: Adverse event	112 [12]	29 [13]
WIP: Lack of efficacy	56 [14]	28 [15]
WIP: Physician Decision	14 [16]	27 [17]
WIP: Withdrawal by Participant	91 [18]	78 [19]
Completed	1498	1493
Not completed	47	54
Protocol deviation	-	1
Physician decision	2	1
Lack of efficacy	3	1
Adverse event, serious fatal	8	8
Adverse event, non-fatal	1	1
Consent withdrawn by subject	15	17
Lost to follow-up	18	25

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 3341 participants were screened and 3109 participants (Par.) were enrolled in this study. Of which, 3092 participants were randomized and received the study treatment. The remaining 17 participants were randomized in error (those who were recorded as screen failures and also randomized) and did not receive investigational product (IP).
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participant randomized but did not start investigational product.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.

Justification: This number indicates the number of participant randomized but did not start investigational product.

[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participant randomized but did not start investigational product.

[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: This number indicates the number of participant randomized but did not start investigational product.

Baseline characteristics

Reporting groups

Reporting group title	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI

Reporting group description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Reporting group title	Non-ELLIPTA MITT

Reporting group description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Reporting group values	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI	Non-ELLIPTA MITT	Total
Number of subjects	1545	1547	3092
Age categorical Units: Subjects			
Total Participants	1545	1547	3092
Age Continuous Units: Years			
arithmetic mean	67.8	67.8	
standard deviation	± 8.78	± 8.59	-
Sex: Female, Male Units: Participants			
Female	708	729	1437
Male	837	818	1655
Race/Ethnicity, Customized Units: Subjects			
Asian- Central/South Asian Heritage	12	7	19
Asian- East Asian Heritage	0	1	1
Asian- South East Asian Heritage	1	6	7
Black or African American	3	4	7
White- Arabic/North African Heritage	6	7	13
White- White/Caucasian/European Heritage	1523	1521	3044
White and Black or African American	0	1	1

End points

End points reporting groups

Reporting group title	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI

Reporting group description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Reporting group title	Non-ELLIPTA MITT

Reporting group description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Primary: Number of responders and non-responders based on the chronic obstructive pulmonary disease assessment test (CAT) at Week 24 and number of participants with imputed CAT score at Week 24

End point title	Number of responders and non-responders based on the chronic obstructive pulmonary disease assessment test (CAT) at Week 24 and number of participants with imputed CAT score at Week 24

End point description:

The CAT is a 8-item questionnaire. Par. rated their experience as 0 (no impact) to 5 (maximum impact). CAT score was calculated by summing the non-missing scores of the 8 items with a range of 0-40 (higher scores: greater disease impact). Responders had a change from Baseline score >=2 and non-responders had a change from Baseline score <2 at Week 24. Change from Baseline was Week 24 value minus the Baseline value (Day 1). A composite strategy was applied when intercurrent events of randomized treatment modification, change in pulmonary rehabilitation or start of oxygen therapy occurred, otherwise a treatment policy strategy was applied. Missing Week 24 CAT data were imputed assuming missing at random. Intent-to-Treat (ITT) Population comprised of all randomized participants (who received a randomization number), excluding those who were randomized in error (a screen failure and also randomized). Only those participants with non-missing covariates were included in the analysis.

End point type	Primary

End point timeframe:

At Week 24

End point values	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI	Non-ELLIPTA MITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1539[1]	1543[2]		
Units: Participants				
Responders	731	616		
Non-responders	756	835		
Participants with imputed CAT score	52	92		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical comparison is presented for combined data of responders, non-responders and those with imputed CAT score at Week 24.

Comparison groups	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI v Non-ELLIPTA MITT
Number of subjects included in analysis	3082
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	1.51

Notes:

[3] - Analysis was performed using logistic regression model with covariates of treatment group, Baseline CAT score, number of exacerbations in the prior year, actual prior medication use strata and country.

Secondary: Change from Baseline in forced expiratory volume in 1 second (FEV1) at Week 24

End point title	Change from Baseline in forced expiratory volume in 1 second (FEV1) at Week 24

End point description:

FEV1 is a measure of lung function and is defined as the maximal amount of air that can be forcefully exhaled in one second. FEV1 measurements were collected using a spirometer. Baseline was defined as the value recorded at Day 1. Change from Baseline was calculated as FEV1 value at Week 24 minus the Baseline value. A treatment policy strategy was used for the intercurrent events of randomized treatment discontinuation, randomized treatment modification, change of pulmonary rehabilitation status and start of oxygen therapy. Only those participants with non-missing covariates were included in the analysis. FEV1 Population comprised of all participants of the ITT population for whom a spirometry assessment was performed at any of Visit 1 (Day 1) or Visit 2 (Week 24). Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

Baseline (Day 1) and at Week 24

End point values	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI	Non-ELLIPTA MITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	691[4]	675[5]		
Units: Liters				
least squares mean (standard error)	1.446 (± 0.0105)	1.396 (± 0.0108)		

Notes:

[4] - FEV1 Population

[5] - FEV1 Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using an ANCOVA with covariates of treatment group, Baseline FEV1, actual prior medication use strata, country and timing of spirometry.

Comparison groups	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI v Non-ELLIPTA MITT
Number of subjects included in analysis	1366
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.026
upper limit	0.073
Variability estimate	Standard error of the mean
Dispersion value	0.0121

Secondary: Percentage of participants making at least 1 critical error in inhalation technique at Week 24

End point title	Percentage of participants making at least 1 critical error in inhalation technique at Week 24

End point description:

Participants were trained on the correct use of their inhaler devices. All participants who had spirometry measured were to have an assessment of inhaler errors. During the assessment, participants were asked to demonstrate inhaler use when taking their regular dose of medication. A critical error is defined as an error that is most likely to result in no or significantly reduced medication being inhaled. These errors were recorded in an error checklist, during the assessment. A hypothetical strategy was used for the intercurrent event of randomized treatment modification. Percentage of participants making at least 1 critical error in inhalation technique at the Week 24 is presented. Critical error Population comprised of all participants of the ITT population for whom a critical error assessment was performed at Visit 2 (Week 24). Only those participants with data available at the specified data points were analyzed.

End point type	Secondary

End point timeframe:

At Week 24

End point values	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI	Non-ELLIPTA MITT		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	653[6]	230[7]		
Units: Percentage of Participants	6	3		

Notes:

[6] - Critical error Population

[7] - Critical error Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Analysis was performed using logistic regression model with covariates of treatment group, actual prior medication use strata and country.

Comparison groups	FF /UMEC/VI: 100 mcg/62.5 mcg/25 mcg by ELLIPTA DPI v Non-ELLIPTA MITT
Number of subjects included in analysis	883
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.103
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	4.53

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs) and non-serious AEs (non-SAEs) were collected from the start of study treatment up to Week 24

Adverse event reporting additional description:

Data is reported for the ITT Population which comprised of all randomized participants (who received a randomization number), excluding those who were randomized in error. All SAEs were collected. Non-SAEs which were only drug-related or that lead to withdrawal from study/study treatment were collected.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	FF/UMEC/VI 100/62.5/25

Reporting group description:

Eligible participants received a combination of fluticasone furoate (FF) blended with lactose in the first strip (100 microgram [mcg] per blister); and umeclidinium bromide (UMEC) and vilanterol (VI) blended with lactose and magnesium stearate in second strip (62.5 mcg UMEC per blister and 25 mcg VI per blister), a single inhalation once daily in the same TRELEGY ELLIPTA dry powder inhaler (DPI) via inhalation route for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Reporting group title	Non-Ellipta MITT

Reporting group description:

Eligible participants received the inhaled corticosteroid (ICS)/long-acting muscarinic receptor antagonist (LAMA)/long-acting beta agonist (LABA) products twice daily as prescribed by the physician for a period of 24 weeks. Participants were administered other prescribed COPD medications such as rescue medications according to usual practice, as suggested by physician.

Serious adverse events	FF/UMEC/VI 100/62.5/25	Non-Ellipta MITT	
Total subjects affected by serious adverse events			
subjects affected / exposed	114 / 1545 (7.38%)	114 / 1547 (7.37%)	
number of deaths (all causes)	8	8	
number of deaths resulting from adverse events			
Vascular disorders			
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 1545 (0.13%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 1545 (0.06%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	

Hypertensive crisis			
subjects affected / exposed	2 / 1545 (0.13%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 1545 (0.06%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 1545 (0.06%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Prostate cancer			
subjects affected / exposed	1 / 1545 (0.06%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage II			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesothelioma			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-small cell lung cancer metastatic			

subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pancreatic carcinoma			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural mesothelioma			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pituitary tumour benign			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer limited stage			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
T-cell lymphoma stage IV			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 1545 (0.00%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	0 / 1545 (0.00%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 1545 (0.13%)	3 / 1547 (0.19%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	2 / 1545 (0.13%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	2 / 1545 (0.13%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 1545 (0.00%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Alcohol poisoning			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	5 / 1545 (0.32%)	5 / 1547 (0.32%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac failure			
subjects affected / exposed	3 / 1545 (0.19%)	7 / 1547 (0.45%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	4 / 1545 (0.26%)	5 / 1547 (0.32%)	
occurrences causally related to treatment / all	1 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	5 / 1545 (0.32%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	1 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	2 / 1545 (0.13%)	0 / 1547 (0.00%)	

occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery disease		
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Aortic valve stenosis		
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac arrest		
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Cardiac asthma		
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure chronic		
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiogenic shock		
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cor pulmonale		
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	26 / 1545 (1.68%)	28 / 1547 (1.81%)	
occurrences causally related to treatment / all	2 / 28	1 / 29	
deaths causally related to treatment / all	0 / 2	0 / 1	
Pleural effusion			
subjects affected / exposed	0 / 1545 (0.00%)	4 / 1547 (0.26%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	3 / 1545 (0.19%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dyspnoea			
subjects affected / exposed	1 / 1545 (0.06%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 1545 (0.19%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 1545 (0.00%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Syncope			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem infarction			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous thrombosis			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reversible ischaemic neurological deficit			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sensory loss			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vestibular disorder			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to	0 / 1	0 / 0	

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diverticulum intestinal			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated umbilical hernia			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	

deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal haemorrhage			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 1545 (0.00%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bladder perforation			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysuria			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolysis			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock hypoglycaemic			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	26 / 1545 (1.68%)	30 / 1547 (1.94%)	
occurrences causally related to treatment / all	5 / 27	4 / 30	
deaths causally related to treatment / all	0 / 2	0 / 2	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	6 / 1545 (0.39%)	9 / 1547 (0.58%)	
occurrences causally related to treatment / all	3 / 6	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 1545 (0.19%)	2 / 1547 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			
subjects affected / exposed	2 / 1545 (0.13%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 1545 (0.06%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corynebacterium infection			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	

occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus infection			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Necrotising fasciitis			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	

deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder abscess			
subjects affected / exposed	1 / 1545 (0.06%)	0 / 1547 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 1545 (0.00%)	1 / 1547 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	FF/UMEC/VI 100/62.5/25	Non-Ellipta MITT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 1545 (2.07%)	3 / 1547 (0.19%)	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	32 / 1545 (2.07%)	3 / 1547 (0.19%)	
occurrences (all)	32	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2018	Amendment 01: Addition of health Canada requirements for reporting of unusual failure in efficacy for new drugs to the marketed health products directorate in the section: additional adverse event reporting requirements for Canadian investigators; change to allow collection of both pre-and postbronchodilator spirometry at Visit 1 in the section: study assessment and procedures: lung function; collection of participant pulmonary rehabilitation programme details in the section: treatments: concomitant therapy; wording added to describe the reporting requirements for medical devices and defective inhalers in the section: safety assessments; consenting Visit 0 added the maximum time allowed between consent, screening and randomization was set to 6 weeks in schedule of activities; editing for clarity/ consistency and corrections of typographical errors throughout the document.
28 September 2018	Amendment 02: Addition of requirement to collect the most recent historical eosinophil count data in schedule of activities; changed source of safety information used by the investigator for Trelegy from the summary of participant characteristics to the investigator brochure in the section: risk mitigation; addition of requirement to collect the most recent historical eosinophil count data in the section: data collection; rationale for collection of historical eosinophil counts, whole blood count and % eosinophils was added; changed source of safety information used by the investigator for Trelegy from the summary of participant characteristics to the investigator brochure in the section: treatment of overdose; to provide clarity on the reporting requirements and what a drug/device combination is in the section: GSK medical device GSK drug/device combinations incidents; changed source of safety information used by the investigator for Trelegy from the summary of participant characteristics to the investigator brochure in the section: medications; addition of references to provide background to eosinophil data collection in the section: references.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported