Clinical trial results:
A 52-week, Double-Blind, Randomized, Placebo Controlled Parallel Group Study to Evaluate the Effect of Roflumilast 500 ug on Exacerbation Rate in Subjects with Chronic Obstructive Pulmonary Disease (COPD) Treated with a Fixed Dose Combination of Long-Acting Beta Agonist and Inhaled Corticosteroid (LABA/ICS)

Summary

EudraCT number	2011-003606-24
Trial protocol	ES IT
Global end of trial date	24 November 2015

Results information

Result version number	v1 (current)
This version publication date	15 December 2016
First version publication date	15 December 2016

Trial information

Trial identification

Sponsor protocol code	ROF-MD-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01443845
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Forest Laboratories, LLC, an Allergan affiliate
Sponsor organisation address	Harborside Financial Center Plaza V, Suite 1900, Jersey City, United States, 07311-4994
Public contact	Clinical Trial Registries Team, Forest Laboratories, LLC, an Allergan affiliate, +1 1-800-347-4500, IR-CTRegistration@allergan.com
Scientific contact	Therapeutic Area Head, Forest Laboratories, LLC, an Allergan affiliate, +1 1-800-347-4500, IR-CTRegistration@allergan.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	06 January 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:

To demonstrate the additional benefit of roflumilast added on to fixed dose combination LABA/ICS (Advair® 250/50ug 1 puff b.i.d or Symbicort® 160/4.5ug 2 puffs b.i.d) in the reduction of exacerbations in subjects with severe to very severe COPD.

Protection of trial subjects:

At each study center, the Investigator was responsible for ensuring that the investigation was conducted according to the signed Investigator agreement, the protocol, the study procedures manual, and Good Clinical Practice (GCP) guidelines; for protecting the rights, safety, and welfare of patients under the Investigator's care; and for the control of drugs under investigation. The Investigator at each study center was responsible for the management of the study, which consisted of maintaining the study file and patient records, corresponding with the Institutional Review Board(IRB)/Independent Ethics Committee(IEC), and completing the electronic case report forms (eCRFs).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 29
Country: Number of subjects enrolled	Malaysia: 13
Country: Number of subjects enrolled	Thailand: 34
Country: Number of subjects enrolled	Mexico: 44
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Colombia: 17
Country: Number of subjects enrolled	United States: 915
Country: Number of subjects enrolled	Ukraine: 190
Country: Number of subjects enrolled	Argentina: 396
Country: Number of subjects enrolled	Russian Federation: 154
Country: Number of subjects enrolled	Philippines: 261
Country: Number of subjects enrolled	Peru: 71
Country: Number of subjects enrolled	Romania: 109
Country: Number of subjects enrolled	Serbia: 94
Country: Number of subjects enrolled	Spain: 13

Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	2354
EEA total number of subjects	123

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)	1181
From 65 to 84 years	1154
85 years and over	19

Subject disposition

Recruitment

Recruitment details:

Recruitment occurred from September 2011 to October 2014 for a total of 380 study centers screened patients for the study: Italy, Spain, United States, Ukraine, Argentina, Russia, Philippines, Romania, Serbia, Canada, Malaysia, Thailand, Mexico, Peru and Taiwan

Pre-assignment

Screening details:

The study consisted of 2 weeks of single-blind placebo lead-in with fixed-dose combination (FDC) long-acting β2-agonist(s) (LABA)/inhaled corticosteroid(s) (ICS) treatment followed by 52 weeks of double-blind treatment in addition to maintenance FDC LABA/ICS.

Pre-assignment period milestones

Number of subjects started	2354
Number of subjects completed	2352

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 1
Reason: Number of subjects	Adverse event, non-fatal: 1

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

During the double-blind treatment period, all parties involved in the study (e.g., patients, Investigators, site personnel, Regional Site Managers [RSMs], clinical research assistants, and the Sponsor) were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Dose-matched placebo, oral administration, once per day.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral administration, once per day

Arm title	Roflumilast

Arm description:

Roflumilast 500 µg, oral administration, once per day

Arm type	Experimental

Investigational medicinal product name	Roflumilast
Investigational medicinal product code	
Other name	Daxas, Daliresp
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

One 500 microgram (µg) tablet, oral administration, once per day.

Number of subjects in period 1[1]	Placebo	Roflumilast
Started	1174	1178
Completed	922	841
Not completed	252	337
Adverse event, serious fatal	25	30
Consent withdrawn by subject	63	67
Deterioration in pulmonary function	1	4
Other reasons, including COPD exacerbations	44	44
Adverse event, non-fatal	38	108
Site terminated by Sponsor- e.g. military conflict	20	21
Lost to follow-up	9	13
Protocol deviation	42	45
Lack of efficacy	10	5

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: The safety population (numbering 2352 patients) of the trial does not include 2 patients from the enrolled population (numbering 2354 patients), due to a protocol deviation for one patient and an adverse event for a second patient.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Dose-matched placebo, oral administration, once per day.	
Reporting group title	Roflumilast
Reporting group description:	
Roflumilast 500 µg, oral administration, once per day	

Reporting group values	Placebo	Roflumilast	Total
Number of subjects	1174	1178	2352
Age categorical Units: Subjects			
Adults 40-65 years	634	640	1274
Adults over 65 years	540	538	1078
Age continuous Units: years			
arithmetic mean	64.5	64.4	
standard deviation	± 8.4	± 8.8	-
Gender categorical Units: Subjects			
Male	794	821	1615
Female	380	357	737
Race Units: Subjects			
White	944	935	1879
Black or African American	27	35	62
Asian	170	167	337
American Indian or Alaska Native	6	16	22
Native Hawaiian or Other Pacific Islander	0	2	2
Other	27	23	50
Ethnicity Units: Subjects			
Hispanic or Latino	272	268	540
Not Hispanic or Latino	902	910	1812
ICS/LABA Therapy			
Patients long-acting β2-agonist(s) (LABA)/inhaled corticosteroid(s) (ICS) therapy			
Units: Subjects			
Advair	766	768	1534
Symbicort	408	410	818
Long-acting muscarinic antagonist(s) (LAMA) use			
Pateints using LAMA medication			
Units: Subjects			
LAMA	546	548	1094
No-LAMA	628	630	1258
BMI Category			

Body-Mass Index Category.			
Units: Subjects			
Under weight: < 18.5	95	100	195
Normal weight: >= 18.5 to < 25	480	468	948
Over weight: >= 25 to < 30	347	342	689
Obese: >= 30	252	268	520
Weight			
Units: Kg			
arithmetic mean	72.57	73.63	
standard deviation	± 18.67	± 19.57	-
Height			
Units: cm			
arithmetic mean	167.53	167.8	
standard deviation	± 9.39	± 9.35	-
BMI			
Body-Mass Index			
Units: kg/m2			
arithmetic mean	25.72	25.99	
standard deviation	± 5.72	± 5.91	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Dose-matched placebo, oral administration, once per day.	
Reporting group title	Roflumilast
Reporting group description:	
Roflumilast 500 µg, oral administration, once per day	

Primary: Rate of moderate or severe COPD exacerbations per patient per year.

End point title	Rate of moderate or severe COPD exacerbations per patient per year.
End point description:	
Rate of moderate or severe COPD exacerbations, defined as requiring oral or parenteral glucocorticosteroids (moderate) or requiring hospitalization and/or leading to death (severe), during the double-blind treatment period.	
End point type	Primary
End point timeframe:	
Baseline to Week 52	

End point values	Placebo	Roflumilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1174[1]	1178[2]		
Units: COPD exacerbations per patient per year				
number (confidence interval 95%)	1.27 (1.17 to 1.39)	1.17 (1.06 to 1.28)		

Notes:

[1] - Intent-to-Treat Study Population

[2] - Intent-to-Treat Study Population

Statistical analyses

Statistical analysis title	Rate ratio (Roflumilast/Placebo)
Statistical analysis description:	
A rate ratio < 1 represents a favorable outcome for the test treatment.	
Comparison groups	Placebo v Roflumilast
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1634 [3]
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	0.92

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.04
Variability estimate	Standard error of the mean
Dispersion value	0.063

Notes:

[3] - p-values are based on a negative binomial regression with factors Treatment and LAMA use.

Statistical analysis title	Subgroup Analysis - By Sex - Male
Comparison groups	Placebo v Roflumilast
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0195
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	0.97
Variability estimate	Standard error of the mean
Dispersion value	0.08

Statistical analysis title	Subgroup Analysis - By Sex - Female
Comparison groups	Placebo v Roflumilast
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3164
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	1.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	1.35
Variability estimate	Standard error of the mean
Dispersion value	0.101

Statistical analysis title	Subgroup Analysis - By LABA/ICS Thearapy - Advair

Statistical analysis description:

Subgroup analysis between patients taking Advair verses patients taking Symbicort as LABA/ICS therapy.

Comparison groups	Placebo v Roflumilast
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0385
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	0.99
Variability estimate	Standard error of the mean
Dispersion value	0.076

Statistical analysis title	Subgroup Analysis -By LABA/ICS Thearapy -Symbicort

Statistical analysis description:

Subgroup analysis between patients taking Advair verses patients taking Symbicort as LABA/ICS therapy.

Comparison groups	Placebo v Roflumilast
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6475
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.32
Variability estimate	Standard error of the mean
Dispersion value	0.114

Secondary: Rate of COPD exacerbations that led to hospitalization or death (ie, severe COPD exacerbations)

End point title	Rate of COPD exacerbations that led to hospitalization or death (ie, severe COPD exacerbations)

End point description:

Rate of moderate or severe COPD exacerbations, defined as requiring hospitalization and/or leading to death (severe), during the double-blind treatment period.

End point type	Secondary

End point timeframe: Week 0 (Visit 2) to Week 52

End point values	Placebo	Roflumilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1174[4]	1178[5]		
Units: COPD exacerbations per patient per year				
number (confidence interval 95%)	0.29 (0.25 to 0.34)	0.28 (0.23 to 0.33)		

Notes:

[4] - Intent-to Treat Population

[5] - Intent-to-Treat Population

Statistical analyses

Statistical analysis title	Rate ratio (Roflumilast/Placebo)
Statistical analysis description: Rate ratio < 1 represents a favorable outcome for the test treatment.	
Comparison groups	Roflumilast v Placebo
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6354 [6]
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.75
upper limit	1.19
Variability estimate	Standard error of the mean
Dispersion value	0.118

Notes:

[6] - p-values are based on a negative binomial regression with factors Treatment and LAMA use.

Secondary: Rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics

End point title	Rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics
End point description: Rate of moderate or severe COPD exacerbations treated with antibiotics during the double-blind treatment period.	
End point type	Secondary
End point timeframe: Week 0 (Visit 2) to Week 52	

End point values	Placebo	Roflumilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1174[7]	1178[8]		
Units: COPD Exacerbations per Patient per Year				
number (confidence interval 95%)	1.45 (1.34 to 1.57)	1.31 (1.2 to 1.43)		

Notes:

[7] - Intent-to-Treat Population

[8] - Intent-to-Treat Population

Statistical analyses

Statistical analysis title	Rate ratio (Roflumilast/Placebo)

Statistical analysis description:

A rate ratio < 1 represents a favorable outcome for the test treatment.

Comparison groups	Roflumilast v Placebo
Number of subjects included in analysis	2352
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0884 [9]
Method	negative binomial regression
Parameter estimate	Rate Ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1.02
Variability estimate	Standard error of the mean
Dispersion value	0.06

Notes:

[9] - p-values are based on a negative binomial regression with factors Treatment and LAMA use.

Secondary: Mean change from randomization (Visit 2) over 52 weeks of treatment in predose forced expiratory volume in 1 second (FEV1)

End point title	Mean change from randomization (Visit 2) over 52 weeks of treatment in predose forced expiratory volume in 1 second (FEV1)

End point description:

Mean change from randomization (Visit 2) over 52 weeks of treatment in predose forced expiratory volume in 1 second (FEV1)

End point type	Secondary

End point timeframe:

Week 0 (Visit 2) to Week 52

End point values	Placebo	Roflumilast		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1105[10]	1054[11]		
Units: Liters				
least squares mean (standard error)	-0.0091 (± 0.0047)	0.0441 (± 0.0048)		

Notes:

[10] - Intent-to-Treat Population who the completed 52-week treatment period

[11] - Intent-to-Treat Population who the completed 52-week treatment period

Statistical analyses

Statistical analysis title	LS Mean difference (Roflumilast - Placebo)
Comparison groups	Placebo v Roflumilast
Number of subjects included in analysis	2159
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [12]
Method	Mixed Model for Repeated Measures (MMRM)
Parameter estimate	Mean difference (final values)
Point estimate	0.0532
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.04
upper limit	0.0664
Variability estimate	Standard error of the mean
Dispersion value	0.0067

Notes:

[12] - The MMRM analysis is based on all postbaseline observed data using a mixed model with terms for treatment, baseline, visit,
LAMA use, treatment-by-visit and baseline-by-visit interactions.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data was collected from the start of the 52-week double-blind treatment period, to 30 days after the end of treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18

Reporting groups

Reporting group title	Placebo

Reporting group description:

Dose-matched placebo, oral administration, once per day.

Reporting group title	Roflumilast

Reporting group description:

Roflumilast 500 µg, oral administration, once per day

Serious adverse events	Placebo	Roflumilast	
Total subjects affected by serious adverse events			
subjects affected / exposed	162 / 1174 (13.80%)	180 / 1178 (15.28%)	
number of deaths (all causes)	25	30	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Gastric cancer			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	3 / 1174 (0.26%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenosquamous cell lung cancer			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer stage 0			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epithelioid mesothelioma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cancer			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal squamous cell carcinoma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma metastatic			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lung			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to lymph nodes			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to spine			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spleen			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine carcinoma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia vera			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small cell lung cancer limited stage			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung squamous cell carcinoma stage III			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer stage III			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			

subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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	1 / 1174 (0.09%)	0 / 1178 (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 of lung			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 1174 (0.00%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	2 / 1174 (0.17%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Angiodysplasia			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemic shock			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	3 / 1174 (0.26%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intermittent claudication			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Superior vena cava syndrome			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Femoral artery occlusion			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Accelerated hypertension			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Non-cardiac chest pain			

subjects affected / exposed	3 / 1174 (0.26%)	6 / 1178 (0.51%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Sudden cardiac death			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Death			
subjects affected / exposed	3 / 1174 (0.26%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
Fatigue			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Discomfort			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oedema peripheral			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral swelling			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pyrexia			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest pain			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seasonal allergy			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Adnexa uteri mass			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adnexal torsion			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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			
Acute respiratory failure			
subjects affected / exposed	6 / 1174 (0.51%)	7 / 1178 (0.59%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 4	0 / 3	
Respiratory failure			
subjects affected / exposed	5 / 1174 (0.43%)	7 / 1178 (0.59%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 3	
Pneumothorax			
subjects affected / exposed	2 / 1174 (0.17%)	4 / 1178 (0.34%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dyspnoea			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Laryngeal granuloma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory muscle weakness			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic obstructive pulmonary disease			

subjects affected / exposed	3 / 1174 (0.26%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Chronic respiratory failure			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasal polyps			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obliterative bronchiolitis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bullous lung disease			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hydrothorax			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperventilation			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary embolism			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus congestion			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sputum retention			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lung infiltration			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Completed suicide			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Confusional state			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Depression			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Major depression			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Schizophrenia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Mental status changes			

subjects affected / exposed	2 / 1174 (0.17%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Insomnia			
subjects affected / exposed	2 / 1174 (0.17%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	2 / 2	1 / 2	
deaths causally related to treatment / all	2 / 2	1 / 2	
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tinea pedis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nutritional condition abnormal			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Weight increased			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 1174 (0.34%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 1	

Femoral neck fracture			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heat stroke			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ligament sprain			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary contusion			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			

subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Road traffic accident			
subjects affected / exposed	3 / 1174 (0.26%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choledochal cyst			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertrophic cardiomyopathy			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 1174 (0.09%)	7 / 1178 (0.59%)	
occurrences causally related to treatment / all	0 / 1	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	0 / 1174 (0.00%)	5 / 1178 (0.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 5	
Atrial fibrillation			
subjects affected / exposed	5 / 1174 (0.43%)	4 / 1178 (0.34%)	
occurrences causally related to treatment / all	0 / 5	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 5	
Angina pectoris			
subjects affected / exposed	1 / 1174 (0.09%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	3 / 1174 (0.26%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 3	0 / 3	
Cardiogenic shock			
subjects affected / exposed	0 / 1174 (0.00%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Supraventricular tachycardia			
subjects affected / exposed	0 / 1174 (0.00%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	1 / 1174 (0.09%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	3 / 1174 (0.26%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 3	
Myocardial infarction			
subjects affected / exposed	1 / 1174 (0.09%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Acute coronary syndrome			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Arrhythmia			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	4 / 1174 (0.34%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomyopathy			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	2 / 1174 (0.17%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cor pulmonale acute			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Coronary artery insufficiency			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Left ventricular failure			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 1	
Stress cardiomyopathy			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial rupture			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tachycardia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiomegaly			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 1174 (0.17%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 1174 (0.17%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cervical radiculopathy			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ischaemic stroke			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebral ventricle dilatation			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dizziness			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Hydrocephalus			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lumbar radiculopathy			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 1174 (0.00%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Vascular encephalopathy			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Drooling			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hemiparesis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 1174 (0.00%)	4 / 1178 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 2	
Iron deficiency anaemia			

subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Anaemia macrocytic			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyphaema			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Keratitis			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mydriasis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 1174 (0.09%)	5 / 1178 (0.42%)	
occurrences causally related to treatment / all	0 / 1	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nausea			
subjects affected / exposed	0 / 1174 (0.00%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 1	1 / 2	
Colitis ischaemic			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	2 / 1174 (0.17%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal hernia			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 2	
Abdominal strangulated hernia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food poisoning			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal angiodysplasia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal hypertensive gastropathy			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varices oesophageal			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 2	
Dyspepsia			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Erosive duodenitis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis erosive			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 1174 (0.09%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Abdominal pain upper			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Faeces soft			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemorrhoidal haemorrhage			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Rectal haemorrhage			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Abdominal discomfort			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Dysphagia			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Salivary hypersecretion			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	2 / 1174 (0.17%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	3 / 1174 (0.26%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 1	
Erythema			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Night sweats			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pruritus			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus ureteric			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pollakiuria			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Urinary retention			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Azotaemia			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 1174 (0.09%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Cervical spinal stenosis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lumbar spinal stenosis			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patellofemoral pain syndrome			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyalgia rheumatica			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bursitis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteochondrosis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (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	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Muscle spasms			
subjects affected / exposed	2 / 1174 (0.17%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Muscular weakness			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neck pain			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Periarthritis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Osteopenia			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	45 / 1174 (3.83%)	47 / 1178 (3.99%)	
occurrences causally related to treatment / all	2 / 48	0 / 52	
deaths causally related to treatment / all	0 / 5	0 / 11	
Sepsis			
subjects affected / exposed	4 / 1174 (0.34%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastroenteritis			
subjects affected / exposed	1 / 1174 (0.09%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	1 / 1	0 / 1	
Pneumonia bacterial			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 1174 (0.17%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Amoebic dysentery			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			

subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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	2 / 1174 (0.17%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			
subjects affected / exposed	7 / 1174 (0.60%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
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	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mycobacterium avium complex infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orchitis			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Subcutaneous abscess			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tooth infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 2	
Urosepsis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Viral infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic hepatitis C			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related sepsis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			

subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonal			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary tuberculosis			
subjects affected / exposed	2 / 1174 (0.17%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Systemic candida			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis viral			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tuberculosis			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal sepsis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bronchitis bacterial			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Candida infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fungal infection			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Furuncle			
subjects affected / exposed	1 / 1174 (0.09%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasopharyngitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Onychomycosis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tracheitis			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pharyngitis			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 1174 (0.09%)	3 / 1178 (0.25%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	1 / 1	0 / 3	
Hyponatraemia			
subjects affected / exposed	0 / 1174 (0.00%)	2 / 1178 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cachexia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Decreased appetite			
subjects affected / exposed	3 / 1174 (0.26%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	2 / 3	1 / 1	
deaths causally related to treatment / all	2 / 3	0 / 0	
Dehydration			

subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malnutrition			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Fluid imbalance			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gout			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercholesterolaemia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hyperglycaemia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypoalbuminaemia			
subjects affected / exposed	0 / 1174 (0.00%)	1 / 1178 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyslipidaemia			

subjects affected / exposed	1 / 1174 (0.09%)	0 / 1178 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Roflumilast	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	188 / 1174 (16.01%)	317 / 1178 (26.91%)	
Investigations			
Weight decreased			
subjects affected / exposed	27 / 1174 (2.30%)	91 / 1178 (7.72%)	
occurrences (all)	28	91	
Nervous system disorders			
Headache			
subjects affected / exposed	48 / 1174 (4.09%)	80 / 1178 (6.79%)	
occurrences (all)	56	96	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	36 / 1174 (3.07%)	119 / 1178 (10.10%)	
occurrences (all)	38	137	
Nausea			
subjects affected / exposed	30 / 1174 (2.56%)	62 / 1178 (5.26%)	
occurrences (all)	32	71	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	66 / 1174 (5.62%)	60 / 1178 (5.09%)	
occurrences (all)	103	75	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 August 2011	• Per FDA request, an MMRM would be used for the secondary efficacy parameter. The dependent variable would be the change from randomization (Visit 2) to each scheduled post-randomization visit (encompassing all available measurements in a patient) during the treatment period • Stratification up to 60% of patients on LAMA added onto ICS/LABA • As per FDA request, changed the inclusion criterion for FEV1 predicted from < 60% to ≤ 50% • Defined counting and merging exacerbations occurring within 10 days of each other as a single exacerbation • Added urine pregnancy testing to Visit 4, 5, 6, 7, and 8 for women of childbearing potential • Per FDA request, added follow-up visit assessments for patients discontinuing, including FEV1, exacerbation, safety, and concomitant medication data collection • Decreased the washout period for theophylline from 3 months to 1 month prior to enrollment
02 February 2012	• MACE and the specified subcategories of MACE would be presented by treatment group • MACE would be evaluated according to pre-defined criteria by a MACE Adjudication Committee • Provided a clarification of the assessments to be performed in patients who discontinued double-blind investigational product • Provided clarifications to the inclusion and exclusion criteria and the schedule of evaluations • Provided additional information on the C-SSRS and administration of the eC-SSRS • Provided additional information on the sensitivity analyses to be performed for the primary and secondary efficacy parameters
15 May 2013	• With respect to FEV1 measurements, changed the term prebronchodilator to predose • Clarified how to handle missed and skipped visits • Added guidance on how to prepare a patient for the screening visit • Updated the MACE section that reflected what was written in the Committee Charter • Updated drug dispensing table • Clarified the reading of ECGs

02 April 2014	• COPD exacerbations that met criteria for an SAE were recorded in the COPD exacerbation section of the EDC as soon as possible after their occurrence and were subject to on-going safety monitoring and evaluation • Examples of acceptable qualifying documentation for COPD exacerbations were added to the inclusion criteria, while a patient interview was removed as an acceptable method of documentation • An offset variable in the negative binomial model for COPD exacerbations was added to exclude the days during which new exacerbations could not occur; ie, the days when the patient was experiencing existing moderate or severe exacerbations and 10 days after each moderate or severe exacerbation • Additional telephone contacts were added so patients were assessed for COPD exacerbations every 4 weeks between visits • PK sampling instructions were clarified and updated in text and in Appendix IV • Appendices VII (Daliresp package insert), VIII (Advair package insert), and IX (Symbicort package insert) of the protocol were updated
06 August 2015	Added 2 secondary efficacy endpoints (rate of COPD exacerbations that led to hospitalization or death [ie, severe COPD exacerbations] and rate of moderate or severe COPD exacerbations or COPD exacerbations treated with antibiotics), which were previously identified as additional efficacy parameters • Replaced the Poisson regression with Pearson Chi-square correction for scale with the Poisson regression with robust variance estimate using the sandwich method, for consistency with statistical methods for other exacerbation endpoints • Required the assessment of Hy's Law criteria as a laboratory assessment and described how the data would be summarized

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported