

**Clinical trial results:**

Multicenter, randomized, double-blind, double-dummy, active-comparator, event-driven, superiority phase III study of secondary prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source (ESUS), comparing rivaroxaban 15 mg once daily with aspirin 100 mg (NAVIGATE ESUS)

Summary

EudraCT number	2013-000768-27
Trial protocol	SE IE PT CZ BE ES IT HU FI DK GB AT GR
Global end of trial date	15 February 2018

Results information

Result version number	v1
This version publication date	06 December 2018
First version publication date	06 December 2018

Trial information**Trial identification**

Sponsor protocol code	BAY59-7939/16573
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02313909
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG , clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG , clinical-trials-contact@bayer.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	15 February 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	15 February 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective of this study was to evaluate whether rivaroxaban (Xarelto, BAY59-7939) was superior to acetylsalicylic acid (Aspirin) in reducing the risk of recurrent stroke and systemic embolism in subjects with a recent embolic stroke of undetermined source (ESUS).

Protection of trial subjects:

The conduct of this clinical study met all 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 Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. 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	23 December 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 284
Country: Number of subjects enrolled	Portugal: 154
Country: Number of subjects enrolled	Spain: 618
Country: Number of subjects enrolled	Sweden: 71
Country: Number of subjects enrolled	United Kingdom: 435
Country: Number of subjects enrolled	Austria: 174
Country: Number of subjects enrolled	Belgium: 90
Country: Number of subjects enrolled	Czech Republic: 243
Country: Number of subjects enrolled	Denmark: 146
Country: Number of subjects enrolled	Finland: 131
Country: Number of subjects enrolled	France: 288
Country: Number of subjects enrolled	Germany: 198
Country: Number of subjects enrolled	Greece: 76
Country: Number of subjects enrolled	Hungary: 224
Country: Number of subjects enrolled	Ireland: 13
Country: Number of subjects enrolled	Italy: 334
Country: Number of subjects enrolled	Australia: 119

Country: Number of subjects enrolled	Israel: 60
Country: Number of subjects enrolled	South Africa: 49
Country: Number of subjects enrolled	Switzerland: 125
Country: Number of subjects enrolled	Russian Federation: 328
Country: Number of subjects enrolled	Turkey: 39
Country: Number of subjects enrolled	China: 491
Country: Number of subjects enrolled	Japan: 647
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 212
Country: Number of subjects enrolled	Canada: 573
Country: Number of subjects enrolled	United States: 345
Country: Number of subjects enrolled	Argentina: 265
Country: Number of subjects enrolled	Brazil: 179
Country: Number of subjects enrolled	Chile: 194
Country: Number of subjects enrolled	Mexico: 108
Worldwide total number of subjects	7213
EEA total number of subjects	3479

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)	2943
From 65 to 84 years	4047
85 years and over	223

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 31 countries between 23 December 2014 (first subject first visit) and 15 February 2018 (last subject last visit).

Pre-assignment

Screening details:

Overall, 7582 subjects were screened; of these 369 subjects were screen failures. A total of 7213 subjects were randomized, of which 92 never took study drug; 3562 were treated with rivaroxaban/placebo and 3559 were treated with acetylsalicylic acid/placebo.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban 15 mg OD

Arm description:

Subjects received rivaroxaban 15 milligram (mg) immediate-release film-coated tablet and matching placebo of acetylsalicylic acid orally once daily (OD).

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY59-7939
Other name	Xarelto
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received rivaroxaban 15 mg immediate-release film-coated tablet orally OD.

Investigational medicinal product name	Placebo matched to acetylsalicylic acid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo of acetylsalicylic acid 100 mg enteric-coated tablet orally OD.

Arm title	Acetylsalicylic acid 100 mg OD
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Arm description:

Subjects received acetylsalicylic acid 100 mg enteric-coated tablet and matching placebo of rivaroxaban orally OD.

Arm type	Experimental
Investigational medicinal product name	Acetylsalicylic acid
Investigational medicinal product code	BAY1019036
Other name	Aspirin
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received acetylsalicylic acid 100 mg enteric-coated tablet orally OD.

Investigational medicinal product name	Placebo matched to rivaroxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received matching placebo of rivaroxaban 15 mg immediate-release film-coated tablet orally OD.

Number of subjects in period 1	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD
Started	3609	3604
Treated	3562	3559
Completed	3552	3554
Not completed	57	50
Consent withdrawn by subject	33	33
Lost to follow-up	24	17

Baseline characteristics

Reporting groups

Reporting group title	Rivaroxaban 15 mg OD
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Reporting group description:

Subjects received rivaroxaban 15 milligram (mg) immediate-release film-coated tablet and matching placebo of acetylsalicylic acid orally once daily (OD).

Reporting group title	Acetylsalicylic acid 100 mg OD
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Reporting group description:

Subjects received acetylsalicylic acid 100 mg enteric-coated tablet and matching placebo of rivaroxaban orally OD.

Reporting group values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD	Total
Number of subjects	3609	3604	7213
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	66.9 ± 9.8	66.9 ± 9.8	-
Gender categorical Units: Subjects			
Female	1377	1400	2777
Male	2232	2204	4436
Race Units: Subjects			
White	2613	2605	5218
Black or African American	51	60	111
Asian	716	698	1414
Other	229	241	470
Stroke or TIA (prior to qualifying stroke) or Other medical history			
The other medical history refers to number of subjects with one medical history finding other than stroke or Transient ischemic attack (TIA).			
Units: Subjects			
Stroke or TIA (prior to qualifying stroke)	620	643	1263
Other medical history	2989	2961	5950
Time from qualifying stroke to randomization Units: days median inter-quartile range (Q1-Q3)	38.0 15.0 to 89.0	36.0 14.0 to 86.5	-

End points

End points reporting groups

Reporting group title	Rivaroxaban 15 mg OD
Reporting group description: Subjects received rivaroxaban 15 milligram (mg) immediate-release film-coated tablet and matching placebo of acetylsalicylic acid orally once daily (OD).	
Reporting group title	Acetylsalicylic acid 100 mg OD
Reporting group description: Subjects received acetylsalicylic acid 100 mg enteric-coated tablet and matching placebo of rivaroxaban orally OD.	
Subject analysis set title	Intention-to-treat analysis set (ITT)
Subject analysis set type	Intention-to-treat
Subject analysis set description: ITT included all randomized subjects (N= 7213).	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: SAF included all randomized subjects who received at least one dose of study drug (N= 7121).	

Primary: Time From Randomization to First Occurrence of any of the Components of Composite Efficacy Outcome (Adjudicated)

End point title	Time From Randomization to First Occurrence of any of the Components of Composite Efficacy Outcome (Adjudicated)
End point description: Components of composite efficacy outcome (adjudicated) includes stroke (ischemic, hemorrhagic, and undefined stroke, TIA with positive neuroimaging) and systemic embolism. Incidence rate estimated as number of subjects with incident events divided by cumulative at-risk time, where subject is no longer at risk once an incident event occurred.	
End point type	Primary
End point timeframe: From randomization until the efficacy cut-off date (median 326 days)	

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[1]	3604 ^[2]		
Units: event/100 subject-years				
number (confidence interval 95%)	5.14 (4.40 to 5.97)	4.78 (4.07 to 5.58)		

Notes:

[1] - ITT

[2] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis: Stroke + Systemic embolism
Statistical analysis description: Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was	

compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.

Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.51884
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.33

Primary: Time from Randomization to First Occurrence of a Major Bleeding Event According to the International Society on Thrombosis and Haemostasis (ISTH) Criteria (Adjudicated)

End point title	Time from Randomization to First Occurrence of a Major Bleeding Event According to the International Society on Thrombosis and Haemostasis (ISTH) Criteria (Adjudicated)
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End point description:

Major bleeding event (as per ISTH), defined as bleeding event that met at least one of following: fatal bleeding; symptomatic bleeding in a critical area or organ (intraarticular, intramuscular with compartment syndrome, intraocular, intraspinal, pericardial, or retroperitoneal); symptomatic intracranial haemorrhage; clinically overt bleeding associated with a recent decrease in the hemoglobin level of greater than or equal to (\geq) 2 grams per decilitre (g/dL) (20 grams per liter [g/L]; 1.24 millimoles per liter [mmol/L]) compared to the most recent hemoglobin value available before the event; clinically overt bleeding leading to transfusion of 2 or more units of packed red blood cells or whole blood. The results were based on classification of events that have been positively adjudicated as major bleeding events. Incidence rate estimated as number of subjects with incident events divided by cumulative at-risk time, where subject is no longer at risk once an incident event occurred.

End point type	Primary
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End point timeframe:

From randomization until the efficacy cut-off date (median 326 days)

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[3]	3604 ^[4]		
Units: event/100 subject-years				
number (confidence interval 95%)	1.82 (1.39 to 2.33)	0.67 (0.42 to 1.00)		

Notes:

[3] - ITT

[4] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis: ISTH major bleeding events
Statistical analysis description:	
Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.	
Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.68
upper limit	4.39

Secondary: Time from Randomization to First Occurrence of Any of the Following: Cardiovascular Death, Recurrent Stroke, Systemic Embolism and Myocardial Infarction

End point title	Time from Randomization to First Occurrence of Any of the Following: Cardiovascular Death, Recurrent Stroke, Systemic Embolism and Myocardial Infarction
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End point description:

Incidence rate estimated as number of subjects with incident events divided by cumulative at-risk time, where subject is no longer at risk once an incident event occurred. Cardiovascular death includes death due to haemorrhage and death with undetermined/unknown cause. Systemic embolism is defined as abrupt vascular insufficiency associated with clinical or radiological evidence of arterial occlusion in the absence of other likely mechanisms. The diagnosis of myocardial infarction requires the combination of: 1)evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); and 2)supporting information derived from the clinical presentation, electrocardiographic changes, or the results of myocardial or coronary artery imaging.

End point type	Secondary
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End point timeframe:

From randomization until the efficacy cut-off date (median 326 days)

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[5]	3604 ^[6]		
Units: event/100 subject-years				
number (confidence interval 95%)	6.20 (5.38 to 7.10)	5.85 (5.05 to 6.73)		

Notes:

[5] - ITT

[6] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description: Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Confidence intervals were calculated, if at least 1 event in each treatment arm existed. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.	
Comparison groups	Acetylsalicylic acid 100 mg OD v Rivaroxaban 15 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.56922
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.29

Secondary: Time from Randomization to First Occurrence of All-Cause Mortality

End point title	Time from Randomization to First Occurrence of All-Cause Mortality
End point description: All-cause mortality includes all deaths of subjects due to any cause.	
End point type	Secondary
End point timeframe: From randomization until the efficacy cut-off date (median 326 days)	

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[7]	3604 ^[8]		
Units: event/100 subject-years				
number (confidence interval 95%)	1.88 (1.45 to 2.40)	1.50 (1.12 to 1.97)		

Notes:

[7] - ITT

[8] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis: All-cause mortality
Statistical analysis description: Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Confidence intervals were	

calculated, if at least 1 event in each treatment arm existed. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.

Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.22078
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.81

Secondary: Time from Randomization to First Occurrence of the Following: Stroke, Ischemic Stroke, Disabling Stroke (Modified Rankin Score \geq 4), Cardiovascular Death (Including Death due to Hemorrhage and Death with Undetermined/Unknown Cause), Myocardial Infarction

End point title	Time from Randomization to First Occurrence of the Following: Stroke, Ischemic Stroke, Disabling Stroke (Modified Rankin Score \geq 4), Cardiovascular Death (Including Death due to Hemorrhage and Death with Undetermined/Unknown Cause), Myocardial Infarction
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End point description:

Disabling stroke is defined as stroke with modified Rankin score (mRS) greater than or equal to (\geq) 4 as assessed by investigator. mRS spans 0-6, running from perfect health to death. A score of 0-3 indicates functional status ranging from no symptoms to "moderate disability" (defined in the mRS as requiring some help, but able to walk without assistance); mRS 4-6 indicates functional status ranging from "moderately severe disability" (unable to walk or to attend to own bodily needs without assistance) through to death. CV death includes death due to haemorrhage and death with undetermined/unknown cause. Diagnosis of myocardial infarction requires combination of: 1) evidence of myocardial necrosis (either changes in cardiac biomarkers or post-mortem pathological findings); 2) supporting information derived from clinical presentation, electrocardiographic changes, or results of myocardial or coronary artery imaging.

End point type	Secondary
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End point timeframe:

From randomization until the efficacy cut-off date (median 326 days)

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[9]	3604 ^[10]		
Units: event/100 subject-years				
number (confidence interval 95%)				
Stroke	5.11 (4.37 to 5.93)	4.71 (4.01 to 5.51)		
Ischemic stroke	4.71 (4.01 to 5.51)	4.56 (3.87 to 5.34)		

Disabling stroke	1.20 (0.86 to 1.62)	0.84 (0.56 to 1.21)		
CVdeath (includes death due to hemorrhage)	0.99 (0.68 to 1.38)	0.66 (0.42 to 1.00)		
Myocardial infarction	0.49 (0.29 to 0.79)	0.67 (0.42 to 1.00)		

Notes:

[9] - ITT

[10] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis 1: Stroke
Statistical analysis description:	
Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.	
Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4797
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.34

Statistical analysis title	Statistical analysis 2: Ischemic stroke
Statistical analysis description:	
Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.	
Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78738
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.29

Statistical analysis title	Statistical analysis 3: Disabling stroke
Statistical analysis description:	
Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.	
Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14822
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.42
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.88
upper limit	2.28

Statistical analysis title	Statistical analysis 4: CV death
Statistical analysis description:	
Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.	
Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.14051
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	2.52

Statistical analysis title	Statistical analysis 5: Myocardial infarction
Statistical analysis description:	
Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided)	

as compared to acetylsalicylic acid arm were based on the log-rank test.

Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.34284
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.38

Secondary: Time from Randomization to First Occurrence of Life-Threatening Bleeding Events

End point title	Time from Randomization to First Occurrence of Life-Threatening Bleeding Events
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End point description:

Life-threatening bleeding was defined as a subset of major bleeding that met at least one of the following criteria: 1) fatal bleeding; 2) symptomatic intracranial haemorrhage; 3) reduction in hemoglobin of at least 5 g/dl (50 g/l; 3.10 mmol/L); 4) transfusion of at least 4 units of packed red cells or whole blood; 5) associated with hypotension requiring the use of intravenous inotropic agents; 6) necessitated surgical intervention. Incidence rate estimated as number of subjects with incident events divided by cumulative at-risk time, where subject is no longer at risk once an incident event occurred.

End point type	Secondary
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End point timeframe:

From randomization until the efficacy cut-off date (median 326 days)

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[11]	3604 ^[12]		
Units: event/100 subject-years				
number (confidence interval 95%)	1.02 (0.71 to 1.42)	0.43 (0.24 to 0.72)		

Notes:

[11] - ITT

[12] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis
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Statistical analysis description:

Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.

Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00443
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.28
upper limit	4.29

Secondary: Time from Randomization to First Occurrence of Clinically Relevant Non-Major Bleeding Events

End point title	Time from Randomization to First Occurrence of Clinically Relevant Non-Major Bleeding Events
End point description:	Non-major clinically relevant bleeding was defined as non-major overt bleeding but required medical attention (example: hospitalization, medical treatment for bleeding), and/or was associated with the study drug interruption of more than 14 days. The results were based on the outcome events at or after randomization until the efficacy cut-off date. Incidence rate estimated as number of subjects with incident events divided by cumulative at-risk time, where subject is no longer at risk once an incident event occurred.
End point type	Secondary
End point timeframe:	From randomization until the efficacy cut-off date (median 326 days)

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[13]	3604 ^[14]		
Units: event/100 subject-years				
number (confidence interval 95%)	3.52 (2.91 to 4.21)	2.32 (1.84 to 2.90)		

Notes:

[13] - ITT

[14] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis
Statistical analysis description:	Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.
Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD

Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.00451
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.13
upper limit	2

Secondary: Time from Randomization to First Occurrence of Intracranial Hemorrhage

End point title	Time from Randomization to First Occurrence of Intracranial Hemorrhage
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End point description:

Intracranial hemorrhage included all bleeding events that occurred in intracerebral, subarachnoid as well as subdural or epidural sites. The below table displays results for all randomized subjects and the outcomes at or after randomization until the efficacy cut-off date. Incidence rate estimated as number of subjects with incident events divided by cumulative at-risk time, where subject is no longer at risk once an incident event occurred.

End point type	Secondary
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End point timeframe:

From randomization until the efficacy cut-off date (median 326 days)

End point values	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3609 ^[15]	3604 ^[16]		
Units: event/100 subject-years				
number (confidence interval 95%)	0.70 (0.45 to 1.04)	0.35 (0.18 to 0.61)		

Notes:

[15] - ITT

[16] - ITT

Statistical analyses

Statistical analysis title	Statistical analysis
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Statistical analysis description:

Risk reduction was estimated with the stratified Cox proportional hazards model. Hazard ratios (95% confidence interval) as compared to acetylsalicylic acid arm were reported. Rivaroxaban treatment was compared with the Acetylsalicylic acid control group using a stratified log-rank test. P-values (two-sided) as compared to acetylsalicylic acid arm were based on the log-rank test.

Comparison groups	Rivaroxaban 15 mg OD v Acetylsalicylic acid 100 mg OD
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Number of subjects included in analysis	7213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04409
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4.02

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study drug administration until 2 days after the last dose of study drug

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Rivaroxaban 15 mg OD
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Reporting group description:

Subjects received rivaroxaban 15 mg immediate-release film-coated tablet and matching placebo of acetylsalicylic acid orally OD up to end of treatment.

Reporting group title	Acetylsalicylic acid 100 mg OD
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Reporting group description:

Subjects received acetylsalicylic acid 100 mg enteric-coated tablet and matching placebo of rivaroxaban orally OD up to end of treatment.

Serious adverse events	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD	
Total subjects affected by serious adverse events			
subjects affected / exposed	466 / 3562 (13.08%)	434 / 3559 (12.19%)	
number of deaths (all causes)	73	58	
number of deaths resulting from adverse events	15	20	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute lymphocytic leukaemia			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma gastric			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Adenocarcinoma of colon			

subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
B-cell lymphoma		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Basal cell carcinoma		
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bile duct adenocarcinoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Bladder cancer		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Bladder neoplasm		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bladder transitional cell carcinoma		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Brain neoplasm malignant		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Cervix carcinoma		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Colon cancer		
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Colorectal cancer stage IV		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Essential thrombocythaemia		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Fallopian tube cancer		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gallbladder cancer		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric cancer		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal carcinoma		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Hodgkin's disease		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Kaposi's sarcoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung adenocarcinoma		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Lung adenocarcinoma stage IV		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage IV		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Lymphoma		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Malignant melanoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Metastases to bone		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myelodysplastic syndrome		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Non-Hodgkin's lymphoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal adenocarcinoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal carcinoma		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Oropharyngeal cancer		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic carcinoma		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatic carcinoma metastatic		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Papillary thyroid cancer		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Parathyroid tumour		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal adenocarcinoma		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal cancer		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal cancer stage III		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal meningioma benign		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of lung		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Squamous cell carcinoma of the tongue		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transitional cell carcinoma		
subjects affected / exposed	3 / 3562 (0.08%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Uterine leiomyoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal adenoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung cancer metastatic		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal adenocarcinoma		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Neuroendocrine tumour		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lung neoplasm malignant		

subjects affected / exposed	1 / 3562 (0.03%)	5 / 3559 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 1
Pancreatic carcinoma stage IV		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Prostate cancer		
subjects affected / exposed	1 / 3562 (0.03%)	8 / 3559 (0.22%)
occurrences causally related to treatment / all	0 / 1	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Benign bone neoplasm		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Brain neoplasm		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal neoplasm		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Oesophageal squamous cell carcinoma		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pituitary tumour benign		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Non-small cell lung cancer		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thyroid cancer			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic uterine cancer			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Inflammatory pseudotumour			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of unknown primary site			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatic cancer			

subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive breast carcinoma			
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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	4 / 3562 (0.11%)	6 / 3559 (0.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			

subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Lymphoedema		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Orthostatic hypotension		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral ischaemia		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Peripheral vascular disorder		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Temporal arteritis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thrombophlebitis superficial		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Varicose vein		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post thrombotic syndrome		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
May-Thurner syndrome			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	5 / 3562 (0.14%)	5 / 3559 (0.14%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Atrial septal defect repair			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Finger amputation			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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			

Asthenia			
subjects affected / exposed	0 / 3562 (0.00%)	3 / 3559 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gait disturbance			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	3 / 3562 (0.08%)	4 / 3559 (0.11%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaphylactic shock			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal graft rejection			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	4 / 3562 (0.11%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Menorrhagia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peyronie's disease			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial dysplasia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Genital haemorrhage			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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			
Acute pulmonary oedema			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 3562 (0.08%)	3 / 3559 (0.08%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Asthma			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic pulmonary fibrosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 3562 (0.08%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 3562 (0.03%)	8 / 3559 (0.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary oedema			

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sleep apnoea syndrome			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary mass			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial disorder			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Adjustment disorder with mixed anxiety and depressed mood			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholism			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			

subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Completed suicide		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 2
Conversion disorder		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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	2 / 3562 (0.06%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Depression		
subjects affected / exposed	3 / 3562 (0.08%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Disorientation		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Depression suicidal		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hallucination, visual		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intentional self-injury		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Mania		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Obsessive-compulsive personality disorder		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Panic disorder		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Panic reaction		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Somnambulism		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Schizophrenia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Suicide attempt		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Alcohol withdrawal syndrome		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurologic somatic symptom disorder			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol use disorder			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	4 / 3562 (0.11%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			

subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholangitis acute		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cholecystitis acute		
subjects affected / exposed	3 / 3562 (0.08%)	4 / 3559 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Cholelithiasis		
subjects affected / exposed	6 / 3562 (0.17%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatic cirrhosis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis acute		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Drug-induced liver injury		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eosinophil count increased			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatic specific antigen increased			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A virus test positive			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Accidental overdose			
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anastomotic ulcer haemorrhage			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carbon monoxide poisoning			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	6 / 3562 (0.17%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	5 / 3562 (0.14%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Foot fracture		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Head injury		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hip fracture		
subjects affected / exposed	1 / 3562 (0.03%)	5 / 3559 (0.14%)
occurrences causally related to treatment / all	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Humerus fracture		
subjects affected / exposed	2 / 3562 (0.06%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Intentional overdose		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Joint dislocation		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Laceration		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament sprain		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Medication error		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Overdose		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Radius fracture		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rib fracture		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Road traffic accident		
subjects affected / exposed	0 / 3562 (0.00%)	4 / 3559 (0.11%)
occurrences causally related to treatment / all	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1
Spinal compression fracture		
subjects affected / exposed	3 / 3562 (0.08%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal fracture		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Subarachnoid haemorrhage		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Wrist fracture		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Traumatic fracture		
subjects affected / exposed	0 / 3562 (0.00%)	3 / 3559 (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 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle strain		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Face injury		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Contusion		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Arterial restenosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Brain contusion		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Thermal burn		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transplant failure		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Limb injury		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Traumatic intracranial haemorrhage		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Upper limb fracture		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ligament rupture		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Bone contusion		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal column injury		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 3562 (0.00%)	3 / 3559 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect dosage administered			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb fracture			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicuspid aortic valve			

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocele			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arteriovenous fistula			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia supraventricular			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			

subjects affected / exposed	36 / 3562 (1.01%)	37 / 3559 (1.04%)
occurrences causally related to treatment / all	0 / 36	0 / 37
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial flutter		
subjects affected / exposed	5 / 3562 (0.14%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 5	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block complete		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Atrioventricular block second degree		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Bradycardia		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac amyloidosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0
Cardiac failure		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure chronic		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cardiac failure congestive		

subjects affected / exposed	3 / 3562 (0.08%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Conduction disorder		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery disease		
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery occlusion		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery stenosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hypertensive heart disease		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myocardial ischaemia		
subjects affected / exposed	1 / 3562 (0.03%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Myocarditis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Palpitations		

subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pericardial effusion		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Sinus bradycardia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Supraventricular tachycardia		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular tachycardia		
subjects affected / exposed	3 / 3562 (0.08%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Atrial thrombosis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Ventricular hypokinesia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Coronary artery insufficiency		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Endocarditis noninfective		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amyotrophic lateral sclerosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Autonomic nervous system imbalance			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain stem haemorrhage			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar haemorrhage			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous thrombosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			

subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Chorea		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Demyelination		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic neuropathy		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Dizziness		
subjects affected / exposed	2 / 3562 (0.06%)	4 / 3559 (0.11%)
occurrences causally related to treatment / all	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Dysarthria		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Epilepsy		
subjects affected / exposed	7 / 3562 (0.20%)	8 / 3559 (0.22%)
occurrences causally related to treatment / all	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Facial paralysis		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Generalised tonic-clonic seizure		

subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Headache		
subjects affected / exposed	2 / 3562 (0.06%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Hemiparesis		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hypoaesthesia		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intracranial aneurysm		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Loss of consciousness		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Migraine with aura		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Migraine		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Multiple sclerosis		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Myelopathy		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Nervous system disorder		
subjects affected / exposed	1 / 3562 (0.03%)	4 / 3559 (0.11%)
occurrences causally related to treatment / all	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0
Paraesthesia		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Polyneuropathy		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Post herpetic neuralgia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Presyncope		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Sciatica		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Seizure		

subjects affected / exposed	9 / 3562 (0.25%)	9 / 3559 (0.25%)
occurrences causally related to treatment / all	0 / 10	0 / 9
deaths causally related to treatment / all	0 / 0	0 / 0
Status epilepticus		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1
Syncope		
subjects affected / exposed	10 / 3562 (0.28%)	8 / 3559 (0.22%)
occurrences causally related to treatment / all	0 / 10	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0
Tension headache		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Transient global amnesia		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vertebrobasilar insufficiency		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Cervical radiculopathy		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Thalamus haemorrhage		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Putamen haemorrhage		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Stroke in evolution		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Partial seizures		
subjects affected / exposed	5 / 3562 (0.14%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Parkinson's disease		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Metabolic encephalopathy		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral artery stenosis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Central pain syndrome		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Cerebral arteriosclerosis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Post stroke seizure		

subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianaesthesia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudostroke			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Focal dyscognitive seizures			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparaesthesia			
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	8 / 3562 (0.22%)	3 / 3559 (0.08%)	
occurrences causally related to treatment / all	3 / 8	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anaemia macrocytic			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Antiphospholipid syndrome			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	4 / 3562 (0.11%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	1 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Microcytic anaemia			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Meniere's disease			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional			

subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	4 / 3562 (0.11%)	8 / 3559 (0.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid ptosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glaucoma			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular oedema			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual impairment			

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular fibrosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ophthalmic vein thrombosis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental caries			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Diverticulum intestinal		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Duodenal ulcer		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Dyspepsia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric haemorrhage		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric ulcer haemorrhage		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal fistula		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroesophageal reflux disease		

subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Haemorrhoids		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Hiatus hernia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Ileus		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Inguinal hernia		
subjects affected / exposed	7 / 3562 (0.20%)	5 / 3559 (0.14%)
occurrences causally related to treatment / all	0 / 7	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal obstruction		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal perforation		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1
Large intestinal ulcer		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Nausea		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis		
subjects affected / exposed	0 / 3562 (0.00%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatitis acute		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Small intestinal obstruction		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Vomiting		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Lower gastrointestinal haemorrhage		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pancreatolithiasis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Large intestine polyp		
subjects affected / exposed	4 / 3562 (0.11%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Gastric volvulus		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric mucosal lesion			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erosive duodenitis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal fissure			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatomyositis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin reaction			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic			
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cyst			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			

subjects affected / exposed	2 / 3562 (0.06%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Renal hypertension		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal haematoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary retention		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Costovertebral angle tenderness		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Renal impairment		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Chronic kidney disease		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Urethral stenosis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Acute kidney injury		

subjects affected / exposed	4 / 3562 (0.11%)	6 / 3559 (0.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ureterolithiasis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Basedow's disease			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Goitre			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis subacute			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	1 / 3562 (0.03%)	3 / 3559 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fasciitis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gouty arthritis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Groin pain			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck pain			

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Osteoarthritis		
subjects affected / exposed	11 / 3562 (0.31%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 12	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Osteonecrosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pain in extremity		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Periarthritis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Rheumatoid arthritis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Rotator cuff syndrome		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal column stenosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Spinal osteoarthritis		

subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Synovial cyst		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Myofascial pain syndrome		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Muscle tightness		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc protrusion		
subjects affected / exposed	3 / 3562 (0.08%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Musculoskeletal chest pain		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Limb discomfort		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Intervertebral disc disorder		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Plica syndrome		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebral foraminal stenosis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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			
Appendicitis			
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Appendicitis perforated			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain abscess			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cellulitis			

subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (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	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Corneal abscess		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic gangrene		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Encephalitis viral		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Endophthalmitis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Erysipelas		

subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis		
subjects affected / exposed	6 / 3562 (0.17%)	3 / 3559 (0.08%)
occurrences causally related to treatment / all	0 / 6	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0
Gastroenteritis viral		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gastrointestinal infection		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hepatitis A		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infected skin ulcer		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Influenza		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Kidney infection		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Liver abscess		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lower respiratory tract infection		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Meningitis		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Orchitis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (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	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Otitis externa		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Paronychia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritoneal abscess		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Peritonitis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia		
subjects affected / exposed	14 / 3562 (0.39%)	14 / 3559 (0.39%)
occurrences causally related to treatment / all	0 / 14	0 / 14
deaths causally related to treatment / all	0 / 1	0 / 2
Postoperative wound infection		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Pyelonephritis chronic		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Renal abscess		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Sepsis		
subjects affected / exposed	3 / 3562 (0.08%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0
Septic shock		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Tooth abscess		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection		
subjects affected / exposed	6 / 3562 (0.17%)	6 / 3559 (0.17%)
occurrences causally related to treatment / all	0 / 6	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0
Vestibular neuronitis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Viral infection		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Urosepsis		
subjects affected / exposed	3 / 3562 (0.08%)	4 / 3559 (0.11%)
occurrences causally related to treatment / all	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0
Rectal abscess		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Escherichia bacteraemia		

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Pneumonia necrotising		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal infection		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease		
subjects affected / exposed	3 / 3562 (0.08%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Neurocysticercosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Enteritis infectious		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Abdominal abscess		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Bursitis infective		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Lung infection		

subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perichondritis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 3562 (0.08%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acarodermatitis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster oticus			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary tract infection bacterial			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumocystis jirovecii pneumonia			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (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			
Diabetes mellitus			

subjects affected / exposed	4 / 3562 (0.11%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic ketoacidosis		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Failure to thrive		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Gout		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences causally related to treatment / all	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0
Hyperglycaemia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Hyponatraemia		
subjects affected / exposed	1 / 3562 (0.03%)	6 / 3559 (0.17%)
occurrences causally related to treatment / all	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0
Obesity		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Shock hypoglycaemic		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic complication		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Diabetic metabolic decompensation		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0
Adult failure to thrive		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences causally related to treatment / all	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Rivaroxaban 15 mg OD	Acetylsalicylic acid 100 mg OD
Total subjects affected by non-serious adverse events		
subjects affected / exposed	308 / 3562 (8.65%)	294 / 3559 (8.26%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Breast cancer		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Basosquamous carcinoma		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Breast neoplasm		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Metastases to bone		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Essential thrombocythaemia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Superficial spreading melanoma stage unspecified		

subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1	
Flushing			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Hypertension			
subjects affected / exposed occurrences (all)	11 / 3562 (0.31%) 11	7 / 3559 (0.20%) 8	
Hypertensive crisis			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Intermittent claudication			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Hypotension			
subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1	
Phlebitis superficial			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Thrombophlebitis superficial			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	2 / 3559 (0.06%) 2	
Varicose vein			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Deep vein thrombosis			
subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1	
Vascular pain			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	

Peripheral arterial occlusive disease subjects affected / exposed occurrences (all)	3 / 3562 (0.08%) 3	0 / 3559 (0.00%) 0	
Surgical and medical procedures			
Tooth extraction subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 3	2 / 3559 (0.06%) 2	
Cataract operation subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Implantable cardiac monitor insertion subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
General disorders and administration site conditions			
Asthenia subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0	
Chest discomfort subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Chest pain subjects affected / exposed occurrences (all)	3 / 3562 (0.08%) 3	4 / 3559 (0.11%) 4	
Chills subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Discomfort subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0	
Fatigue subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	3 / 3559 (0.08%) 3	
Gait disturbance subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Malaise			

subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	2 / 3559 (0.06%) 2	
Oedema peripheral subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	2 / 3559 (0.06%) 2	
Peripheral swelling subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	2 / 3559 (0.06%) 2	
Non-cardiac chest pain subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0	
Immune system disorders			
Hypersensitivity subjects affected / exposed occurrences (all)	3 / 3562 (0.08%) 3	1 / 3559 (0.03%) 3	
Allergy to arthropod sting subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Social circumstances			
Treatment noncompliance subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	5 / 3559 (0.14%) 5	
Reproductive system and breast disorders			
Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Breast mass subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Prostatomegaly subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Prostatitis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences (all)	1	1	
Dry throat			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Dyspnoea			
subjects affected / exposed	4 / 3562 (0.11%)	1 / 3559 (0.03%)	
occurrences (all)	4	1	
Epistaxis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Hiccups			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Pharyngeal ulceration			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Pulmonary microemboli			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 3562 (0.08%)	2 / 3559 (0.06%)	
occurrences (all)	3	2	
Anxiety			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences (all)	1	1	
Insomnia			

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Anxiety disorder			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Impatience			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Abulia			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Mental disorder due to a general medical condition			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Adjustment disorder			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Post stroke depression			
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Hepatic function abnormal			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences (all)	2	2	
Hepatitis			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Hypertransaminaemia			

subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Blood creatine phosphokinase increased subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Blood creatinine increased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Glomerular filtration rate decreased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Coagulation factor VIII level increased subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Haemoglobin decreased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Heart rate increased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Visual acuity tests abnormal subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Transaminases increased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Weight decreased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	2 / 3559 (0.06%) 2	
Blood alkaline phosphatase increased			

subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Hepatic enzyme increased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Liver function test increased subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	2 / 3559 (0.06%) 2	
Alcohol poisoning			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Concussion			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Fall			
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Foot fracture			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Humerus fracture			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Head injury			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Inappropriate schedule of drug administration			
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 2	0 / 3559 (0.00%) 0	
Medication error			

subjects affected / exposed occurrences (all)	10 / 3562 (0.28%) 10	9 / 3559 (0.25%) 9
Overdose subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0
Radius fracture subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Rib fracture subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0
Tendon rupture subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Face injury subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Post procedural haemorrhage subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Contusion subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Limb injury subjects affected / exposed occurrences (all)	3 / 3562 (0.08%) 3	1 / 3559 (0.03%) 1
Drug administration error subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1
Upper limb fracture subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Incorrect dose administered subjects affected / exposed occurrences (all)	6 / 3562 (0.17%) 6	4 / 3559 (0.11%) 4
Skin wound		

subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Labelled drug-drug interaction medication error subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Incorrect dosage administered subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1	
Medication monitoring error subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	3 / 3559 (0.08%) 3	
Intentional product misuse subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1	
Congenital, familial and genetic disorders			
Atrial septal defect subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Fabry's disease subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Factor V Leiden mutation subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Cardiac disorders			
Angina pectoris subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Atrial fibrillation subjects affected / exposed occurrences (all)	60 / 3562 (1.68%) 60	60 / 3559 (1.69%) 60	
Atrial flutter subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0	
Atrial tachycardia			

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Cardiac failure		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Cardiac failure congestive		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Coronary artery disease		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Myocardial ischaemia		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences (all)	2	0
Palpitations		
subjects affected / exposed	3 / 3562 (0.08%)	1 / 3559 (0.03%)
occurrences (all)	3	1
Sinus arrhythmia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Sinus tachycardia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Supraventricular extrasystoles		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Supraventricular tachycardia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Tachycardia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Ventricular fibrillation		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Intracardiac thrombus		

subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Cardiac flutter subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Nervous system disorders			
Amnesia subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Aphasia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Cerebrovascular accident subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Dementia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Dizziness subjects affected / exposed occurrences (all)	5 / 3562 (0.14%) 6	7 / 3559 (0.20%) 7	
Dizziness postural subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Dysarthria subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Dysgeusia subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	2 / 3559 (0.06%) 2	
Facial paralysis subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Epilepsy subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	

Headache		
subjects affected / exposed	10 / 3562 (0.28%)	8 / 3559 (0.22%)
occurrences (all)	10	9
Lethargy		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Hypoaesthesia		
subjects affected / exposed	1 / 3562 (0.03%)	3 / 3559 (0.08%)
occurrences (all)	1	3
Migraine		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Paraesthesia		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1
Parkinsonism		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Presyncope		
subjects affected / exposed	1 / 3562 (0.03%)	2 / 3559 (0.06%)
occurrences (all)	1	2
Sciatica		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences (all)	2	0
Seizure		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Somnolence		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Sensory disturbance		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Speech disorder		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0

Syncope		
subjects affected / exposed	2 / 3562 (0.06%)	3 / 3559 (0.08%)
occurrences (all)	2	4
Vertebral artery occlusion		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Cervical radiculopathy		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Hyposmia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Facial paresis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
IIIrd nerve paresis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Cognitive disorder		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1
Vascular dementia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Stroke in evolution		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Parkinson's disease		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Partial seizures		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1
Cerebral artery stenosis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1

Autonomic neuropathy subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Occipital neuralgia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	2 / 3559 (0.06%) 2	
Antiphospholipid syndrome subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0	
Iron deficiency anaemia subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Thrombocytopenia subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1	
Thrombocytosis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Vertigo subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	4 / 3559 (0.11%) 4	
Vertigo positional subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	2 / 3559 (0.06%) 2	
Eye disorders			
Cataract subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 2	2 / 3559 (0.06%) 2	
Conjunctival haemorrhage			

subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Diabetic retinopathy subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	2 / 3559 (0.06%) 2	
Dry eye subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Episcleritis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Eyelid ptosis subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Keratitis subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Pterygium subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Retinal vein occlusion subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Vision blurred subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Conjunctival hyperaemia subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 2	0 / 3559 (0.00%) 0	
Gastrointestinal disorders			
Abdominal discomfort subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Abdominal pain subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	

Abdominal pain lower subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 3562 (0.14%) 5	7 / 3559 (0.20%) 7
Cheilitis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Chronic gastritis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Constipation subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	1 / 3559 (0.03%) 1
Defaecation urgency subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Diarrhoea subjects affected / exposed occurrences (all)	8 / 3562 (0.22%) 8	3 / 3559 (0.08%) 3
Dyspepsia subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	3 / 3559 (0.08%) 4
Eructation subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Gastric ulcer subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	2 / 3559 (0.06%) 2
Gastritis subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	2 / 3559 (0.06%) 2
Gastritis erosive subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	2 / 3559 (0.06%) 2

Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1
Gastrointestinal disorder subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Gingival swelling subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 2
Gingival bleeding subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Haemorrhoids subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Hyperchlorhydria subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Inflammatory bowel disease subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Inguinal hernia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Lip swelling subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Nausea subjects affected / exposed occurrences (all)	5 / 3562 (0.14%) 5	1 / 3559 (0.03%) 1
Oesophagitis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Toothache subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1

Vomiting			
subjects affected / exposed	2 / 3562 (0.06%)	4 / 3559 (0.11%)	
occurrences (all)	2	4	
Retching			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Palatal disorder			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Colitis microscopic			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Alopecia			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Angioedema			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	2	
Eczema			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Drug eruption			
subjects affected / exposed	0 / 3562 (0.00%)	3 / 3559 (0.08%)	
occurrences (all)	0	3	
Dermatitis allergic			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Erythema			

subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Pruritus		
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1
Rash		
subjects affected / exposed occurrences (all)	4 / 3562 (0.11%) 4	4 / 3559 (0.11%) 4
Rash erythematous		
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Rash papular		
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Rash pruritic		
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Skin lesion		
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Urticaria		
subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	3 / 3559 (0.08%) 3
Skin swelling		
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Precancerous skin lesion		
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0
Solar lentigo		
subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1
Renal and urinary disorders		
Haematuria		
subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0

Renal colic			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences (all)	1	1	
Renal failure			
subjects affected / exposed	3 / 3562 (0.08%)	0 / 3559 (0.00%)	
occurrences (all)	3	0	
Nephrolithiasis			
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)	
occurrences (all)	2	0	
Renal impairment			
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)	
occurrences (all)	2	2	
Chronic kidney disease			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Ureterolithiasis			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Urinary incontinence			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)	
occurrences (all)	1	1	
Thyroiditis subacute			
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Thyroid mass			
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 3562 (0.03%)	4 / 3559 (0.11%)	
occurrences (all)	1	4	
Arthritis			

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Back pain		
subjects affected / exposed	4 / 3562 (0.11%)	3 / 3559 (0.08%)
occurrences (all)	4	3
Bursitis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1
Chondrocalcinosis pyrophosphate		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Gouty arthritis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Haemarthrosis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Joint swelling		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1
Metatarsalgia		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Muscle spasms		
subjects affected / exposed	2 / 3562 (0.06%)	0 / 3559 (0.00%)
occurrences (all)	2	0
Muscular weakness		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences (all)	2	2
Musculoskeletal pain		
subjects affected / exposed	1 / 3562 (0.03%)	4 / 3559 (0.11%)
occurrences (all)	1	4
Myalgia		
subjects affected / exposed	2 / 3562 (0.06%)	2 / 3559 (0.06%)
occurrences (all)	2	2
Myopathy		

subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Osteoarthritis		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences (all)	2	1
Osteochondrosis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1
Pain in extremity		
subjects affected / exposed	3 / 3562 (0.08%)	1 / 3559 (0.03%)
occurrences (all)	3	1
Periostitis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Plantar fasciitis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Spinal osteoarthritis		
subjects affected / exposed	0 / 3562 (0.00%)	2 / 3559 (0.06%)
occurrences (all)	0	2
Synovial cyst		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Tendonitis		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Tenosynovitis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Limb mass		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Infections and infestations		
Bronchitis		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1

Cystitis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Diarrhoea infectious		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Gastroenteritis		
subjects affected / exposed	3 / 3562 (0.08%)	1 / 3559 (0.03%)
occurrences (all)	3	1
Herpes zoster		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Influenza		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	2
Lower respiratory tract infection		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	2	0
Oesophageal candidiasis		
subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)
occurrences (all)	0	1
Pneumonia		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Pneumonia viral		
subjects affected / exposed	1 / 3562 (0.03%)	0 / 3559 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)
occurrences (all)	2	2
Urinary tract infection		
subjects affected / exposed	3 / 3562 (0.08%)	4 / 3559 (0.11%)
occurrences (all)	3	4
Vaginal infection		
subjects affected / exposed	1 / 3562 (0.03%)	1 / 3559 (0.03%)
occurrences (all)	1	1

Vulvovaginitis trichomonal subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Helicobacter infection subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Lung infection subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Respiratory tract infection viral subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Alveolar osteitis subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Metabolism and nutrition disorders			
Diabetes mellitus subjects affected / exposed occurrences (all)	2 / 3562 (0.06%) 2	0 / 3559 (0.00%) 0	
Electrolyte imbalance subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Gout subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	1 / 3559 (0.03%) 1	
Haemochromatosis subjects affected / exposed occurrences (all)	1 / 3562 (0.03%) 1	0 / 3559 (0.00%) 0	
Hypercholesterolaemia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Hyperglycaemia subjects affected / exposed occurrences (all)	0 / 3562 (0.00%) 0	1 / 3559 (0.03%) 1	
Decreased appetite			

subjects affected / exposed	0 / 3562 (0.00%)	1 / 3559 (0.03%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	2 / 3562 (0.06%)	1 / 3559 (0.03%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2015	<p>The following eligibility criteria were revised:</p> <ul style="list-style-type: none">•More details were provided in definition of a lacunar stroke.•Subjects were to be included if there was no stenosis greater than (>) 50% rather than greater than or equal to (>=) 50%.•They were to be excluded if there was an intracranial stenosis > 50%.•For subjects with intracranial arterial occlusions in territory of qualifying stroke, it was clarified that a subject was eligible if investigator believed the occlusion was due to embolism, and not atherosclerotic based on absence of intracranial atherosclerosis elsewhere.•For 24-hour cardiac rhythm monitoring assessment to exclude the presence of Atrial fibrillation (AF), an allowance was added to accept a 20-hour recording to reflect routine practice.•For determination of intra-cardiac thrombus, allowance of transesophageal echocardiography was added as well as transthoracic echocardiography.•Recruitment of subjects was changed from 18 years or older to 50 years of age or older.•Additional clarifications were made to the inclusion criteria regarding subjects enrolled with certain risk factors:<ul style="list-style-type: none">•Clarification that covert/silent strokes on neuroimaging and current tobacco smoker counted as risk factors.•Clarification that each risk factor counted separately (for example, "stroke or Transient ischemic attack (TIA) prior to index stroke, diabetes, hypertension, and heart failure" changed to "stroke or TIA prior to index stroke [includes covert/silent strokes on neuroimaging], diabetes, hypertension, current tobacco smoker, or heart failure").•Age restriction changed from less than (<) 60 years of age with a cap at 10% of the total study population to ≥ 50 years and requirement for an additional risk factor for subjects between 50-59 years.•A statement was added that enrollment in the age group 50-59 years might have been stopped based on a blinded review of the observed overall event rate of confirmed primary efficacy outcomes during the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 October 2017	The study was terminated early on recommendation of the IDMC and concurrence of the co-principal investigators and the sponsor due to no efficacy improvement over aspirin at an interim analysis and very little chance of showing overall benefit if study were completed.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Decimal places were automatically truncated if last decimals is equals to zero.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/29525076>

<http://www.ncbi.nlm.nih.gov/pubmed/29766772>