Clinical trial results:
A phase III, 52 week, randomized, double-blind, 3-arm parallel group study, comparing the efficacy, safety and tolerability of the fixed dose triple combination fluticasone furoate/umeclidinium/vilanterol, with the fixed dose dual combinations of fluticasone furoate/vilanterol and umeclidinium/vilanterol, all administered once-daily in the morning via a dry powder inhaler in subjects with chronic obstructive pulmonary disease

Summary

EudraCT number	2013-003075-35
Trial protocol	NL FI PL SE DE AT CZ BE DK ES NO RO HR
Global end of trial date	17 July 2017

Results information

Result version number	v1
This version publication date	22 July 2018
First version publication date	22 July 2018

Trial information

Trial identification

Sponsor protocol code	116855

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	GlaxoSmithKline
Sponsor organisation address	980 Great West Road, Brentford, Middlesex, United Kingdom,
Public contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,
Scientific contact	GSK Response Center, GlaxoSmithKline, 1 866-435-7343,

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	19 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI), to reduce the annual rate of moderate and severe exacerbations compared with dual therapy of FF/VI or UMEC/VI in participants with, chronic obstructive pulmonary disease (COPD).

Protection of trial subjects:

An Independent data monitoring committee (IDMC) reviewed unblinded safety data periodically throughout the trial to ensure participant safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 June 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 1085
Country: Number of subjects enrolled	Australia: 256
Country: Number of subjects enrolled	Austria: 130
Country: Number of subjects enrolled	Belgium: 139
Country: Number of subjects enrolled	Brazil: 143
Country: Number of subjects enrolled	Canada: 309
Country: Number of subjects enrolled	Chile: 434
Country: Number of subjects enrolled	China: 669
Country: Number of subjects enrolled	Colombia: 62
Country: Number of subjects enrolled	Czech Republic: 150
Country: Number of subjects enrolled	Denmark: 128
Country: Number of subjects enrolled	Finland: 101
Country: Number of subjects enrolled	France: 175
Country: Number of subjects enrolled	Germany: 1408
Country: Number of subjects enrolled	Hong Kong: 50
Country: Number of subjects enrolled	Israel: 265
Country: Number of subjects enrolled	Japan: 470
Country: Number of subjects enrolled	Korea, Republic of: 424
Country: Number of subjects enrolled	Netherlands: 367
Country: Number of subjects enrolled	New Zealand: 103

Country: Number of subjects enrolled	Norway: 122
Country: Number of subjects enrolled	Peru: 253
Country: Number of subjects enrolled	Philippines: 130
Country: Number of subjects enrolled	Poland: 95
Country: Number of subjects enrolled	Puerto Rico: 56
Country: Number of subjects enrolled	Romania: 108
Country: Number of subjects enrolled	Russian Federation: 368
Country: Number of subjects enrolled	Singapore: 25
Country: Number of subjects enrolled	South Africa: 365
Country: Number of subjects enrolled	Spain: 654
Country: Number of subjects enrolled	Sweden: 168
Country: Number of subjects enrolled	Thailand: 174
Country: Number of subjects enrolled	Turkey: 60
Country: Number of subjects enrolled	Ukraine: 113
Country: Number of subjects enrolled	United Kingdom: 292
Country: Number of subjects enrolled	United States: 3936
Country: Number of subjects enrolled	Vietnam: 118
Worldwide total number of subjects	13905
EEA total number of subjects	4037

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)	6312
From 65 to 84 years	7476
85 years and over	117

Subject disposition

Recruitment

Recruitment details:

Participants with chronic obstructive pulmonary disease (COPD), were randomized to the study. Study was conducted from 30 June 2014 to 17 July 2017, at total of 971 sites in 37 countries.

Pre-assignment

Screening details:

A total of 13,906 participants (par.) were registered for the study of which 13099 were screened (807 pre-screen failure) and 10,367 were randomized to the study (2744 screen failure). Of which 12 par. were randomized in error and 10,355 were randomized to actual treatment and included in Intent to treat (ITT) Population.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FF/UMEC/VI

Arm description:

The eligible participants in this arm received Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) as a fixed dose combination (FDC) as 100 microgram (µcg)/62.5µcg/25µcg once daily (QD) via a dry powder inhaler (DPI), in the morning, for duration of 52 weeks.

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

Dosage and administration details:

Administered as 100µcg/62.5µcg/25µcg, QD in morning via DPI for 52-weeks

Arm title	FF/VI

Arm description:

The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.

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

Dosage and administration details:

Administered as 100µcg/25µcg, QD in morning via DPI for 52-weeks

Arm title	UMEC/VI

Arm description:

The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.

Arm type	Active comparator

Investigational medicinal product name	Umeclidinium/ Vilanterol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Administered as 62.5µcg/25µcg, QD in morning via DPI for 52-weeks

Number of subjects in period 1[1]	FF/UMEC/VI	FF/VI	UMEC/VI
Started	4151	4134	2070
Completed Investigational Product (IP)	3393 [2]	3094 [3]	1504 [4]
Not completed IP	758 [5]	1040 [6]	566 [7]
Withdrew IP (WIP): Adverse event	249 [8]	325 [9]	186 [10]
WIP: Lack of efficacy	163 [11]	313 [12]	172 [13]
Withdrew IP: Protocol deviation	32 [14]	41 [15]	19 [16]
WIP (Other): Stopping criteria reached	4 [17]	1 [18]	2 [19]
WIP: Study closed/terminated	5 [20]	2 [21]	5 [22]
WIP: Lost to follow-up	21 [23]	25 [24]	14 [25]
WIP: Investigator discretion	33 [26]	36 [27]	15 [28]
WIP: Withdrawal by participant	250 [29]	296 [30]	153 [31]
WIP :Did not complete Study treatment	1 [32]	1 [33]	0 [34]
Completed	3714	3598	1775
Not completed	437	536	295
Adverse event, serious fatal	85	91	58
Physician decision	47	57	28
Consent withdrawn by subject	192	261	130
Adverse event, non-fatal	77	89	53
Other: Reason not provided by site	1	-	-
Other: Study Closed or terminated	5	2	4
Lost to follow-up	30	36	22

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 13,906 participants (par.) were registered for the study of which 13099 were screened (807 pre-screen failure) and 10,367 were randomized to the study (2744 screen failure). Of which 12 par. were randomized in error and 10,355 were randomized to actual treatment and included in Intent to treat (ITT) Population. For age and country, data only for 13,905 par., has been reported as the age for one participant was not available.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[11] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[12] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[13] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[14] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[15] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[16] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that

completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[17] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[18] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[19] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[20] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[21] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[22] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[23] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[24] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[25] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[26] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[27] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[28] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[29] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.

[30] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[31] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[32] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[33] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.
[34] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: This number indicates the number of participants with withdrawal from investigational product only.

Baseline characteristics

Reporting groups	
Reporting group title	FF/UMEC/VI
Reporting group description:	
The eligible participants in this arm received Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) as a fixed dose combination (FDC) as 100 microgram (µcg)/62.5µcg/25µcg once daily (QD) via a dry powder inhaler (DPI), in the morning, for duration of 52 weeks.	
Reporting group title	FF/VI
Reporting group description:	
The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.	
Reporting group title	UMEC/VI
Reporting group description:	
The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.	

Reporting group values	FF/UMEC/VI	FF/VI	UMEC/VI
Number of subjects	4151	4134	2070
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	65.3	65.3	65.2
standard deviation	± 8.24	± 8.30	± 8.26
Gender categorical Units: Subjects			
Female	1385	1386	714
Male	2766	2748	1356
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	87	86	45
Asian - Central/South Asian Heritage	6	3	1
Asian - East Asian Heritage	362	374	177
Asian - Japanese Heritage	151	152	82
Asian - South East Asian Heritage	149	147	75
Black or African American	122	99	43
Native Hawaiian or other Pacific Islander	2	3	2
White - Arabic/North African Heritage	31	45	24
White - White/Caucasian/European Heritage	3200	3179	1604
Multiple	41	45	17
Unknown	0	1	0

Reporting group values	Total		
Number of subjects	10355		

Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	3485		
Male	6870		
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	218		
Asian - Central/South Asian Heritage	10		
Asian - East Asian Heritage	913		
Asian - Japanese Heritage	385		
Asian - South East Asian Heritage	371		
Black or African American	264		
Native Hawaiian or other Pacific Islander	7		
White - Arabic/North African Heritage	100		
White - White/Caucasian/European Heritage	7983		
Multiple	103		
Unknown	1		

End points

End points reporting groups

Reporting group title	FF/UMEC/VI
Reporting group description:	
The eligible participants in this arm received Fluticasone Furoate (FF)/Umeclidinium (UMEC)/Vilanterol (VI) as a fixed dose combination (FDC) as 100 microgram (µcg)/62.5µcg/25µcg once daily (QD) via a dry powder inhaler (DPI), in the morning, for duration of 52 weeks.	
Reporting group title	FF/VI
Reporting group description:	
The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.	
Reporting group title	UMEC/VI
Reporting group description:	
The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.	

Primary: Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI and FF/VI

End point title	Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI and FF/VI
End point description:	
The annual rate of moderate or severe COPD, exacerbations which occurred during treatment was assessed. Moderate exacerbations were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death. Analysis performed using a generalized linear model assuming a negative binomial distribution. ITT population was used which comprised of all randomized participants, excluding those who were randomized in error. Only those participants with non-missing co-variates were included in the analysis.	
End point type	Primary
End point timeframe:	
Up to Week 52	

End point values	FF/UMEC/VI	FF/VI	UMEC/VI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4145[1]	4133[2]	2069[3]	
Units: Modelled annual exacerbation rate				
least squares mean (confidence interval 95%)				
Modelled annual exacerbation rate	0.91 (0.87 to 0.95)	1.07 (1.02 to 1.12)	1.21 (1.14 to 1.29)	

Notes:

[1] - ITT Population

[2] - ITT Population

[3] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Covariates of treatment group, sex, exacerbation history (<=1, >=2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted Forced expiratory volume in 1 second (FEV1) (Screening) were used.

Comparison groups	UMEC/VI v FF/UMEC/VI
Number of subjects included in analysis	6214
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	< 0.001
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.81

Notes:

[4] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Covariates of treatment group, sex, exacerbation history (<=1, >=2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted FEV1 (Screening) were used.

Comparison groups	FF/VI v FF/UMEC/VI
Number of subjects included in analysis	8278
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	< 0.001
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	0.9

Notes:

[5] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons

Secondary: Change from Baseline in trough FEV1, at Week 52 comparing FF/UMEC/VI with FF/VI

End point title	Change from Baseline in trough FEV1, at Week 52 comparing FF/UMEC/VI with FF/VI[6]

End point description:

FEV1, was defined as the amount of air a person exhales in one second. Change from Baseline, was calculated as the value of FEV1 at Week 52 minus the value at Baseline. Baseline for trough FEV1 was defined as Day 1 (Pre-dose). Only those participants with non-missing co-variates were included in the analysis. The analysis was performed using a Repeated measures model with covariates of treatment group, smoking status (Screening), geographical region, visit, Baseline, Baseline by visit and treatment group by visit interactions.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	FF/UMEC/VI	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3366[7]	3060[8]		
Units: Liter				
least squares mean (standard error)				
Liter	0.094 (± 0.0042)	-0.003 (± 0.0044)		

Notes:

[7] - ITT Population

[8] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI v FF/UMEC/VI
Number of subjects included in analysis	6426
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	< 0.001
Method	Mixed Models Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	0.097
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.085
upper limit	0.109
Variability estimate	Standard error of the mean
Dispersion value	0.0061

Notes:

[9] - The adjusted p-value at Week 52 should be compared against a reference level of 0.05 in order to infer statistical significance for the comparison of FF/UMEC/VI versus (vs) FF/VI at Week 52.

Secondary: Change from Baseline in St. George's Respiratory Questionnaire for (SGRQ) Total Score at Week 52 comparing FF/UMEC/VI with FF/VI

End point title	Change from Baseline in St. George's Respiratory Questionnaire for (SGRQ) Total Score at Week 52 comparing FF/UMEC/VI with FF/VI[10]

End point description:

SGRQ is a disease specific-questionnaire, designed to measure impact of respiratory disease and its treatment on a COPD participant's Health Related Quality of Life (HRQoL). SGRQ contains 14 questions with total of 40 items grouped into three domains (Symptoms, Activity, and Impacts). The overall summary score along with scores for the individual domains of symptoms, activity and impacts were assessed. Score was calculated by summing the pre-assigned weights of answers, dividing by sum of maximum weights for items in SGRQ. Total scores ranged from 0 to 100. A decrease in score indicates improvement in HRQoL and higher score implies worse quality of life. Change from Baseline was calculated as total score at Week 52 minus value at Baseline. Baseline was defined as Day 1. Minimum

clinically important difference (MCID) for this instrument is a 4-point improvement (decrease from Baseline). Only those participants with non-missing co-variates were included in the analysis.

End point type	Secondary

End point timeframe:

Baseline and Week 52

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	FF/UMEC/VI	FF/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3318[11]	3026[12]		
Units: Scores on SGRQ scale				
least squares mean (standard error)				
Scores on SGRQ scale	-5.5 (± 0.23)	-3.7 (± 0.24)		

Notes:

[11] - ITT Population

[12] - ITT Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI v FF/UMEC/VI
Number of subjects included in analysis	6344
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	< 0.001
Method	Mixed Models Repeated Measures
Parameter estimate	Mean difference (net)
Point estimate	-1.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.4
upper limit	-1.1
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[13] - The adjusted p-value at Week 52 should be compared against a reference level of 0.05 in order to infer statistical significance for the comparison of FF/UMEC/VI vs FF/VI at Week 52.

Secondary: Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI

End point title	Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with FF/VI and with UMEC/VI

End point description:

This measures the number of days, to first onset of moderate or severe exacerbations. Moderate exacerbations, were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations, were defined as exacerbations that required hospitalization or resulted in death. Hazard ratio from Cox proportional hazards model with covariates of treatment group, sex, exacerbation history (<=1, >=2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted FEV1 (Screening), have been reported. Only those participants with non-missing co-variates

were included in analysis. The first quartile and median time to onset, are taken from the Kaplan-Meier estimates. If <25% (and <50%) of participants experienced the event within a treatment then Q1 (and median) time to onset are displayed as 99999 which is not applicable for that treatment.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI	FF/VI	UMEC/VI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1959[14]	2039[15]	1036[16]	
Units: Days				
First quartile time to onset	112	81	73	
Median time to onset	99999	99999	306	

Notes:

[14] - ITT population

[15] - ITT population

[16] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/UMEC/VI v FF/VI
Number of subjects included in analysis	3998
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	< 0.001
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	0.91

Notes:

[17] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

Statistical analysis title	Statistical analysis 2
Comparison groups	UMEC/VI v FF/UMEC/VI
Number of subjects included in analysis	2995
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	< 0.001
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.78
upper limit	0.91

Notes:

[18] - The adjusted p-values should be compared against a reference level of 0.05 in order to infer statistical significance for either of the comparisons.

Secondary: Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of participants with a blood eosinophil count >=150 cells per microliter

End point title	Annual rate of on-treatment moderate/severe exacerbations comparing FF/UMEC/VI with UMEC/VI in the subset of participants with a blood eosinophil count >=150 cells per microliter[19]

End point description:

The annual rate of moderate or severe COPD exacerbations during the treatment, for participants with blood eosinophil count >=150 cells per microliter at Baseline, has been reported. . Moderate exacerbations, were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death. Only those participants with non-missing co-variates and non-missing EOS at Baseline were included in the analysis.

End point type	Secondary

End point timeframe:

Up to Week 52

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	FF/UMEC/VI	UMEC/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2296[20]	1195[21]		
Units: Modelled annual exacerbation rate				
least squares mean (confidence interval 95%)				
Modelled annual exacerbation rate	0.95 (0.90 to 1.01)	1.39 (1.29 to 1.51)		

Notes:

[20] - ITT population

[21] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/UMEC/VI v UMEC/VI
Number of subjects included in analysis	3491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial Model
Parameter estimate	Rate ratio
Point estimate	0.68

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	0.75

Secondary: Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of particpants with a blood eosinophil count >=150 cells per microliter at Baseline

End point title	Time to first on-treatment moderate/severe exacerbation comparing FF/UMEC/VI with UMEC/VI in the subset of particpants with a blood eosinophil count >=150 cells per microliter at Baseline[22]

End point description:

This measures the number of days, to the first onset of moderate or severe exacerbations for participants with blood eosinophil count >=150 cells per microliter, at Baseline has been reported. Moderate exacerbations, were defined as exacerbations that required treatment with oral/systemic corticosteroids and/or antibiotics (not involving hospitalization or resulting in death). Severe exacerbations, were defined as exacerbations that required hospitalization or resulted in death. Only those participants with non-missing co-variates and non missing EOS at Baseline were included in the analysis. First quartile and median time to onset are taken from the Kaplan-Meier estimates. If <25% (and <50%) of participants experienced the event within a treatment then Q1 (and median) time to onset are displayed as 99999, not applicable for that treatment.

End point type	Secondary

End point timeframe:

Up to Week 52

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint is only reporting on a subset of the arms that are contained in the baseline period.

End point values	FF/UMEC/VI	UMEC/VI		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2296[23]	1195[24]		
Units: Days				
First quartile time to onset	107	55		
Median time to onset	99999	253		

Notes:

[23] - ITT population

[24] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	UMEC/VI v FF/UMEC/VI
Number of subjects included in analysis	3491
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Cox proportional hazard model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	0.85

Secondary: Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

End point title	Annual rate of on-treatment severe exacerbations comparing FF/UMEC/VI with FF/VI and with UMEC/VI

End point description:

The annual rate of severe COPD exacerbations during the treatment, has been reported. . Severe exacerbations were defined as exacerbations that required hospitalization or resulted in death. The covariates of treatment group, sex, exacerbation history (<=1, >=2 moderate/severe), smoking status (Screening), geographical region and post-bronchodilator percent predicted FEV1 (Screening) were used. Only those participants with non-missing co-variates were included in the analysis.

End point type	Secondary

End point timeframe:

Up to Week 52

End point values	FF/UMEC/VI	FF/VI	UMEC/VI	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	4145[25]	4133[26]	2069[27]	
Units: Modelled annual exacerbation rate				
least squares mean (confidence interval 95%)				
Modelled annual exacerbation rate	0.13 (0.12 to 0.14)	0.15 (0.13 to 0.16)	0.19 (0.17 to 0.22)	

Notes:

[25] - ITT population

[26] - ITT population

[27] - ITT population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	FF/VI v FF/UMEC/VI
Number of subjects included in analysis	8278
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.064
Method	Negative binomial model
Parameter estimate	Rate Ratio
Point estimate	0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.01

Statistical analysis title	Statistical analysis 2
Comparison groups	FF/UMEC/VI v UMEC/VI
Number of subjects included in analysis	6214
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Negative binomial model
Parameter estimate	Rate ratio
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.78

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment Serious adverse events (SAEs) and Adverse events (AEs) are reported from the first dose of randomized medication up to Week 52.

Adverse event reporting additional description:

All AE's and SAE's in the ITT Population were reported. The number of on-treatment deaths are reported from date of first dose of study medication up to the day after the last date of study medication.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

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

Reporting group description:

The eligible participants in this arm received FF/UMEC/VI as a FDC as 100 µcg/62.5µcg/25µcg, QD via a DPI, in the morning, for duration of 52 weeks.

Reporting group title	UMEC/VI 62.5/25

Reporting group description:

The eligible participants in this arm received UMEC/VI 62.5µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.

Reporting group title	FF/VI 100/25

Reporting group description:

The eligible participants in this arm received FF/VI 100µcg/25µcg QD via DPI, in the morning for duration of 52 weeks.

Serious adverse events	FF/UMEC/VI 100/62.5/25	UMEC/VI 62.5/25	FF/VI 100/25
Total subjects affected by serious adverse events			
subjects affected / exposed	895 / 4151 (21.56%)	470 / 2070 (22.71%)	850 / 4134 (20.56%)
number of deaths (all causes)	68	49	76
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 2	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign breast neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign fallopian tube neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bladder neoplasm			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder transitional cell carcinoma stage I			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain neoplasm			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Breast cancer			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial carcinoma			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervix carcinoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Colon cancer stage I			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epiglottic carcinoma			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibroma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glottis carcinoma			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemangioma of spleen			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic angiosarcoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic cancer metastatic			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatic neoplasm			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatocellular carcinoma			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal cancer			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngeal squamous cell carcinoma			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	4 / 4151 (0.10%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung adenocarcinoma stage III			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Lung carcinoma cell type unspecified stage I			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	6 / 4151 (0.14%)	2 / 2070 (0.10%)	10 / 4134 (0.24%)
occurrences causally related to treatment / all	0 / 6	0 / 2	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Lung squamous cell carcinoma stage II			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of ampulla of Vater			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant neoplasm of unknown primary site			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to bone			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Metastases to liver			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lymph nodes			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Monoclonal gammopathy			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine carcinoma			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuroendocrine tumour of the lung			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oesophageal carcinoma			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oral neoplasm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pancreatic neoplasm			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Papilloma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			

subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	4 / 4151 (0.10%)	1 / 2070 (0.05%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyogenic granuloma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcoma			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small cell lung cancer metastatic			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Small intestine carcinoma			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue sarcoma			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of lung			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Squamous cell carcinoma of the cervix			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the oral cavity			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Throat cancer			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsil cancer			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral cancer			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vulval cancer			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Acute aortic syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aneurysm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm rupture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Circulatory collapse			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Deep vein thrombosis			

subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Embolism arterial			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery aneurysm			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemodynamic instability			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	3 / 4151 (0.07%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 3	1 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery aneurysm			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			

subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peripheral artery thrombosis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Peripheral venous disease			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thrombosis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose ulceration			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Surgical and medical procedures			
Hernia repair			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	5 / 4151 (0.12%)	7 / 2070 (0.34%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 5	0 / 7	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Complication associated with device			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Condition aggravated			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	3 / 4151 (0.07%)	2 / 2070 (0.10%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 3	0 / 2	0 / 5
General physical health deterioration			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hernia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Implant site fibrosis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated hernia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Non-cardiac chest pain			
subjects affected / exposed	8 / 4151 (0.19%)	1 / 2070 (0.05%)	10 / 4134 (0.24%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral swelling			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stent-graft endoleak			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Sudden death			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 2
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaphylactic reaction			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Anaphylactic shock			

subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Drug hypersensitivity			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystocele			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ovarian cyst			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Acute respiratory failure			
subjects affected / exposed	23 / 4151 (0.55%)	16 / 2070 (0.77%)	17 / 4134 (0.41%)
occurrences causally related to treatment / all	2 / 27	0 / 20	1 / 17
deaths causally related to treatment / all	1 / 4	0 / 4	0 / 3
Asthma-chronic obstructive pulmonary disease overlap syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis chronic			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choking			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chronic obstructive pulmonary disease			
subjects affected / exposed	443 / 4151 (10.67%)	269 / 2070 (13.00%)	450 / 4134 (10.89%)
occurrences causally related to treatment / all	21 / 554	16 / 337	27 / 569
deaths causally related to treatment / all	1 / 13	1 / 11	1 / 22
Chronic respiratory failure			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Dyspnoea			

subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Lung disorder			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal polyps			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Organising pneumonia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngeal oedema			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pickwickian syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	8 / 4151 (0.19%)	3 / 2070 (0.14%)	11 / 4134 (0.27%)
occurrences causally related to treatment / all	2 / 13	0 / 3	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	5 / 4151 (0.12%)	0 / 2070 (0.00%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 6	0 / 0	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	7 / 4151 (0.17%)	6 / 2070 (0.29%)	7 / 4134 (0.17%)
occurrences causally related to treatment / all	0 / 7	1 / 6	0 / 7
deaths causally related to treatment / all	0 / 1	1 / 3	0 / 0
Pulmonary granuloma			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hilum mass			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary infarction			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Respiratory acidosis			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory arrest			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Respiratory distress			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	22 / 4151 (0.53%)	7 / 2070 (0.34%)	21 / 4134 (0.51%)
occurrences causally related to treatment / all	1 / 23	0 / 7	3 / 21
deaths causally related to treatment / all	0 / 3	0 / 1	1 / 4
Psychiatric disorders			
Affective disorder			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholism			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 4151 (0.02%)	3 / 2070 (0.14%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Completed suicide			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression suicidal			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insomnia			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Major depression			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychotic disorder due to a general medical condition			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Substance-induced psychotic disorder			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Suicide attempt			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Biopsy prostate			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood glucose increased			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibrin D dimer increased			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Occult blood positive			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatic specific antigen increased			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Streptococcus test positive			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transaminases increased			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			

subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	4 / 4151 (0.10%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Animal bite			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemical peritonitis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Chest injury			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Comminuted fracture			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctival laceration			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Facial bones fracture			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			

subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body aspiration			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gastrointestinal disorder postoperative			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gun shot wound			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heat illness			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			

subjects affected / exposed	4 / 4151 (0.10%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	4 / 4151 (0.10%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaw fracture			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple injuries			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Muscle rupture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematuria			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural stroke			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative respiratory failure			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	9 / 4151 (0.22%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 10	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seroma			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin injury			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue injury			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic rupture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress fracture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thermal burn			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulna fracture			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound evisceration			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Developmental hip dysplasia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocele			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial bridging			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Odontogenic cyst			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 4151 (0.00%)	3 / 2070 (0.14%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	13 / 4151 (0.31%)	6 / 2070 (0.29%)	8 / 4134 (0.19%)
occurrences causally related to treatment / all	1 / 14	0 / 6	1 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Angina pectoris			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	7 / 4151 (0.17%)	2 / 2070 (0.10%)	6 / 4134 (0.15%)
occurrences causally related to treatment / all	1 / 8	1 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Atrial fibrillation			
subjects affected / exposed	21 / 4151 (0.51%)	6 / 2070 (0.29%)	13 / 4134 (0.31%)
occurrences causally related to treatment / all	4 / 24	1 / 6	3 / 13
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Atrial flutter			
subjects affected / exposed	3 / 4151 (0.07%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block complete			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular dissociation			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			

subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	4 / 4151 (0.10%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 1
Cardiac disorder			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure			
subjects affected / exposed	12 / 4151 (0.29%)	3 / 2070 (0.14%)	7 / 4134 (0.17%)
occurrences causally related to treatment / all	0 / 12	0 / 3	0 / 8
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 3
Cardiac failure acute			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure chronic			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	21 / 4151 (0.51%)	7 / 2070 (0.34%)	12 / 4134 (0.29%)
occurrences causally related to treatment / all	0 / 28	0 / 10	1 / 12
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac valve disease			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	4 / 4151 (0.10%)	5 / 2070 (0.24%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 4	0 / 5	1 / 4
deaths causally related to treatment / all	0 / 4	0 / 5	1 / 4
Cardiogenic shock			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Cardiomyopathy			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cor pulmonale			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cor pulmonale chronic			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	4 / 4151 (0.10%)	3 / 2070 (0.14%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	1 / 4	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery insufficiency			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Coronary artery occlusion			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	10 / 4151 (0.24%)	7 / 2070 (0.34%)	6 / 4134 (0.15%)
occurrences causally related to treatment / all	0 / 10	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 2	0 / 2	0 / 0
Myocardial ischaemia			
subjects affected / exposed	5 / 4151 (0.12%)	3 / 2070 (0.14%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 6	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Palpitations			

subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prinzmetal angina			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular extrasystoles			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			

subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Ventricular tachycardia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ataxia			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem ischaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem stroke			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Carotid artery occlusion			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	4 / 4151 (0.10%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar infarction			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral amyloid angiopathy			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cerebral infarction			

subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	7 / 4151 (0.17%)	3 / 2070 (0.14%)	6 / 4134 (0.15%)
occurrences causally related to treatment / all	0 / 7	0 / 3	1 / 7
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 3
Cerebrovascular disorder			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular insufficiency			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Guillain-Barre syndrome			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hypoaesthesia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial aneurysm			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	4 / 4151 (0.10%)	0 / 2070 (0.00%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Lacunar infarction			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Migraine			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myoclonus			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parkinson's disease			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral nerve paresis			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post herpetic neuralgia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radicular syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Simple partial seizures			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	6 / 4151 (0.14%)	3 / 2070 (0.14%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tension headache			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thalamic infarction			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	8 / 4151 (0.19%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coagulopathy			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic disorder			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Microcytic anaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Amaurosis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	3 / 4151 (0.07%)	2 / 2070 (0.10%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 3	0 / 2	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract nuclear			

subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctival haemorrhage			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplopia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal adhesions			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal compartment syndrome			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal discomfort			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal distension			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal hernia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	3 / 4151 (0.07%)	2 / 2070 (0.10%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal fistula			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ascites			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ulcerative			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Crohn's disease			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum intestinal haemorrhagic			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenitis			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive duodenitis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erosive oesophagitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polyps			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer haemorrhage			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer perforation			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	4 / 4151 (0.10%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal inflammation			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated umbilical hernia			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	6 / 4151 (0.14%)	1 / 2070 (0.05%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal perforation			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intestinal polyp			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Irritable bowel syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestinal obstruction			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic cyst			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic failure			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	4 / 4151 (0.10%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal fibrosis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Umbilical hernia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Vomiting			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			

subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis chronic			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 4151 (0.02%)	5 / 2070 (0.24%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder polyp			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decubitus ulcer			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkeratosis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neuropathic ulcer			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peau d'orange			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pustular psoriasis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urticaria			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	6 / 4151 (0.14%)	6 / 2070 (0.29%)	9 / 4134 (0.22%)
occurrences causally related to treatment / all	0 / 6	0 / 9	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Bladder disorder			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder stenosis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
End stage renal disease			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Haematuria			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephropathy			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstructive uropathy			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Proteinuria			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Renal aneurysm			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst haemorrhage			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			

subjects affected / exposed	3 / 4151 (0.07%)	2 / 2070 (0.10%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 1
Ureterolithiasis			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary incontinence			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	2 / 4151 (0.05%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	1 / 3	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vesicocutaneous fistula			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Adrenal mass			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperthyroidism			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 4151 (0.10%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Back pain			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone infarction			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Costochondritis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dupuytren's contracture			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoroacetabular impingement			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Groin pain			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc disorder			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			

subjects affected / exposed	1 / 4151 (0.02%)	3 / 2070 (0.14%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar spinal stenosis			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neck pain			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	9 / 4151 (0.22%)	1 / 2070 (0.05%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 9	0 / 1	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoporosis			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal deformity			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal ligament ossification			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal osteoarthritis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylitis			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anal abscess			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendiceal abscess			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			

subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis perforated			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspergillus infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial sepsis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	10 / 4151 (0.24%)	3 / 2070 (0.14%)	10 / 4134 (0.24%)
occurrences causally related to treatment / all	0 / 10	1 / 3	0 / 11
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis bacterial			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carbuncle			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	6 / 4151 (0.14%)	3 / 2070 (0.14%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis staphylococcal			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis infective			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridial infection			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile colitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic abscess			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corona virus infection			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	2 / 4151 (0.05%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis bacterial			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enteritis infectious			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal oesophagitis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 4151 (0.02%)	2 / 2070 (0.10%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis salmonella			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
H1N1 influenza			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Haemophilus infection			
subjects affected / exposed	3 / 4151 (0.07%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter gastritis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Herpes zoster			
subjects affected / exposed	0 / 4151 (0.00%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected skin ulcer			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected varicose vein			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Infection			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious colitis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of bronchiectasis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	8 / 4151 (0.19%)	7 / 2070 (0.34%)	19 / 4134 (0.46%)
occurrences causally related to treatment / all	0 / 8	0 / 8	1 / 20
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	7 / 4151 (0.17%)	5 / 2070 (0.24%)	6 / 4134 (0.15%)
occurrences causally related to treatment / all	0 / 7	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Kidney infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngitis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	7 / 4151 (0.17%)	4 / 2070 (0.19%)	4 / 4134 (0.10%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung abscess			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycobacterial infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mycoplasma infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nosocomial infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oesophageal candidiasis			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral infection			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae virus infection			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parotitis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngotonsillitis			

subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal sepsis			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	184 / 4151 (4.43%)	54 / 2070 (2.61%)	152 / 4134 (3.68%)
occurrences causally related to treatment / all	36 / 198	12 / 55	20 / 165
deaths causally related to treatment / all	0 / 10	0 / 3	0 / 5
Pneumonia bacterial			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	9 / 4134 (0.22%)
occurrences causally related to treatment / all	1 / 3	0 / 0	3 / 9
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia fungal			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia haemophilus			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia influenzal			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia klebsiella			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia necrotising			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pseudomonas infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary tuberculosis			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Pyelonephritis acute			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			

subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection bacterial			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	3 / 4134 (0.07%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	9 / 4151 (0.22%)	6 / 2070 (0.29%)	8 / 4134 (0.19%)
occurrences causally related to treatment / all	0 / 10	0 / 6	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Sepsis syndrome			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	4 / 4151 (0.10%)	3 / 2070 (0.14%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Sinusitis			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal infection			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Streptococcal infection			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subacute endocarditis			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subcutaneous abscess			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdiaphragmatic abscess			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superinfection			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Tonsillitis			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tooth abscess			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheobronchitis			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tuberculosis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	4 / 4151 (0.10%)	4 / 2070 (0.19%)	7 / 4134 (0.17%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Urosepsis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Acetonaemia			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 4151 (0.10%)	2 / 2070 (0.10%)	5 / 4134 (0.12%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 4151 (0.02%)	1 / 2070 (0.05%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fluid overload			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			

subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperlipidaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	3 / 4151 (0.07%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	7 / 4151 (0.17%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	1 / 7	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	5 / 4151 (0.12%)	2 / 2070 (0.10%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 5	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Hypophagia			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency			

subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			
subjects affected / exposed	2 / 4151 (0.05%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obesity			
subjects affected / exposed	1 / 4151 (0.02%)	0 / 2070 (0.00%)	0 / 4134 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 4151 (0.00%)	1 / 2070 (0.05%)	2 / 4134 (0.05%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitamin B12 deficiency			
subjects affected / exposed	0 / 4151 (0.00%)	0 / 2070 (0.00%)	1 / 4134 (0.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	FF/UMEC/VI 100/62.5/25	UMEC/VI 62.5/25	FF/VI 100/25
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1389 / 4151 (33.46%)	596 / 2070 (28.79%)	1278 / 4134 (30.91%)
Nervous system disorders			
Headache			
subjects affected / exposed	233 / 4151 (5.61%)	101 / 2070 (4.88%)	197 / 4134 (4.77%)
occurrences (all)	385	139	332
Respiratory, thoracic and mediastinal			

disorders			
Cough			
subjects affected / exposed	145 / 4151 (3.49%)	58 / 2070 (2.80%)	117 / 4134 (2.83%)
occurrences (all)	168	75	128
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	146 / 4151 (3.52%)	83 / 2070 (4.01%)	139 / 4134 (3.36%)
occurrences (all)	180	101	164
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	520 / 4151 (12.53%)	222 / 2070 (10.72%)	479 / 4134 (11.59%)
occurrences (all)	712	316	658
Upper respiratory tract infection			
subjects affected / exposed	297 / 4151 (7.15%)	117 / 2070 (5.65%)	283 / 4134 (6.85%)
occurrences (all)	401	162	383
Oral candidiasis			
subjects affected / exposed	161 / 4151 (3.88%)	41 / 2070 (1.98%)	146 / 4134 (3.53%)
occurrences (all)	203	50	176
Bronchitis			
subjects affected / exposed	142 / 4151 (3.42%)	70 / 2070 (3.38%)	120 / 4134 (2.90%)
occurrences (all)	165	83	152
Pneumonia			
subjects affected / exposed	121 / 4151 (2.91%)	41 / 2070 (1.98%)	127 / 4134 (3.07%)
occurrences (all)	131	43	135

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2014	Clarified approval status of products in the protocol, added wording concerning hematology collection, and corrected minor errors in the Time and Events Table
10 April 2014	Added post-bronchodilator FEV1 to each visit and included this as an other efficacy endpoint. A mortality endpoint was also added as an other efficacy endpoint. Other changes included changing the predicted FEV1 reference values from NHANES III to the European Respiratory Society Global Lung Function Initiative and to correct minor errors in CAT, contraceptive methods, and ECG wording.
05 December 2014	Clarified that SAEs in China would be recorded from the time the consent form was signed until the 7-day safety follow-up visit/telephone contact had been completed, or until Visit 7 (telephone contact) for participant who discontinued study treatment but continued in the study
12 May 2015	Clarified that none of the study sites in China would participate in genetic research in this study and addition of a China-specific sub-study to collect the unit-cost data for healthcare utilization among participants recruited in China.
30 June 2016	Simplified the statistical hierarchy for the analysis of secondary endpoints. In addition, there were minor changes to the definitions of the analysis populations, changes in model terms that were included in the primary efficacy endpoint analysis, and clarification on the primary endpoint sensitivity analysis. For the safety analysis, there were minor changes to clarify the analyses of Pneumonia AEs and Major Adverse Cardiac Events (MACE)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported