



Clinical trial results:

Multicenter, Randomized, Active-Controlled Efficacy And Safety Study Comparing Extended Duration Betrixaban With Standard Of Care Enoxaparin For The Prevention Of Venous Thromboembolism In Acute Medically Ill Patients

Summary

EudraCT number	2012-000255-13
Trial protocol	BE LV DE ES GB PL LT AT DK CZ BG IT FI SK
Global end of trial date	31 January 2016

Results information

Result version number	v1 (current)
This version publication date	02 December 2017
First version publication date	02 December 2017

Trial information

Trial identification

Sponsor protocol code	11-019
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01583218
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Portola Pharmaceuticals, Inc.
Sponsor organisation address	270 East Grand Avenue, South San Francisco, United States,
Public contact	Janice Castillo (VP Reg Affairs), Portola Pharmaceuticals, Inc., 001 650-246-7360, jcastillo@portola.com
Scientific contact	Janice Castillo (VP Reg Affairs), Portola Pharmaceuticals, Inc., 001 650-246-7360, jcastillo@portola.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 December 2015
Global end of trial reached?	Yes
Global end of trial date	31 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Demonstrate the superiority of extended duration (35 days + 7 day window, i.e. 35-42 days allowed) anticoagulation with betrixaban as compared to the standard of care (10 ± 4 days) with enoxaparin for prevention of VTE in patients who are at risk due to acute medical illness

Protection of trial subjects:

The conduct of this clinical study met local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative signed informed consent form and could withdraw from the study at any time. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 369
Country: Number of subjects enrolled	Slovakia: 105
Country: Number of subjects enrolled	Spain: 412
Country: Number of subjects enrolled	United Kingdom: 22
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Bulgaria: 431
Country: Number of subjects enrolled	Czech Republic: 237
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Estonia: 205
Country: Number of subjects enrolled	Finland: 26
Country: Number of subjects enrolled	France: 292
Country: Number of subjects enrolled	Germany: 196
Country: Number of subjects enrolled	Hungary: 252
Country: Number of subjects enrolled	Italy: 261
Country: Number of subjects enrolled	Latvia: 319
Country: Number of subjects enrolled	Lithuania: 470

Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Belarus: 69
Country: Number of subjects enrolled	Croatia: 92
Country: Number of subjects enrolled	Georgia: 260
Country: Number of subjects enrolled	Romania: 170
Country: Number of subjects enrolled	Russian Federation: 971
Country: Number of subjects enrolled	Serbia: 115
Country: Number of subjects enrolled	Turkey: 54
Country: Number of subjects enrolled	Ukraine: 886
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Israel: 99
Country: Number of subjects enrolled	South Africa: 91
Country: Number of subjects enrolled	Argentina: 215
Country: Number of subjects enrolled	Brazil: 57
Country: Number of subjects enrolled	Chile: 44
Country: Number of subjects enrolled	Peru: 152
Country: Number of subjects enrolled	Canada: 51
Country: Number of subjects enrolled	United States: 527
Worldwide total number of subjects	7513
EEA total number of subjects	3901

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)	782
From 65 to 84 years	5569
85 years and over	1162

Subject disposition

Recruitment

Recruitment details:

Patients enrolled with one of the diagnoses: acutely decompensated heart failure, acute respiratory failure, acute infection, rheumatic disease, and ischemic stroke. They also were required to meet additional criteria that placed them at high prolonged risk of VTE. Patients were randomized 1:1 to either betrixaban or enoxaparin treatment group.

Pre-assignment

Screening details:

To maintain the blind, patients assigned to the betrixaban group received betrixaban capsules for 35 to 42 days and daily subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days, and patients assigned to the enoxaparin group received daily SQ injections of enoxaparin for 10 ± 4 days and betrixaban placebo capsules for 35 to 42 days.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Betrixaban

Arm description:

Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days

Arm type	Experimental
Investigational medicinal product name	Betrixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Daily oral (PO) betrixaban capsules for 35 to 42 days

Arm title	Enoxaparin
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Arm description:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days

Arm type	Active comparator
Investigational medicinal product name	Enoxaparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days

Number of subjects in period 1	Betrixaban	Enoxaparin
Started	3759	3754
Completed	3470	3471
Not completed	289	283
Adverse event, serious fatal	206	211
Patient was randomized due to mistake	1	-
Patient deemed ineligible after randomization	2	-
Subject moved to another province	-	1
Cannot Contact Patient Directly	1	2
WOC on day of randomization, no IP administered	1	-
Patient was early terminated from the study	-	1
Patient randomized but not dosed	17	16
Consent withdrawn by subject	43	29
Adverse event, non-fatal	3	3
Patient did not wish to attend visit at the clinic	-	1
Patient/Family Decision	3	-
Source document/coordinator missing	-	2
Lost to follow-up	11	17
Patient was assessed via phone in person	1	-

Baseline characteristics

Reporting groups

Reporting group title	Betrixaban
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Reporting group description:

Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days

Reporting group title	Enoxaparin
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Reporting group description:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days

Reporting group values	Betrixaban	Enoxaparin	Total
Number of subjects	3759	3754	7513
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	384	398	782
From 65-84 years	2767	2802	5569
85 years and over	608	554	1162
Gender categorical Units: Subjects			
Female	2054	2034	4088
Male	1705	1720	3425

End points

End points reporting groups

Reporting group title	Betrixaban
Reporting group description: Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days	
Reporting group title	Enoxaparin
Reporting group description: Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days	

Primary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3

End point title	Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3
End point description: Percentage of participants experiencing either symptomatic DVT, non-fatal PE, VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3, or a blinded ultrasound core laboratory measuring of asymptomatic proximal DVT between randomization and Day 47. Visit 3 is between day 35-42 after randomization (day 1).	
End point type	Primary
End point timeframe: Between randomization and Day 47 (max)	

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1914	1956		
Units: Number of Participants				
number (confidence interval 95%)	6.90 (5.76 to 8.03)	8.49 (7.25 to 9.72)		

Statistical analyses

Statistical analysis title	Primary: Efficacy Endpoint
Statistical analysis description: Cohort 1 (participants with baseline D-dimer ≥ 2 x ULN as determined by the local lab) of the PEOP population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.	
Comparison groups	Betrixaban v Enoxaparin

Number of subjects included in analysis	3870
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.054
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk Reduction (RRR)
Point estimate	0.194
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.353

Primary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3

End point title	Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3
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End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3, or a blinded ultrasound core laboratory measuring of asymptomatic proximal DVT between randomization and Day 47. Visit 3 is between day 35-42 after randomization (day 1).

End point type	Primary
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End point timeframe:

Between randomization and Day 47 (max)

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2842	2893		
Units: Number of Participants				
number (confidence interval 95%)	5.63 (4.78 to 6.48)	7.05 (6.12 to 7.98)		

Statistical analyses

Statistical analysis title	Primary: Efficacy Endpoint
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Statistical analysis description:

Cohort 2 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab or age ≥ 75 years) of the PEOP population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

Comparison groups	Betrixaban v Enoxaparin
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Number of subjects included in analysis	5735
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.029
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk Reduction (RRR)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.023
upper limit	0.345

Primary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3

End point title	Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, VTE-related death, or asymptomatic proximal DVT, through Visit 3
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End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3, or a blinded ultrasound core laboratory measuring of asymptomatic proximal DVT between randomization and Day 47. Visit 3 is between day 35-42 after randomization (day 1).

End point type	Primary
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End point timeframe:

Between randomization and Day 47 (max)

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3112	3174		
Units: Number of Participants				
number (confidence interval 95%)	5.30 (4.51 to 6.09)	7.03 (6.14 to 7.91)		

Statistical analyses

Statistical analysis title	Primary: Efficacy Endpoint
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Statistical analysis description:

The PEOP population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

Comparison groups	Betrixaban v Enoxaparin
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Number of subjects included in analysis	6286
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.006
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk Reduction (RRR)
Point estimate	0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.077
upper limit	0.375

Primary: Percentage of participants experiencing major bleeding through seven days after discontinuation of all study medication

End point title	Percentage of participants experiencing major bleeding through seven days after discontinuation of all study medication
End point description: Percentage of participants experiencing at least one major bleeding adjudicated by a blinded independent CEC between randomization (day 1) and up to seven days after discontinuation of all study medication.	
End point type	Primary
End point timeframe: Between randomization and Day 49 (max)	

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3716	3716		
Units: Number of Participants				
number (confidence interval 95%)	0.67 (0.41 to 0.94)	0.57 (0.32 to 0.81)		

Statistical analyses

Statistical analysis title	Primary: Safety Analysis
Statistical analysis description: Safety population which consisted of all participants who had taken at least one dose of study drug.	
Comparison groups	Betrixaban v Enoxaparin

Number of subjects included in analysis	7432
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.554
Method	Chi-squared

Secondary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3

End point title	Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3
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End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, or VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3. Visit 3 is between day 35-42 after randomization (day 1).

End point type	Secondary
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End point timeframe:

Between randomization and Day 42 (max)

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2314	2313		
Units: Number of Participants				
number (confidence interval 95%)	1.30 (0.84 to 1.76)	1.90 (1.35 to 2.46)		

Statistical analyses

Statistical analysis title	Secondary: Efficacy Analysis
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Statistical analysis description:

Cohort 1 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab) of the mITT population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

Comparison groups	Betrixaban v Enoxaparin
Number of subjects included in analysis	4627
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.092
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk Reduction (RRR)
Point estimate	0.326

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.069
upper limit	0.576

Secondary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3

End point title	Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3
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End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, or VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3. Visit 3 is between day 35-42 after randomization (day 1).

End point type	Secondary
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End point timeframe:

Between randomization and Day 42 (max)

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3407	3391		
Units: Number of Participants				
number (confidence interval 95%)	1.03 (0.69 to 1.37)	1.45 (1.04 to 1.85)		

Statistical analyses

Statistical analysis title	Secondary: Efficacy Analysis
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Statistical analysis description:

Cohort 2 (participants with baseline D-dimer $\geq 2 \times$ ULN as determined by the local lab or age ≥ 75 years) of the mITT population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

Comparison groups	Betrixaban v Enoxaparin
Number of subjects included in analysis	6798
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk Reduction (RRR)
Point estimate	0.295

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.085
upper limit	0.542

Secondary: Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3

End point title	Percentage of participants experiencing the composite event of symptomatic DVT, non-fatal PE, or VTE-related death, through Visit 3
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End point description:

Percentage of participants experiencing either symptomatic DVT, non-fatal PE, or VTE related death adjudicated by a blinded independent CEC between randomization and on or before Visit 3 or Day 42 if patient did not have a Visit 3. Visit 3 is between day 35-42 after randomization (day 1).

End point type	Secondary
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End point timeframe:

Between randomization and Day 42 (max)

End point values	Betrixaban	Enoxaparin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3721	3720		
Units: Number of Participants				
number (confidence interval 95%)	0.94 (0.63 to 1.25)	1.45 (1.07 to 1.84)		

Statistical analyses

Statistical analysis title	Secondary: Efficacy Analysis
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Statistical analysis description:

The mITT population which consisted of all participants who had taken at least one dose of study drug and who had follow-up assessment data on one or more primary or secondary efficacy components.

Comparison groups	Betrixaban v Enoxaparin
Number of subjects included in analysis	7441
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.039
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk Reduction (RRR)
Point estimate	0.358

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.02
upper limit	0.58

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose date (including) till the end of study

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Betrixaban
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Reporting group description:

Daily oral (PO) betrixaban capsules for 35 to 42 days and subcutaneous (SQ) injections of enoxaparin placebo for 10 ± 4 days

Reporting group title	Enoxaparin
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Reporting group description:

Daily subcutaneous (SQ) injections of enoxaparin for 10 ± 4 days and oral (PO) betrixaban placebo capsules for 35 to 42 days

Serious adverse events	Betrixaban	Enoxaparin	
Total subjects affected by serious adverse events			
subjects affected / exposed	657 / 3716 (17.68%)	615 / 3716 (16.55%)	
number of deaths (all causes)	213	214	
number of deaths resulting from adverse events	206	211	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	10 / 3716 (0.27%)	8 / 3716 (0.22%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 4	0 / 4	
Cervix carcinoma			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	3 / 3716 (0.08%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenocarcinoma of colon			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric cancer			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic neoplasm			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cancer			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Rectal cancer			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Brain neoplasm			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Breast cancer metastatic			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchial carcinoma			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colorectal adenocarcinoma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Colorectal cancer			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal stromal tumour			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung carcinoma cell type unspecified stage IV			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant pleural effusion			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningioma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metastases to liver			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastasis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myeloid leukaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm malignant			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-Hodgkin's lymphoma			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic carcinoma metastatic			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasma cell myeloma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plasmacytoma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural mesothelioma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell lung cancer			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Throat cancer			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval cancer			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	16 / 3716 (0.43%)	38 / 3716 (1.02%)	
occurrences causally related to treatment / all	0 / 16	0 / 38	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	8 / 3716 (0.22%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematoma			
subjects affected / exposed	5 / 3716 (0.13%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	4 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			

subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic dissection			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic vasculitis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aneurysm			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angiopathy			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Arterial disorder			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial stenosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bleeding varicose vein			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism arterial			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Essential hypertension			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral artery aneurysm			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal haematoma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral vascular disorder			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis superficial			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary artery bypass			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma surgery			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip arthroplasty			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hospitalisation			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg amputation			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve repair			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgery			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	9 / 3716 (0.24%)	16 / 3716 (0.43%)	
occurrences causally related to treatment / all	0 / 9	0 / 16	
deaths causally related to treatment / all	0 / 9	0 / 16	
Sudden cardiac death			
subjects affected / exposed	6 / 3716 (0.16%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 6	0 / 5	
Multi-organ failure			
subjects affected / exposed	3 / 3716 (0.08%)	6 / 3716 (0.16%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 6	
General physical health deterioration			
subjects affected / exposed	6 / 3716 (0.16%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 5	0 / 1	
Sudden death			
subjects affected / exposed	3 / 3716 (0.08%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 3	1 / 3	
Non-cardiac chest pain			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	3 / 3716 (0.08%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac death			

subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Chest pain			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter site haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device malfunction			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discomfort			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosis			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthermia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture site haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcer			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic reaction			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Social circumstances			
Activities of daily living impaired			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix haemorrhage uterine			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	38 / 3716 (1.02%)	43 / 3716 (1.16%)	
occurrences causally related to treatment / all	0 / 41	0 / 47	
deaths causally related to treatment / all	0 / 8	0 / 6	
Respiratory failure			
subjects affected / exposed	30 / 3716 (0.81%)	17 / 3716 (0.46%)	
occurrences causally related to treatment / all	0 / 32	1 / 17	
deaths causally related to treatment / all	0 / 13	1 / 7	
Pulmonary embolism			
subjects affected / exposed	11 / 3716 (0.30%)	26 / 3716 (0.70%)	
occurrences causally related to treatment / all	0 / 11	0 / 26	
deaths causally related to treatment / all	0 / 6	0 / 10	
Acute respiratory failure			
subjects affected / exposed	13 / 3716 (0.35%)	9 / 3716 (0.24%)	
occurrences causally related to treatment / all	0 / 13	0 / 10	
deaths causally related to treatment / all	0 / 11	0 / 4	
Epistaxis			
subjects affected / exposed	10 / 3716 (0.27%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	10 / 10	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	6 / 3716 (0.16%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	0 / 6	0 / 4	
deaths causally related to treatment / all	0 / 3	0 / 0	
Pulmonary fibrosis			
subjects affected / exposed	3 / 3716 (0.08%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 2	

Pleural effusion			
subjects affected / exposed	2 / 3716 (0.05%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	3 / 3716 (0.08%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	6 / 3716 (0.16%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 3716 (0.08%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	3 / 3716 (0.08%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	2 / 3716 (0.05%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Chronic respiratory failure			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			

subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis chronic			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			

subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alveolitis allergic			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial obstruction			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chylothorax			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranasal cyst			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Major depression			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Hepatic enzyme increased			
subjects affected / exposed	2 / 3716 (0.05%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	2 / 2	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration bronchial			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Alanine aminotransferase increased			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical condition abnormal			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatine increased			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urine present			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheterisation cardiac			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 3716 (0.03%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 3716 (0.08%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 3716 (0.00%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical vertebral fracture			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			

subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accident			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Accidental overdose			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Latrogenic injury			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Patella fracture			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax traumatic			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pubis fracture			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin injury			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord injury			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haematoma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	83 / 3716 (2.23%)	66 / 3716 (1.78%)	
occurrences causally related to treatment / all	0 / 85	0 / 70	
deaths causally related to treatment / all	0 / 30	0 / 33	
Atrial fibrillation			

subjects affected / exposed	11 / 3716 (0.30%)	23 / 3716 (0.62%)	
occurrences causally related to treatment / all	0 / 12	0 / 23	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	10 / 3716 (0.27%)	15 / 3716 (0.40%)	
occurrences causally related to treatment / all	0 / 12	0 / 17	
deaths causally related to treatment / all	0 / 2	0 / 3	
Cardiac failure acute			
subjects affected / exposed	10 / 3716 (0.27%)	12 / 3716 (0.32%)	
occurrences causally related to treatment / all	0 / 10	0 / 12	
deaths causally related to treatment / all	0 / 3	0 / 8	
Cardiac failure chronic			
subjects affected / exposed	13 / 3716 (0.35%)	9 / 3716 (0.24%)	
occurrences causally related to treatment / all	0 / 15	0 / 11	
deaths causally related to treatment / all	0 / 5	0 / 2	
Acute myocardial infarction			
subjects affected / exposed	6 / 3716 (0.16%)	12 / 3716 (0.32%)	
occurrences causally related to treatment / all	0 / 6	0 / 12	
deaths causally related to treatment / all	0 / 4	0 / 2	
Myocardial infarction			
subjects affected / exposed	7 / 3716 (0.19%)	10 / 3716 (0.27%)	
occurrences causally related to treatment / all	0 / 7	0 / 10	
deaths causally related to treatment / all	0 / 2	0 / 5	
Cardiogenic shock			
subjects affected / exposed	9 / 3716 (0.24%)	6 / 3716 (0.16%)	
occurrences causally related to treatment / all	0 / 9	0 / 6	
deaths causally related to treatment / all	0 / 6	0 / 5	
Cardiac arrest			
subjects affected / exposed	7 / 3716 (0.19%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 5	0 / 5	
Coronary artery disease			

subjects affected / exposed	8 / 3716 (0.22%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	3 / 3716 (0.08%)	7 / 3716 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	6 / 3716 (0.16%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 7	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	5 / 3716 (0.13%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	2 / 3716 (0.05%)	6 / 3716 (0.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Angina pectoris			
subjects affected / exposed	5 / 3716 (0.13%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	3 / 3716 (0.08%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Cardiopulmonary failure			
subjects affected / exposed	1 / 3716 (0.03%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 3	
Ventricular tachycardia			

subjects affected / exposed	4 / 3716 (0.11%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	2 / 3716 (0.05%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiovascular disorder			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 3716 (0.00%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
Ventricular fibrillation			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial flutter			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cor pulmonale			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute left ventricular failure			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinoatrial block			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tricuspid valve incompetence			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular hypokinesia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	19 / 3716 (0.51%)	35 / 3716 (0.94%)	
occurrences causally related to treatment / all	0 / 19	0 / 35	
deaths causally related to treatment / all	0 / 6	0 / 12	
Brain oedema			
subjects affected / exposed	8 / 3716 (0.22%)	10 / 3716 (0.27%)	
occurrences causally related to treatment / all	0 / 8	0 / 10	
deaths causally related to treatment / all	0 / 5	0 / 9	
Cerebrovascular accident			
subjects affected / exposed	7 / 3716 (0.19%)	6 / 3716 (0.16%)	
occurrences causally related to treatment / all	0 / 7	0 / 7	
deaths causally related to treatment / all	0 / 1	0 / 4	
Syncope			

subjects affected / exposed	4 / 3716 (0.11%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	3 / 3716 (0.08%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	2 / 3716 (0.05%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			
subjects affected / exposed	2 / 3716 (0.05%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	4 / 3716 (0.11%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic transformation stroke			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar infarction			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebral ischaemia			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemic coma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorder			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neuroglycopenia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paralysis flaccid			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyneuropathy			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Presyncope			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Unresponsive to stimuli			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 3716 (0.22%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	2 / 8	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic anaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythaemia			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous haematoma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	18 / 3716 (0.48%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	14 / 18	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	15 / 3716 (0.40%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	11 / 15	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Abdominal pain			
subjects affected / exposed	2 / 3716 (0.05%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer haemorrhage			
subjects affected / exposed	3 / 3716 (0.08%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	1 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 3716 (0.03%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 3716 (0.00%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	0 / 0	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 3716 (0.00%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer haemorrhage			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			

subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal ischaemia			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Melaena			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngo-oesophageal diverticulum			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal strangulated hernia			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer perforation			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenal haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorder			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal necrosis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Large intestinal haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer haemorrhage			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	4 / 3716 (0.11%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bile duct stone			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular injury			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic hepatitis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	3 / 3716 (0.08%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decubitus ulcer			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute generalised exanthematous pustulosis			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis bullous			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecchymosis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petechiae			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin disorder			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	10 / 3716 (0.27%)	15 / 3716 (0.40%)	
occurrences causally related to treatment / all	2 / 10	1 / 15	
deaths causally related to treatment / all	0 / 1	0 / 3	
Renal failure acute			
subjects affected / exposed	12 / 3716 (0.32%)	11 / 3716 (0.30%)	
occurrences causally related to treatment / all	0 / 12	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			

subjects affected / exposed	17 / 3716 (0.46%)	5 / 3716 (0.13%)	
occurrences causally related to treatment / all	11 / 17	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	8 / 3716 (0.22%)	4 / 3716 (0.11%)	
occurrences causally related to treatment / all	1 / 9	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage urinary tract			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	3 / 3716 (0.08%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute prerenal failure			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glomerulonephritis rapidly progressive			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral haemorrhage			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoparathyroidism			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cervical spinal stenosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chondrocalcinosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coccydynia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc disorder			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteochondrosis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polymyositis			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Scleroderma			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Synovial cyst			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	46 / 3716 (1.24%)	64 / 3716 (1.72%)	
occurrences causally related to treatment / all	0 / 49	0 / 66	
deaths causally related to treatment / all	0 / 8	0 / 15	
Urinary tract infection			
subjects affected / exposed	13 / 3716 (0.35%)	11 / 3716 (0.30%)	
occurrences causally related to treatment / all	0 / 13	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	13 / 3716 (0.35%)	7 / 3716 (0.19%)	
occurrences causally related to treatment / all	0 / 13	0 / 7	
deaths causally related to treatment / all	0 / 9	0 / 2	
Septic shock			
subjects affected / exposed	7 / 3716 (0.19%)	8 / 3716 (0.22%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 5	0 / 5	
Cellulitis			
subjects affected / exposed	3 / 3716 (0.08%)	7 / 3716 (0.19%)	
occurrences causally related to treatment / all	0 / 3	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	1 / 3716 (0.03%)	6 / 3716 (0.16%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	4 / 3716 (0.11%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Erysipelas			
subjects affected / exposed	4 / 3716 (0.11%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	4 / 3716 (0.11%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumonia			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Infected skin ulcer			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			

subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	2 / 3716 (0.05%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium colitis			
subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal bacterial infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious pleural effusion			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral discitis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nosocomial infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia staphylococcal			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal sepsis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pseudomonas infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoas abscess			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyelocystitis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomembranous colitis			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary tuberculosis			

subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Tracheobronchitis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abscess bacterial			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone abscess			

subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis bacterial			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridial infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Enterococcal infection			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epididymitis			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile infection			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gallbladder empyema			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 3716 (0.03%)	3 / 3716 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 3716 (0.03%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	0 / 3716 (0.00%)	2 / 3716 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gout			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	2 / 3716 (0.05%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 3716 (0.03%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hypercalcaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypernatraemia			

subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperphosphataemia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypovolaemia			
subjects affected / exposed	0 / 3716 (0.00%)	1 / 3716 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 1 diabetes mellitus			
subjects affected / exposed	1 / 3716 (0.03%)	0 / 3716 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Betrixaban	Enoxaparin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	879 / 3716 (23.65%)	779 / 3716 (20.96%)	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	29 / 3716 (0.78%)	58 / 3716 (1.56%)	
occurrences (all)	29	59	
Hypertension			
subjects affected / exposed	88 / 3716 (2.37%)	80 / 3716 (2.15%)	
occurrences (all)	95	86	
Cardiac disorders			

Atrial fibrillation subjects affected / exposed occurrences (all)	50 / 3716 (1.35%) 53	85 / 3716 (2.29%) 89	
Cardiac failure subjects affected / exposed occurrences (all)	48 / 3716 (1.29%) 49	32 / 3716 (0.86%) 33	
Mitral valve incompetence subjects affected / exposed occurrences (all)	41 / 3716 (1.10%) 41	49 / 3716 (1.32%) 49	
Tricuspid valve incompetence subjects affected / exposed occurrences (all)	38 / 3716 (1.02%) 38	41 / 3716 (1.10%) 41	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	74 / 3716 (1.99%) 77	59 / 3716 (1.59%) 65	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	44 / 3716 (1.18%) 44	29 / 3716 (0.78%) 35	
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all)	39 / 3716 (1.05%) 39	19 / 3716 (0.51%) 19	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	109 / 3716 (2.93%) 114	102 / 3716 (2.74%) 102	
Diarrhoea subjects affected / exposed occurrences (all)	63 / 3716 (1.70%) 68	59 / 3716 (1.59%) 61	
Nausea subjects affected / exposed occurrences (all)	67 / 3716 (1.80%) 72	55 / 3716 (1.48%) 57	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	53 / 3716 (1.43%)	41 / 3716 (1.10%)	
occurrences (all)	55	44	
Epistaxis			
subjects affected / exposed	48 / 3716 (1.29%)	19 / 3716 (0.51%)	
occurrences (all)	54	19	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	87 / 3716 (2.34%)	89 / 3716 (2.40%)	
occurrences (all)	90	90	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	46 / 3716 (1.24%)	23 / 3716 (0.62%)	
occurrences (all)	49	25	
Renal cyst			
subjects affected / exposed	55 / 3716 (1.48%)	47 / 3716 (1.26%)	
occurrences (all)	55	47	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	110 / 3716 (2.96%)	78 / 3716 (2.10%)	
occurrences (all)	112	84	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	91 / 3716 (2.45%)	84 / 3716 (2.26%)	
occurrences (all)	100	90	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2012	•Modification of Inclusion and Exclusion Criteria. •Addition of Day 4 of study procedures. •Modification of Statistical Considerations. •Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency.
15 February 2013	•Modification of Inclusion and Exclusion Criteria. •Addition of a Post Randomization Dose Reductions. •Modification of Statistical Considerations. •Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency.
04 June 2014	•Modification of Inclusion and Exclusion Criteria to exclude enrollment of patients in the biomarker negative subgroup (age <75 and D-dimer <2x ULN) •Modification of Statistical Considerations. •Modification to Outcome Adjudication and Definitions to align with modifications to the Clinical Events Committee (CEC) Charter •Additional clarifications, deletions and administrative corrections were made throughout the document and Appendices to improve clarity and consistency.
28 January 2016	•Update to Statistical Analysis

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported