Clinical trial results:
A 12-month, open label, randomised, effectiveness study to evaluate fluticasone furoate (FF, GW685698)/vilanterol (VI, GW642444) Inhalation Powder delivered once daily via a Novel Dry Powder Inhaler (NDPI) compared with the existing COPD maintenance therapy alone in subjects with Chronic Obstructive Pulmonary Disease (COPD).

Summary

EudraCT number	2011-002452-13
Trial protocol	GB
Global end of trial date	24 November 2015
Results information	
Result version number	v2 (current)
This version publication date	10 June 2017
First version publication date	21 September 2016
Version creation reason	• Correction of full data set 95% CIs additionally presented for the LS mean annual rate.

Trial information

Trial identification	
Sponsor protocol code	HZC115151
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	Clincial Trials Helpdesk, GlaxoSmithKline Research & Development Ltd, +44 0208990 44 66, GSKClinicalSupportHD@gsk.com
Scientific contact	Clincial Trials Helpdesk, GlaxoSmithKline Research & Development Ltd, +44 0208990 44 66, 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	23 May 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 November 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study is to compare the effectiveness and safety of fluticasone furoate (FF)/vilanterol (VI) Inhalation Powder 100mcg/25mcg with other maintenance therapy over twelve months in a large UK primary care population of subjects with COPD. FF/VI will be administered once-daily (QD) in the morning via the Novel Dry Powder Inhaler (NDPI).

Protection of trial subjects:

N/A

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 3161
Worldwide total number of subjects	3161
EEA total number of subjects	3161

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)	1242
From 65 to 84 years	1804

85 years and over	115

Subject disposition

Recruitment

Recruitment details:

This was a multicenter, randomized, stratified, open-label study to evaluate the effectiveness and safety of fluticasone fuorate (FF)/vilanterol (VI) in participants (Par) followed in primary care who had a diagnosis of and received regular treatment for Chronic Obstructive Pulmonary Disease (COPD).

Pre-assignment

Screening details:

Participants (par.) were randomized 1:1 to receive 1 inhalation of FF/VI 100 microgram (mcg)/25 mcg once daily (QD) or continued their existing maintenance therapy for 12 months. 2802 par. were randomized (3 par. randomized to the FF/VI arm did not receive study medication). A total of 2799 par. comprised the Intent to Treat (ITT) Population.

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	Usual Care

Arm description:

Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months.

Arm type	Active comparator
Investigational medicinal product name	Usual Care (LABA or LABA/LAMA or ICS or ICS/LABA or LABA or ICS/LABA+LAMA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, powder
Routes of administration	Inhalation use

Dosage and administration details:

Inhaled corticosteroid alone or in combination with a long acting bronchodilator or, Long-acting bronchodilator alone or, triple maintenance therapy At appropriate dosing as instructed

Arm title	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Arm description:

Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally.

Arm type	Experimental
Investigational medicinal product name	FF 100 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, powder
Routes of administration	Inhalation use

Dosage and administration details:

It is available as dry white powder containing 100 mcg of Fluticasone Furoate blended with lactose per blister and was administered by DPI, once daily in the morning.

Investigational medicinal product name	VI 25 mcg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation vapour, powder
Routes of administration	Inhalation use

Dosage and administration details:

It is available as dry white powder containing 25 mcg of Vilanterol micronized drug (as the 'M' salt triphenylacetate) blended with lactose and magnesium stearate per blister and was administered by DPI, once daily in the morning.

Number of subjects in period 1[1]	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg
Started	1403	1396
Completed	1309	1291
Not completed	94	105
Adverse event, serious fatal	29	43
Physician decision	9	3
Consent withdrawn by subject	14	17
Met Protocol-defined stopping criteria	8	10
Lost to follow-up	29	25
Protocol deviation	5	6
Lack of efficacy	-	1

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: There were a total of 3161 participants enrolled into this study and 2799 participants were included in the ITT population (all randomised participants who received a prescription of study medication).

Baseline characteristics

Reporting groups	
Reporting group title	Usual Care
Reporting group description:	
Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months.	
Reporting group title	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg
Reporting group description:	
Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally.	

Reporting group values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg	Total
Number of subjects	1403	1396	2799
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.7	66.6	
standard deviation	± 9.93	± 9.9	-
Gender categorical Units: Subjects			
Female	671	698	1369
Male	732	698	1430
Race Units: Subjects			
African American/African Heritage	3	5	8
Asian-Central/South Asian Heritage	5	6	11
Asian-East Asian Heritage	1	0	1
Asian-South East Asian Heritage	1	0	1
White-Arabic/North African Heritage	1	3	4
White-White/Caucasian/European Heritage	1387	1376	2763
Mixed Race	5	5	10
Unknown	0	1	1

End points

End points reporting groups

Reporting group title	Usual Care
Reporting group description:	
Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months.	
Reporting group title	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg
Reporting group description:	
Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally.	

Primary: Mean Annual Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations

End point title	Mean Annual Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations
End point description:	
Mean annual rate of moderate or severe COPD exacerbations during treatment were assessed. Moderate exacerbation: participant received exacerbation-related prescription of oral corticosteroids and/ or antibiotic (with/without National Health Service [NHS] contact) not requiring hospitalisation. Severe exacerbation: an exacerbation-related hospitalisation. Analysis method was Generalised Linear Model (GLM) assuming the negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable, adjusted for randomized treatment, baseline COPD maintenance therapy per randomisation stratification, number of moderate/severe COPD exacerbations in previous year and smoking status at baseline. Intent to treat (ITT) population: all randomised participants who received a prescription of study medication. Primary Efficacy Analysis Population: all ITT participants who had at least one moderate/severe exacerbation in the year prior to randomization.	
End point type	Primary
End point timeframe:	
Up to 54 weeks	

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1134	1135		
Units: Exacerbations per participant per year				
least squares mean (confidence interval 95%)	1.9 (1.8 to 2.01)	1.74 (1.65 to 1.84)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg v Usual Care
Number of subjects included in analysis	2269
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.025
Method	Generalized Linear Model
Parameter estimate	Adjusted treatment ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	0.99

Secondary: Number of participants with serious adverse events (SAEs) of penumonia during the study

End point title	Number of participants with serious adverse events (SAEs) of penumonia during the study

End point description:

Incidence of SAE of pneumonia was defined for each randomized treatment group as the proportion (number) of participants in that group who experienced at least one SAE of pneumonia in the Pneumonia Adverse Event of Special Interest subgroup during the treatment period (from start date of exposure to stop date of exposure + 28 days). Non-inferiority is demonstrated if the upper limit of the two-sided 95% confidence interval for the incidence ratio is less than 2.

End point type	Secondary

End point timeframe:

Up to 58 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[1]	1396[2]		
Units: Participants				
number (not applicable)	83	94		

Notes:

[1] - ITT Population

[2] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation comments: Calculated as % of participants who had at least one SAE of pneumonia in the FF/VI group divided by the % of participants who had at least one SAE of pneumonia in the Usual Care group

Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg
Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Incidence ratio
Point estimate	1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.5

Secondary: Mean number of serious adverse events of pnuemonia during the study

End point title	Mean number of serious adverse events of pnuemonia during the study

End point description:

The mean number of SAE of pneumonia over the treatment period (from first date of exposure to last date of exposure + 28 days was calculated. Analysis was performed using a negative binomial regression model with covariates of randomized treatment and with logarithm of time on treatment as an offset variable.

End point type	Secondary

End point timeframe:

Up to 58 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403	1396		
Units: Mean Number of SAE				
least squares mean (confidence interval 95%)	0.07 (0.06 to 0.09)	0.08 (0.06 to 0.09)		

Statistical analyses

Statistical analysis title	Statistical Ananlysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.632
Method	Generalized Linear Model
Parameter estimate	Adjusted treatment ratio
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.47

Secondary: Time to the first serious adverse event of pneumonia occuring in a year

End point title	Time to the first serious adverse event of pneumonia occuring in a year

End point description:

The analysis method was a Cox proportional hazards model adjusted for randomized treatment. Analyses included those on-treatment SAEs of pneumonia that had an onset over the first 364 days of exposure, as defined. Participants who did not have an SAE of pneumonia during the first 364 days of the treatment period (start date of exposure to end date of exposure + 28 days were considered censored.

End point type	Secondary

End point timeframe:

Up to 52 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[3]	1396[4]		
Units: Participants				
number (not applicable)	80	89		

Notes:

[3] - ITT Population

[4] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.439
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.52

Secondary: Number of COPD-related secondary care contacts expressed as Least Square Mean

End point title	Number of COPD-related secondary care contacts expressed as Least Square Mean

End point description:

A COPD-related secondary care contact was defined as an inpatient admission or a specialist outpatient visit or an accident & emergency (A&E) contact. A participant with an A&E contact and subsequent inpatient admission was considered to have had two healthcare contacts. Inpatient admissions recorded at two hospitals on the same day, this was counted as a single (inpatient admission) secondary care contact. COPD-related contacts were identified using predefined lists of ICD-10 codes, specialty descriptions and diagnosis codes recorded in the patients electronic health record (EHR). GLM assuming the negative binomial distribution with log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, baseline COPD maintenance therapy per randomisation stratification, number of moderate/severe COPD exacerbations in the previous year to randomisation and smoking status at baseline.

End point type	Secondary

End point timeframe:

Up to 54 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403	1396		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)	1.48 (1.3 to 1.67)	1.57 (1.39 to 1.78)		

Statistical analyses

Statistical analysis title	Statistical Ananlysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.488
Method	Generalized linear model
Parameter estimate	Adjusted treatment ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	1.27

Secondary: Number of COPD-related primary care contacts expressed using Least Square Mean

End point title	Number of COPD-related primary care contacts expressed using Least Square Mean

End point description:

A COPD-related primary care contact was defined as a primary care contact on a given calendar date with either a nurse, general physician (GP) or other healthcare professional that were considered as COPD-related, if the most prominent signs and symptoms the participant was presenting were as a direct result of the participant's COPD, as per Readcodes recorded in the patients electronic health record (EHR). The analysis method was General Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, baseline COPD maintenance therapy per randomisation stratification, number of moderate/severe COPD exacerbations in the previous year to randomisation and smoking status at baseline.

End point type	Secondary

End point timeframe:

Up to 54 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403	1396		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)	2.46 (2.34 to 2.58)	2.42 (2.3 to 2.53)		

Statistical analyses

Statistical analysis title	Statistical Ananlysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.622
Method	Generalized Linear Model
Parameter estimate	Adjusted treatment ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.05

Secondary: Number of all secondary care contacts expressed using Least Square Mean

End point title	Number of all secondary care contacts expressed using Least Square Mean

End point description:

A secondary care contact was defined as an inpatient admission or a specialist outpatient visit or an A&E contact. A participant with an A&E contact and subsequent inpatient admission was considered to have had two healthcare contacts. In the situation where inpatient admissions were recorded at two hospitals on the same day, this was counted as a single secondary care contact. The analysis method was General Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomised treatment, baseline COPD maintenance therapy per randomization stratification, number of moderate/severe COPD exacerbations in the previous year to randomization and smoking status at baseline.

End point type	Secondary

End point timeframe:

Up to 54 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403	1396		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)	9.36 (8.74 to 10.02)	9.81 (9.17 to 10.51)		

Statistical analyses

Statistical analysis title	Statistical Ananlysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.336
Method	Generalized Linear Model
Parameter estimate	Adjusted treatment ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.15

Secondary: Number of all primary care contacts expressed using Least Square Mean

End point title	Number of all primary care contacts expressed using Least Square Mean

End point description:

A primary care contact was defined as contact with a either a nurse, general practitioner, or other healthcare professional. The analysis method was General Linear Model assuming an underlying negative binomial distribution with a log-link function and logarithm of time on treatment as an offset variable and adjusted for randomized treatment, baseline COPD maintenance therapy per randomization stratification, number of moderate/severe COPD exacerbations in the previous year to randomization and smoking status at baseline.

End point type	Secondary

End point timeframe:

Up to 54 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403	1396		
Units: Contacts per participant per year				
least squares mean (confidence interval 95%)	18.88 (18.06 to 19.74)	21.2 (20.27 to 22.16)		

Statistical analyses

Statistical analysis title	Statistical Ananlysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Generalized Linear Model
Parameter estimate	Adjusted treatment ratio
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.05
upper limit	1.2

Secondary: Time to an event of discontinuation of initial therapy occurring in a year

End point title	Time to an event of discontinuation of initial therapy occurring in a year

End point description:

Initial therapy was defined as the treatment that the subject was randomised to at randomisation. Discontinuation of initial therapy was defined as any modification of initial therapy. These included stepping up, stepping down or switching to another class/class combination, or withdrawal from the study. Switching within the same drug class did not count unless participant switched from FF/VI to a different ICS/LABA. The analysis method was a Cox proportional hazards model adjusted for randomized treatment. The probability of discontinuation of initial therapy was measured from the date of randomisation (i.e., exposure start date) to the date of discontinuation of initial therapy to which the participant was randomized, or date of treatment termination (Visit 6 or early withdrawal visit) for participants who completed the study without discontinuing the initial therapy (censored).

End point type	Secondary

End point timeframe:

Up to 364 days

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[5]	1396[6]		
Units: Participants				
number (not applicable)	219	374		

Notes:

[5] - ITT Population

[6] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation comments: A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual Care.

Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Cox proportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.6
upper limit	2.23

Secondary: Time to the addition of a further COPD controller medication occurring in a year

End point title	Time to the addition of a further COPD controller medication occurring in a year

End point description:

The date of an event for addition of a further COPD controller medication was defined as the exposure start date of the first modified treatment medication that included a new COPD maintenance therapy of a new class of drug (to the initial therapy) during the study treatment period, as collected on the investigational product page of the eCRF. Participants who did not add any COPD controller medication during the study were censored at the end of the treatment period (Day 364). This was equivalent to stepping up, defined as the addition of at least one new class of drug. The probability of an event was measured from the date of randomization (i.e., treatment initiation) to the date of a change event. The analysis method was a Cox proportional hazards model adjusted for randomized treatment.

End point type	Secondary

End point timeframe:

Up to 364 days

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[7]	1396[8]		
Units: Participants				
number (not applicable)	142	72		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation comments: A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual Care

Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001
Method	Cox proprotional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	0.66

Secondary: Time to first moderate/severe exacerbations occurring in a year

End point title	Time to first moderate/severe exacerbations occurring in a year

End point description:

The date of an event for moderate / severe COPD exacerbation was defined as the exacerbation onset date. The analysis method was a Cox proportional hazards model adjusted for randomized treatment. The probability of a first moderate / severe exacerbation was measured from the date of randomization (i.e., treatment initiation) to the onset date of first moderate or severe COPD exacerbation, as recorded on eCRF, or date of treatment termination (Visit 6 or early withdrawal visit) for participants who completed the study without any moderate or severe exacerbations (censored). Participants who completed the study without a moderate or severe COPD exacerbation and analyses of time to first moderate/severe exacerbation were censored at Day 364.

End point type	Secondary

End point timeframe:

Up to 364 days

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[9]	1396[10]		
Units: Participants				
number (not applicable)	977	947		

Notes:

[9] - ITT Population

[10] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Estimation comments: A hazard ratio <1 indicates a lower risk with FF/VI compared with Usual Care

Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.111
Method	Cox porportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.85
upper limit	1.02

Secondary: Time to first moderate/severe exacerbations on initial therapy occurring in a year

End point title	Time to first moderate/severe exacerbations on initial therapy occurring in a year

End point description:

The date of an event for moderate / severe COPD exacerbation was defined as the exacerbation onset date. The analysis method was a Cox proportional hazards model adjusted for randomized treatment. The probability of first moderate / severe exacerbation on initial therapy was measured from the date of randomization (i.e., exposure start date) to the onset date of first moderate or severe COPD exacerbation, or to the date of discontinuation of initial therapy (analysis was censored at date of discontinuation of initial therapy) for participants who completed the study without any moderate or severe exacerbations on initial therapy.

End point type	Secondary

End point timeframe:

Up to 364 days

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[11]	1396[12]		
Units: Participants				
number (not applicable)	943	852		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.081
Method	Cox porportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.01

Secondary: Time to first severe exacerbations occurring in a year

End point title	Time to first severe exacerbations occurring in a year

End point description:

The date of an event for severe exacerbation was defined as the exacerbation onset date. Participants who completed the study without a severe exacerbation were censored. The analysis method was a Cox proportional hazards model adjusted for randomized treatment.
The probability of first severe exacerbation was measured from the date of randomization (i.e., treatment initiation) to the onset date of first severe exacerbation, as recorded on eCRF, or date of treatment termination (Visit 6 or early withdrawal visit) for participants who completed the study without any severe exacerbations (censored). At Day 364, all participants who have not experienced a severe exacerbation are considered censored, regardless of whether their on-treatment phase continues beyond day 364, including those who withdrew early.

End point type	Secondary

End point timeframe:

Up to 364 days

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[13]	1396[14]		
Units: Participants				
number (not applicable)	97	122		

Notes:

[13] - ITT Population

[14] - ITT Population

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Usual Care v Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg

Number of subjects included in analysis	2799
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075
Method	Cox porportional hazards model
Parameter estimate	Hazard ratio (HR)
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.66

Secondary: Number of participants with Fatal serious adverse events of pneumonia

End point title	Number of participants with Fatal serious adverse events of pneumonia

End point description:

All SAEs included in the AE subgroup of special interest of "pneumonia" were considered as an SAE of pneumonias. A fatal SAE was defined as a SAE with outcome of fatal for study participant. The number of participants with fatal SAEs of pneumonia was assessed over 14 months.

End point type	Secondary

End point timeframe:

Up to 58 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[15]	1396[16]		
Units: Participants				
number (not applicable)	13	13		

Notes:

[15] - ITT Population

[16] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with non-serious adverse drug reactions (ADR)

End point title	Number of participants with non-serious adverse drug reactions (ADR)

End point description:

The number of participants with non-serious ADRs was assessed for up to 54 weeks. An ADR is any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, for which there is a reasonable possibility that the untoward occurrence is causally related to the medicinal product. A non-serious ADR included one of the following: exacerbation of chronic or intermittent pre-existing condition; signs, symptoms, or the clinical sequelae of a

suspected interaction; signs, symptoms, or new conditions detected or diagnosed after study treatment administration.

End point type	Secondary

End point timeframe:

Up to 54 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[17]	1396[18]		
Units: Participants				
number (not applicable)	88	192		

Notes:

[17] - ITT Population

[18] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with serious adverse events

End point title	Number of participants with serious adverse events

End point description:

SAEs assessed included medical occurrence that, at any dose, results in death, is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, is a significant medical event in the investigator's judgment, or is an event of possible drug-induced liver injury with hyperbilirubinemia. SAEs were includes if the onset date was on or after the treatment start date and on or before the treatment stop date. However, the window for an SAE of pneumonia was longer and included 28 days post study treatment stop date.

End point type	Secondary

End point timeframe:

Up to 56 weeks

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[19]	1396[20]		
Units: Participants				
number (not applicable)	383	404		

Notes:

[19] - ITT Population

[20] - ITT Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with serious adverse drug reactions

End point title	Number of participants with serious adverse drug reactions

End point description:

A serious adverse drug reactions (SADR) is any untoward medical occurrence suspected to be medicinal product-related that at any dose: results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.

End point type	Secondary

End point timeframe:

Upto 12 months

End point values	Usual Care	Fluticasone fuorate (FF)/Vilanterol (VI) 100 mcg/25 mcg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1403[21]	1396[22]		
Units: Participants				
number (not applicable)	10	23		

Notes:

[21] - ITT Population

[22] - ITT Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious adverse events (SAEs; from Visit 1) and non-serious AE and adverse drug reactions (from Visit 2) were collected from study medication start until the end of treatment (up to Visit 6 or withdrawal, i.e, approximately 54 weeks)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Usual Care

Reporting group description:

Participants continued their existing maintenance therapy that included one of the following: an inhaled corticosteroid (ICS) alone or Long Acting Beta Agonist (LABA) alone or Long Acting Muscarinic Antagonist (LAMA) alone or combination of any two (ICS+LABA/ ICS+LAMA/ LABA+LAMA) or triple therapy (ICS+LABA+LAMA) at the appropriate dosing schedule, for 12 months

Reporting group title	FF/VI 100 mcg/25 mcg

Reporting group description:

Participants were prescribed one inhalation of fluticasone fuorate /vilaneterol (FF/VI) 100 mcg/25 mcg via dry powder inhaler (DPI) once daily in the morning for 12 months in lieu of existing maintenance therapy. Participants on previous triple therapy received LAMA therapy additionally.

Serious adverse events	Usual Care	FF/VI 100 mcg/25 mcg	
Total subjects affected by serious adverse events			
subjects affected / exposed	383 / 1403 (27.30%)	404 / 1396 (28.94%)	
number of deaths (all causes)	50	77	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bowen’s disease			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial carcinoma			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carcinoma in situ of skin			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid body tumour			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia recurrent			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colon adenoma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon neoplasm			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal carcinoma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal tract adenoma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma multiforme			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Glottis carcinoma			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer metastatic			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic neoplasm			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung cancer metastatic			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung carcinoma cell type unspecified recurrent			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	7 / 1403 (0.50%)	10 / 1396 (0.72%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 5	
Lung squamous cell carcinoma recurrent			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage 0			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage IV			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphoma			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mantle cell lymphoma			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to liver			
subjects affected / exposed	3 / 1403 (0.21%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Metastases to lung			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	0 / 1403 (0.00%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
Myelodysplastic syndrome			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer recurrent			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic adenoma			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal cancer			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Refractory anaemia with an excess of blasts			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal neoplasm			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of Lung			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ureteral neoplasm			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric cancer			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			
subjects affected / exposed	3 / 1403 (0.21%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	2 / 1403 (0.14%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aortic thrombosis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood pressure inadequately controlled			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 1403 (0.21%)	9 / 1396 (0.64%)	
occurrences causally related to treatment / all	0 / 3	1 / 9	
deaths causally related to treatment / all	0 / 0	1 / 1	
Extremity necrosis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery occlusion			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	3 / 1403 (0.21%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			

subjects affected / exposed	0 / 1403 (0.00%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Carotid endarterectomy			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	8 / 1403 (0.57%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 8	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cyst			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypothermia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 1403 (0.07%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent-graft endoleak			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unintentional medical device removal			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent occlusion			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic granulomatous angiitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Drug hypersensitivity			

subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Postmenopausal haemorrhage			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (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			
Asthma			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atelectasis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial secretion retention			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	4 / 1403 (0.29%)	6 / 1396 (0.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 2	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	70 / 1403 (4.99%)	86 / 1396 (6.16%)	
occurrences causally related to treatment / all	1 / 82	4 / 94	
deaths causally related to treatment / all	0 / 4	0 / 5	
Dyspnoea			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	3 / 1403 (0.21%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal oedema			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pickwickian syndrome			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural fibrosis			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonitis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 1403 (0.14%)	8 / 1396 (0.57%)	
occurrences causally related to treatment / all	0 / 2	1 / 8	
deaths causally related to treatment / all	0 / 0	1 / 3	
Pulmonary hypertension			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
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	9 / 1403 (0.64%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 10	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory acidosis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			

subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	24 / 1403 (1.71%)	15 / 1396 (1.07%)	
occurrences causally related to treatment / all	0 / 28	0 / 18	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sputum retention			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stridor			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	2 / 1403 (0.14%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium tremens			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Self-injurious ideation			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood electrolytes abnormal			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			

subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio increased			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	6 / 1403 (0.43%)	15 / 1396 (1.07%)	
occurrences causally related to treatment / all	0 / 6	1 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal function test abnormal			
subjects affected / exposed	9 / 1403 (0.64%)	12 / 1396 (0.86%)	
occurrences causally related to treatment / all	0 / 9	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			

subjects affected / exposed	4 / 1403 (0.29%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	5 / 1403 (0.36%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brachial plexus injury			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac valve rupture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chemical injury			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contrast media reaction			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	9 / 1403 (0.64%)	15 / 1396 (1.07%)	
occurrences causally related to treatment / all	0 / 11	0 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	3 / 1403 (0.21%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	2 / 1403 (0.14%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foreign body aspiration			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	4 / 1403 (0.29%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	2 / 1403 (0.14%)	8 / 1396 (0.57%)	
occurrences causally related to treatment / all	0 / 2	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	3 / 1403 (0.21%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intentional overdose			
subjects affected / exposed	2 / 1403 (0.14%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	3 / 1403 (0.21%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			

subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	3 / 1403 (0.21%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation mucositis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	5 / 1403 (0.36%)	8 / 1396 (0.57%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	9 / 1403 (0.64%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			

subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic rupture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Stress fracture			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 1403 (0.00%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral injury			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	12 / 1403 (0.86%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 13	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	9 / 1403 (0.64%)	13 / 1396 (0.93%)	
occurrences causally related to treatment / all	0 / 10	0 / 15	
deaths causally related to treatment / all	0 / 2	0 / 2	
Angina pectoris			
subjects affected / exposed	9 / 1403 (0.64%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	4 / 1403 (0.29%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Aortic valve incompetence			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Atrial fibrillation			
subjects affected / exposed	29 / 1403 (2.07%)	27 / 1396 (1.93%)	
occurrences causally related to treatment / all	1 / 33	2 / 28	
deaths causally related to treatment / all	0 / 1	0 / 2	
Atrial flutter			
subjects affected / exposed	2 / 1403 (0.14%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradyarrhythmia			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			

subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure			
subjects affected / exposed	11 / 1403 (0.78%)	10 / 1396 (0.72%)	
occurrences causally related to treatment / all	0 / 11	0 / 11	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure acute			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive			
subjects affected / exposed	5 / 1403 (0.36%)	6 / 1396 (0.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
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	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cor pulmonale			
subjects affected / exposed	2 / 1403 (0.14%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diastolic dysfunction			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	4 / 1403 (0.29%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Left ventricular failure			
subjects affected / exposed	3 / 1403 (0.21%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	3 / 1403 (0.21%)	6 / 1396 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial ischaemia			
subjects affected / exposed	3 / 1403 (0.21%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Palpitations			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Right ventricular failure			

subjects affected / exposed	0 / 1403 (0.00%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus tachycardia			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 1403 (0.00%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	3 / 1403 (0.21%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Basal ganglia infarction			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain injury			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain mass			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery aneurysm			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery disease			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			

subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid sinus syndrome			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral infarction			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	5 / 1403 (0.36%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 6	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebrovascular disorder			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cervical myelopathy			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia with Lewy bodies			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug withdrawal convulsions			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic encephalopathy			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	6 / 1403 (0.43%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningism			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peroneal nerve palsy			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculitis brachial			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiculopathy			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	4 / 1403 (0.29%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	10 / 1403 (0.71%)	11 / 1396 (0.79%)	
occurrences causally related to treatment / all	0 / 10	1 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	9 / 1403 (0.64%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	1 / 11	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve paralysis			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular dementia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paresis			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	6 / 1403 (0.43%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coagulopathy			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			

subjects affected / exposed	4 / 1403 (0.29%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pernicious anaemia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness unilateral			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			

subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal artery occlusion			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vision blurred			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 1403 (0.29%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Barrett’s oesophagus			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coeliac disease			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	5 / 1403 (0.36%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 1403 (0.14%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulum			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Diverticulum intestinal			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Duodenitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyskinesia oesophageal			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric dysplasia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 1403 (0.14%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1403 (0.07%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal hypomotility			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	2 / 1403 (0.14%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haemorrhage			

subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestine perforation			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstruction gastric			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal spasm			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic insufficiency			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis chronic			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Alcoholic liver disease			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Autoimmune hepatitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 1403 (0.00%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	3 / 1403 (0.21%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 1403 (0.00%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder perforation			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic function abnormal			
subjects affected / exposed	3 / 1403 (0.21%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jaundice cholestatic			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Miliaria			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (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			
Acute kidney injury			
subjects affected / exposed	16 / 1403 (1.14%)	23 / 1396 (1.65%)	
occurrences causally related to treatment / all	0 / 19	1 / 24	
deaths causally related to treatment / all	0 / 2	0 / 2	
Acute prerenal failure			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	5 / 1403 (0.36%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			

subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal disorder			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	7 / 1403 (0.50%)	10 / 1396 (0.72%)	
occurrences causally related to treatment / all	0 / 7	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal mass			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sterile pyuria			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	7 / 1403 (0.50%)	8 / 1396 (0.57%)	
occurrences causally related to treatment / all	0 / 8	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperparathyroidism primary			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			

subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic ormone secretion			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	3 / 1403 (0.21%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compartment syndrome			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mobility decreased			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle necrosis			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	6 / 1403 (0.43%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid arthritis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue swelling			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal sepsis			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abscess limb			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess oral			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis infective			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial infection			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary sepsis			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 1403 (0.07%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cellulitis			
subjects affected / exposed	9 / 1403 (0.64%)	14 / 1396 (1.00%)	
occurrences causally related to treatment / all	0 / 11	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 1403 (0.29%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes virus infection			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster meningoencephalitis			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of bronchiectasis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	47 / 1403 (3.35%)	50 / 1396 (3.58%)	
occurrences causally related to treatment / all	0 / 56	1 / 57	
deaths causally related to treatment / all	0 / 2	0 / 2	
Influenza			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	10 / 1403 (0.71%)	12 / 1396 (0.86%)	
occurrences causally related to treatment / all	1 / 10	2 / 12	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung abscess			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycetoma mycotic			

subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic herpes zoster			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	3 / 1403 (0.21%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis externa			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic abscess			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	81 / 1403 (5.77%)	89 / 1396 (6.38%)	
occurrences causally related to treatment / all	4 / 94	3 / 98	
deaths causally related to treatment / all	1 / 13	0 / 12	
Pneumonia streptococcal			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			

subjects affected / exposed	10 / 1403 (0.71%)	9 / 1396 (0.64%)	
occurrences causally related to treatment / all	0 / 11	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 1	
Septic embolus			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary tract infection			
subjects affected / exposed	12 / 1403 (0.86%)	9 / 1396 (0.64%)	
occurrences causally related to treatment / all	0 / 12	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 1403 (0.07%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella zoster virus infection			

subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral labyrinthitis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Cachexia			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	2 / 1403 (0.14%)	6 / 1396 (0.43%)	
occurrences causally related to treatment / all	0 / 2	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 1403 (0.07%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	2 / 1403 (0.14%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	6 / 1403 (0.43%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			

subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemochromatosis			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	1 / 1403 (0.07%)	4 / 1396 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperosmolar hyperglycaemic state			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocalcaemia			
subjects affected / exposed	1 / 1403 (0.07%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	0 / 1403 (0.00%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 1403 (0.14%)	2 / 1396 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypomagnesaemia			

subjects affected / exposed	2 / 1403 (0.14%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	7 / 1403 (0.50%)	7 / 1396 (0.50%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypophagia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypophosphataemia			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	1 / 1403 (0.07%)	0 / 1396 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			
subjects affected / exposed	3 / 1403 (0.21%)	5 / 1396 (0.36%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obesity			
subjects affected / exposed	0 / 1403 (0.00%)	1 / 1396 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Type 2 diabetes mellitus			
subjects affected / exposed	5 / 1403 (0.36%)	3 / 1396 (0.21%)	
occurrences causally related to treatment / all	0 / 5	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Usual Care	FF/VI 100 mcg/25 mcg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	40 / 1403 (2.85%)	56 / 1396 (4.01%)	
Infections and infestations			
Oral candidiasis	Additional description: In this study, only information regarding non- serious adverse drug reactions (ADRs) and serious adverse events (SAEs) were detected, documented and reported.		
subjects affected / exposed	40 / 1403 (2.85%)	56 / 1396 (4.01%)	
occurrences (all)	42	57	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 July 2013	Study design was amended: total # of par. required for study; changes (chg) to the Time Interval (int) for Visit 1; clarified the definition of a moderate exacerbation and NHS contacts in relation to the primary endpoint; clarified the secondary endpoint as COPD related rather than respiratory; added the # of actuations in salbutamol inhalers; added changes in relation to childbearing potential and to exclusion criteria 3 in relation to par. with unstable COPD; added chg in relation to ECG QTc prolongation; included the requirement (req) for signed consent form in definition of screen failure; added short-acting-beta2 agonist as generic class; added a statement (stat) on Adherence as Medication (med.) Possession Ratio; added a stat that all concomitant med. used in the study were to be recorded; removed the list of permitted COPD med. and added stat that all COPD med. were permitted with exceptions listed in Section 4.9.2; added new paragraphs in the section on Prohibited Med. and Non-Drug Therapies; amended the Time &Events Table to include chg in the Visit 1 time interval; genetic sampling and height and weight in the demographic information; added a new section Baseline Cardiovascular Co-Morbid Conditions and Severe Pneumonia History; added definition of History of Pneumonia; state that par. unable to perform spirometry would not be excluded; added the FF/VI in Section 5.3.1 to replace study drug or investigational drug; added a new Section 5.1.4 titled Research data not required for eCRF (crude EHR data); added a new genetics section Amend Section 7.2.1 on Sample Size Assumption to take into account reduced # of par.; added a new reference in relation to GOLD in the Primary Objectives; amended the Study Schematic in relation to the time interval at Visit 1 from Day -30 to Day -60; added a new Appendix 10.4 Genetic section; added a new Appendix 10.5 which identifies all the changes to the protocol; and minor formatting changes.
21 August 2013	Removed Section 5.1.1; History of serious pneumonia, defined as the total number of episodes with a pneumonia diagnosis for the hospitalization, in the 12 months prior to randomization were identified based on the EHR and recorded in the eCRF; added to Section5.1.4: History of serious pneumonia, defined as the total number of episodes with a pneumonia diagnosis for the hospitalization, in the 3 years prior to randomization were identified based on the EHR. In Section 4.4.1, the following text 'used due to SAE' was deleted.
30 September 2013	All references to 'this protocol amendment' changed to 'protocol amendment 1'; all references to Salford, Greater Manchester expanded to Salford and South Manchester, Greater Manchester, to reflect the increase in regional sites. Reference to eligible population in Salford removed as catchment area is now beyond Salford; NHS contacts text changed to include healthcare professionals; withdrawal of FF/VI reference clarified to show they can continue in the study on a maintenance therapy. Reference to study medication clarified to indicate FF/VI medication; reference to concomitant medications used clarified to reflect concomitant medication prescribed and dispensed; reference to collection of pharmacy data 'drug trade name' changed to 'drug name'. Table 2 corrected to remove incorrectly shaded cells. Crude EHR data amended to add additional secondary care site, University Hospital South Manchester. Genetics research; erroneous references added in error and text modified to reflect current standard text.
09 December 2013	Updated author list; Secondary objectives and safety endpoints updated to include pneumonia SAEs and analysis. Addition of pharmacy EHR as source of dispensing data and exclusion criteria to exclude 8. Subjects whose current medications include RELVAR™, ELLIPTA™ are not eligible to enter the study. If patients change to RELVAR™, ELLIPTA™ as their maintenance therapy, they should be withdrawn from the study. Data Analysis and Statistical Considerations updated to reflect the additional endpoint for pneumonia SAEs; References added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported