

**Clinical trial results:**

A prospective Randomised, open label, blinded endpoint (PROBE) study to Evaluate DUAL antithrombotic therapy with dabigatran etexilate (110mg and 150mg b.i.d.) plus clopidogrel or ticagrelor vs. triple therapy strategy with warfarin (INR 2.0 – 3.0) plus clopidogrel or ticagrelor and aspirin in patients with non valvular atrial fibrillation (NVAf) that have undergone a percutaneous coronary intervention (PCI) with stenting (RE-DUAL PCI)

Summary

EudraCT number	2013-003201-26
Trial protocol	SE DK GR DE PT HU ES FI NL CZ AT IT BE IE SK SI GB BG HR
Global end of trial date	15 June 2017

Results information

Result version number	v2 (current)
This version publication date	13 December 2021
First version publication date	21 June 2018
Version creation reason	

Trial information**Trial identification**

Sponsor protocol code	1160.186
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02164864
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	173 Binger Strasse, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination Clinical Trial Information Disclosure, Boehringer Ingelheim, 001 8002430127, clintriage.rdg@boehringer-ingelheim.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	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	12 July 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 June 2017
Global end of trial reached?	Yes
Global end of trial date	05 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to compare a dual antithrombotic regimen of 110 mg dabigatran etexilate (DE 110) twice daily plus clopidogrel or ticagrelor (110 mg DE-DAT) and 150 mg dabigatran etexilate (DE 150) twice daily plus clopidogrel or ticagrelor (150 mg DE-DAT) with a triple antithrombotic therapy (TAT) of warfarin plus clopidogrel or ticagrelor plus aspirin (warfarin-TAT) in patients with non-valvular atrial fibrillation (NVAf) that underwent a percutaneous coronary intervention (PCI) with stenting.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 August 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects**Subjects enrolled per country**

Country: Number of subjects enrolled	Argentina: 52
Country: Number of subjects enrolled	Australia: 31
Country: Number of subjects enrolled	Austria: 19
Country: Number of subjects enrolled	Belgium: 47
Country: Number of subjects enrolled	Brazil: 34
Country: Number of subjects enrolled	Bulgaria: 77
Country: Number of subjects enrolled	Canada: 56
Country: Number of subjects enrolled	Chile: 13
Country: Number of subjects enrolled	Colombia: 12
Country: Number of subjects enrolled	Croatia: 41
Country: Number of subjects enrolled	Czechia: 50
Country: Number of subjects enrolled	Denmark: 61
Country: Number of subjects enrolled	Finland: 45
Country: Number of subjects enrolled	France: 102

Country: Number of subjects enrolled	Germany: 486
Country: Number of subjects enrolled	Greece: 101
Country: Number of subjects enrolled	Hong Kong: 17
Country: Number of subjects enrolled	Hungary: 119
Country: Number of subjects enrolled	India: 35
Country: Number of subjects enrolled	Ireland: 15
Country: Number of subjects enrolled	Israel: 37
Country: Number of subjects enrolled	Italy: 91
Country: Number of subjects enrolled	Japan: 117
Country: Number of subjects enrolled	Korea, Republic of: 85
Country: Number of subjects enrolled	Mexico: 12
Country: Number of subjects enrolled	Netherlands: 55
Country: Number of subjects enrolled	New Zealand: 5
Country: Number of subjects enrolled	Norway: 62
Country: Number of subjects enrolled	Poland: 99
Country: Number of subjects enrolled	Portugal: 45
Country: Number of subjects enrolled	Russian Federation: 131
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	Slovakia: 40
Country: Number of subjects enrolled	Slovenia: 16
Country: Number of subjects enrolled	Spain: 121
Country: Number of subjects enrolled	Sweden: 47
Country: Number of subjects enrolled	Taiwan: 37
Country: Number of subjects enrolled	Thailand: 30
Country: Number of subjects enrolled	Turkey: 168
Country: Number of subjects enrolled	United Kingdom: 69
Country: Number of subjects enrolled	United States: 156
Worldwide total number of subjects	2845
EEA total number of subjects	1739

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)	652
From 65 to 84 years	2089
85 years and over	104

Subject disposition

Recruitment

Recruitment details:

Patients aged ≥ 80 years in the United States of America (USA) were assigned to 110 milligram (mg) Dual antithrombotic therapy with dabigatran etexilate (DE-DAT), 150 mg DE-DAT, or warfarin. All other patients aged ≥ 80 years (for Japan ≥ 70 years) outside of the USA were assigned to 110 mg DE-DAT or warfarin.

Pre-assignment

Screening details:

All patients (Pts) were screened for eligibility to participate in trial. Pts attended specialist sites to ensure that they met all implemented inclusion/exclusion criteria. Pts were not to be randomised to trial drug if any of specific entry criteria was violated. In this study, 2725 Pts were entered & randomised. 2678 Pts were treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

A prospective Randomised, open label, blinded endpoint (PROBE) study.

Arms

Are arms mutually exclusive?	Yes
Arm title	Dabigatran Etexilate 110mg

Arm description:

Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.

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

Dosage and administration details:

Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.

Arm title	Dabigatran Etexilate 150mg
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Arm description:

Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.

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

Dosage and administration details:

Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.

Arm title	Warfarin
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Arm description:

Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible

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

Dosage and administration details:

Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible

Number of subjects in period 1^[1]	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin
Started	981	763	981
Completed	886	703	849
Not completed	95	60	132
Protocol deviation	2	4	1
Non-Fatal	10	10	8
Consent withdrawn, not due to AE	21	8	56
Fatal	55	31	51
Other than stated	3	4	14
Lost to follow-up	4	3	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one of the trial medication. No Statistical analysis

Baseline characteristics

Reporting groups

Reporting group title	Dabigatran Etexilate 110mg
Reporting group description:	
Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.	
Reporting group title	Dabigatran Etexilate 150mg
Reporting group description:	
Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.	
Reporting group title	Warfarin
Reporting group description:	
Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible	

Reporting group values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin
Number of subjects	981	763	981
Age categorical			
Units: Subjects			

Age Continuous			
Full analysis set (FAS): All consenting patients randomised were analysed in the treatment group to which they were randomised regardless of whether they took trial medication. The start date of the observation period for this analysis set was the date of randomisation. Patients who discontinued trial medication were followed until the end of the trial. Patients who were lost to follow-up for vital status were censored for the primary endpoint at the time of their last known vital status.			
Units: years			
arithmetic mean	71.5	68.6	71.7
standard deviation	± 8.87	± 7.65	± 8.90
Sex: Female, Male			
Number of subjects is categorized as Male or Female			
Units: Subjects			
Female	253	171	231
Male	728	592	750
Race/Ethnicity, Customized			
The details on Race has been provided			
Units: Subjects			
Asian	116	79	125
Black	5	7	3
White	851	658	835
Other	5	8	7
Missing	4	11	11
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	70	46	59
Not Hispanic or Latino	903	700	904
Unknown or Not Reported	8	17	18
Age, Customized			
Units: Subjects			

<80: EU/ROW	725	699	718
<80: USA	54	53	61
≥80: EU/ROW	189	3	192
≥80: USA	13	8	10

Reporting group values	Total		
Number of subjects	2725		
Age categorical			
Units: Subjects			

Age Continuous			
Full analysis set (FAS): All consenting patients randomised were analysed in the treatment group to which they were randomised regardless of whether they took trial medication. The start date of the observation period for this analysis set was the date of randomisation. Patients who discontinued trial medication were followed until the end of the trial. Patients who were lost to follow-up for vital status were censored for the primary endpoint at the time of their last known vital status.			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Number of subjects is categorized as Male or Female			
Units: Subjects			
Female	655		
Male	2070		
Race/Ethnicity, Customized			
The details on Race has been provided			
Units: Subjects			
Asian	320		
Black	15		
White	2344		
Other	20		
Missing	26		
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	175		
Not Hispanic or Latino	2507		
Unknown or Not Reported	43		
Age, Customized			
Units: Subjects			
<80: EU/ROW	2142		
<80: USA	168		
≥80: EU/ROW	384		
≥80: USA	31		

End points

End points reporting groups

Reporting group title	Dabigatran Etexilate 110mg
Reporting group description: Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.	
Reporting group title	Dabigatran Etexilate 150mg
Reporting group description: Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.	
Reporting group title	Warfarin
Reporting group description: Patients were orally administered warfarin 1 mg, 3 mg, or 5 mg tablets once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible	
Subject analysis set title	Warfarin (Excluding elder patient outside USA)
Subject analysis set type	Full analysis
Subject analysis set description: Patients were orally administered warfarin once daily. The warfarin dose was titrated as needed to maintain the target INR of 2.0 to 3.0 ; 2.0 to 2.5 if feasible. Elderly patients who were outside the USA were excluded.	
Subject analysis set title	All Dabigatran Etexilate
Subject analysis set type	Full analysis
Subject analysis set description: Patients in combined Dabigatran Etexilate group (ie 110 mg DE + 150 mg DE).	

Primary: Time to first adjudicated ISTH MBE or CRNMBE.

End point title	Time to first adjudicated ISTH MBE or CRNMBE.
End point description: The patients having event of time to first adjudicated International Society of Thrombosis and Haemostasis (ISTH) Major Bleeding Event (MBE) or Clinically Relevant Non Major Bleeding Event (CRNMBE).	
End point type	Primary
End point timeframe: up to 30 months	

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[1]	763 ^[2]	981 ^[3]	764 ^[4]
Units: participants with event	151	154	264	196

Notes:

[1] - Full Analysis set (FAS) following the intention-to-treat principle.

[2] - Full Analysis set (FAS) following the intention-to-treat principle.

[3] - Full Analysis set (FAS) following the intention-to-treat principle.

[4] - Full Analysis set (FAS) following the intention-to-treat principle.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: A pre-defined hierarchical testing approach was used. This was the first step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etxilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[5]
P-value	< 0.0001 ^[6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.63

Notes:

[5] - The upper bound of the Wald confidence interval (CI) of the HR of Dabigatran Etxilate 110mg vs Warfarin (one-sided 97.5%) was compared with this noninferiority margin for the testing of non-inferiority. All non-inferiority tests were based on a margin of 1.38.

[6] - A pre-defined hierarchical testing approach was used. P values for noninferiority were calculated at a one-sided alpha level of 0.025

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: A pre-defined hierarchical testing approach was used. This was the second step in hierarchy. Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model. All non-inferiority tests were based on a margin of 1.38.	
Comparison groups	Dabigatran Etxilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.001 ^[7]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.88

Notes:

[7] - P-values for non-inferiority were calculated at a one-sided alpha level of 0.025

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: A pre-defined hierarchical testing approach was used. This was the fourth step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80	

or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 ^[8]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.63

Notes:

[8] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
A pre-defined hierarchical testing approach was used. This was the sixth step in hierarchy. Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002 ^[9]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	0.88

Notes:

[9] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to adjudicated Undetermined cause of death

End point title	Time to adjudicated Undetermined cause of death
End point description:	
The patients having event of time to adjudicated Undetermined cause of death. This is referred to a death not attributable to CV death or to a non-CV cause. Inability to classify the cause of death may have been due to lack of information (e.g. the only available information was "patient died") or when there was insufficient supporting information or detail to assign the cause of death.	
End point type	Secondary
End point timeframe:	
up to 30 months	

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[10]	763 ^[11]	981 ^[12]	764 ^[13]
Units: participants with event	4	5	4	3

Notes:

[10] - FAS

[11] - FAS

[12] - FAS

[13] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9862 ^[14]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	3.95

Notes:

[14] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5277 ^[15]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38

upper limit	6.64
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Notes:

[15] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to adjudicated Non-CV

End point title	Time to adjudicated Non-CV
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End point description:

The patients having event of time to adjudicated Non-cardiovascular (Non-CV). Non-CV death was defined as any death with a specific cause that was not thought to be CV. These were possible examples of non-CV causes of death: Pulmonary, Renal, Gastrointestinal, Hepatobiliary, Pancreatic Infection(included sepsis), Inflammatory (e.g. systemic inflammatory response syndrome) or immune (including autoimmune), Haemorrhage that was neither CV bleeding nor a stroke, Non-CV procedure or surgery, Trauma, Suicide, Non-prescription drug reaction or overdose, Prescription drug reaction or overdose, Neurological (non-CV), Malignancy, Other non-CV

End point type	Secondary
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End point timeframe:

up to 30 months

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[16]	763 ^[17]	981 ^[18]	764 ^[19]
Units: participants with event	14	4	13	8

Notes:

[16] - FAS

[17] - FAS

[18] - FAS

[19] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.238 ^[20]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	1.61

Notes:

[20] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etxilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8853 ^[21]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.25

Notes:

[21] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Secondary: Time to adjudicated CV

End point title	Time to adjudicated CV
End point description: The patients having event of time to adjudicated Cardiovascular (CV) death. CV death included death resulting from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, death due to CV procedures, death due to CV haemorrhage, and death due to other CV causes.	
End point type	Secondary
End point timeframe: up to 30 months	

End point values	Dabigatran Etxilate 110mg	Dabigatran Etxilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[22]	763 ^[23]	981 ^[24]	764 ^[25]
Units: participants with event	37	21	31	24

Notes:

[22] - FAS

[23] - FAS

[24] - FAS

[25] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5252 ^[26]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.72
upper limit	1.88

Notes:

[26] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.567 ^[27]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.51

Notes:

[27] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to adjudicated all cause death

End point title	Time to adjudicated all cause death
End point description:	
The patients having event of time to adjudicated all cause death. All cause death is defined as the death from any cause included CV death, non-CV death, and undetermined cause of death.	
End point type	Secondary
End point timeframe:	
up to 30 months	

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[28]	763 ^[29]	981 ^[30]	764 ^[31]
Units: participants with event	55	30	48	35

Notes:

[28] - FAS

[29] - FAS

[30] - FAS

[31] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5579 ^[32]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	1.65

Notes:

[32] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4414 ^[33]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.34

Notes:

[33] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated MI

End point title	Time to first adjudicated MI
End point description: The patients having event of time to first adjudicated Myocardial Infarction (MI).	
End point type	Secondary
End point timeframe: up to 30 months	

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[34]	763 ^[35]	981 ^[36]	764 ^[37]
Units: participants with event	44	26	29	22

Notes:

[34] - FAS

[35] - FAS

[36] - FAS

[37] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.6144 ^[38]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.16
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	2.04

Notes:

[38] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0861 [39]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.51
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	2.41

Notes:

[39] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Secondary: Time to first adjudicated Stroke

End point title	Time to first adjudicated Stroke
End point description: The patients having event of time to first adjudicated Stroke. Stroke was defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of haemorrhage or infarction	
End point type	Secondary
End point timeframe: up to 30 months	

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981	763	981	764
Units: participants with event	17	9	13	8

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan

and <80 or >=80 years old elsewhere].

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4803 ^[40]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	2.67

Notes:

[40] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8537 ^[41]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	2.83

Notes:

[41] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated SE

End point title	Time to first adjudicated SE
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End point description:

The patients having event of time to first adjudicated Systemic embolism (SE). SE is an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts) and had to be documented by angiography, surgery, scintigraphy, or autopsy.

End point type	Secondary
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End point timeframe:

up to 30 months

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[42]	763 ^[43]	981 ^[44]	764 ^[45]
Units: participants with event	3	1	3	3

Notes:

[42] - FAS

[43] - FAS

[44] - FAS

[45] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9388 ^[46]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.19
upper limit	4.66

Notes:

[46] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.303 ^[47]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03

upper limit	2.93
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Notes:

[47] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated ST

End point title	Time to first adjudicated ST
End point description: The patients having event of time to first adjudicated Stent Thrombosis (ST).	
End point type	Secondary
End point timeframe: up to 30 months	

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981	763	981	764
Units: participants with event	15	7	8	7

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model	
Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1546 ^[48]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	4.4

Notes:

[48] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard

model

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9789 [49]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	2.81

Notes:

[49] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to composite endpoint of death + MI + stroke

End point title	Time to composite endpoint of death + MI + stroke
End point description:	The patients having event of time to the composite endpoint of death + myocardial infarction (MI) + stroke
End point type	Secondary
End point timeframe:	up to 30 months

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[50]	763 ^[51]	981 ^[52]	764 ^[53]
Units: participants with event	107	60	80	57

Notes:

[50] - FAS

[51] - FAS

[52] - FAS

[53] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.
Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other

P-value	= 0.0484 ^[54]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.79

Notes:

[54] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8903 ^[55]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.47

Notes:

[55] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to composite event of death or first thrombotic event

End point title	Time to composite event of death or first thrombotic event
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End point description:

The patients having event of time to death or first thrombotic event (all death, myocardial infarction (MI), stroke/systemic embolism (SE))

End point type	Secondary
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End point timeframe:

up to 30 months

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[56]	763 ^[57]	981 ^[58]	764 ^[59]
Units: participants with event	108	60	83	60

Notes:

[56] - FAS

[57] - FAS

[58] - FAS

[59] - FAS

End point values	All Dabigatran Etexilate			
Subject group type	Subject analysis set			
Number of subjects analysed	1744 ^[60]			
Units: participants with event	168			

Notes:

[60] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

A pre-defined hierarchical testing approach was used. This was the fifth step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere].

Comparison groups	Warfarin v All Dabigatran Etexilate
Number of subjects included in analysis	2725
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[61]
P-value	= 0.1128 ^[62]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.53

Notes:

[61] - The upper bound of the Wald confidence interval (CI) of the HR of All Dabigatran Etexilate (110mg and 150 mg) vs Warfarin (one-sided 97.5%) was compared with this noninferiority margin for the testing of non-inferiority. All non-inferiority tests were based on a margin of 1.38.

[62] - P values for noninferiority were calculated at a one-sided alpha level of 0.025

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or >=70 in Japan and <80 or >=80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified

Analysis type	other
P-value	= 0.072 ^[63]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.73

Notes:

[63] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.875 ^[64]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.39

Notes:

[64] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to first adjudicated unplanned revascularisation by PCI/CABG

End point title	Time to first adjudicated unplanned revascularisation by PCI/CABG
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End point description:

The patients having event of time to first event for adjudicated unplanned revascularisation by Percutaneous Coronary Intervention/Coronary Artery Bypass Graft

End point type	Secondary
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End point timeframe:

up to 30 months

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[65]	763 ^[66]	981 ^[67]	764 ^[68]
Units: participants with event	76	51	69	52

Notes:

[65] - FAS

[66] - FAS

[67] - FAS

[68] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.608 ^[69]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	1.51

Notes:

[69] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8348 ^[70]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65

upper limit	1.41
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Notes:

[70] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Secondary: Time to death or first thrombotic event or unplanned revascularisation by PCI/CABG

End point title	Time to death or first thrombotic event or unplanned revascularisation by PCI/CABG
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End point description:

The patients having event of time to death or first thrombotic event (all death, myocardial infarction, stroke/systemic embolism) or unplanned revascularisation by Percutaneous Coronary Intervention/Coronary Artery Bypass Graft

End point type	Secondary
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End point timeframe:

up to 30 months

End point values	Dabigatran Etexilate 110mg	Dabigatran Etexilate 150mg	Warfarin	Warfarin (Excluding elder patient outside USA)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	981 ^[71]	763 ^[72]	981 ^[73]	764 ^[74]
Units: participants with event	149	90	131	98

Notes:

[71] - FAS

[72] - FAS

[73] - FAS

[74] - FAS

End point values	All Dabigatran Etexilate			
Subject group type	Subject analysis set			
Number of subjects analysed	1744 ^[75]			
Units: participants with event	239			

Notes:

[75] - FAS

Statistical analyses

Statistical analysis title	Statistical Analysis 1
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Statistical analysis description:

A pre-defined hierarchical testing approach was used. This was the third step in hierarchy. The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere].

Comparison groups	Warfarin v All Dabigatran Etexilate
Number of subjects included in analysis	2725
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[76]
P-value	= 0.0047 ^[77]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)

Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	1.29

Notes:

[76] - The upper bound of the Wald confidence interval (CI) of the HR of All Dabigatran Etexilate (110mg and 150 mg) vs Warfarin (one-sided 97.5%) was compared with this noninferiority margin for the testing of non-inferiority. All non-inferiority tests were based on a margin of 1.38.

[77] - P values for noninferiority were calculated at a one-sided alpha level of 0.025

Statistical analysis title	Statistical Analysis 3
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Statistical analysis description:

Unstratified Cox proportional hazards model was used and elderly patients outside the USA were excluded. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model.

Comparison groups	Dabigatran Etexilate 150mg v Warfarin (Excluding elder patient outside USA)
Number of subjects included in analysis	1527
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4432 [78]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.19

Notes:

[78] - Wald 2-sided p-value from (unstratified) Cox proportional hazards model

Statistical analysis title	Statistical Analysis 2
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Statistical analysis description:

The Cox proportional hazard model is stratified by age, non-elderly vs elderly [<70 or ≥ 70 in Japan and <80 or ≥ 80 years old elsewhere]. Hazard Ratio (HR) and Wald confidence intervals are derived from a Cox proportional-hazard model

Comparison groups	Dabigatran Etexilate 110mg v Warfarin
Number of subjects included in analysis	1962
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3002 [79]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.43

Notes:

[79] - Wald 2-sided p-value from (stratified) Cox proportional hazards model

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 6 days after the last drug administration.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	Dabigatran Etexilate 110mg
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Reporting group description:

Patients were orally administered Dabigatran Etexilate 110mg capsule twice daily (BID) for at least 6 months.

Reporting group title	Warfarin
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Reporting group description:

Patients were orally administered one tablet of warfarin 1 mg, 3 mg, or 5 mg once daily for at least 6 months. The warfarin dose was titrated as needed to maintain the target International normalised ratio (INR) of 2.0 to 3.0 (2.0 to 2.6 for Japanese patients aged ≥ 70 years); 2.0 to 2.5 if feasible

Reporting group title	Dabigatran Etexilate 150mg
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Reporting group description:

Patients were orally administered Dabigatran Etexilate 150mg capsule twice daily (BID) for at least 6 months.

Serious adverse events	Dabigatran Etexilate 110mg	Warfarin	Dabigatran Etexilate 150mg
Total subjects affected by serious adverse events			
subjects affected / exposed	415 / 972 (42.70%)	396 / 948 (41.77%)	300 / 758 (39.58%)
number of deaths (all causes)	38	41	24
number of deaths resulting from adverse events	38	41	24
Vascular disorders			
Aneurysm			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angiodysplasia			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic dissection rupture			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Aortic necrosis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	3 / 972 (0.31%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic thrombosis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortitis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial occlusive disease			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriovenous fistula			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Circulatory collapse			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic vascular disorder			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extremity necrosis			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral artery dissection			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	2 / 972 (0.21%)	7 / 948 (0.74%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	1 / 2	6 / 7	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage			
subjects affected / exposed	2 / 972 (0.21%)	6 / 948 (0.63%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	2 / 2	4 / 6	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	6 / 972 (0.62%)	1 / 948 (0.11%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	0 / 6	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			
subjects affected / exposed	8 / 972 (0.82%)	11 / 948 (1.16%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 9	0 / 13	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive emergency			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 972 (0.10%)	6 / 948 (0.63%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 6	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemic shock			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iliac artery occlusion			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intermittent claudication			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemia			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orthostatic hypotension			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	5 / 972 (0.51%)	5 / 948 (0.53%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 6	0 / 5	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery occlusion			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral artery stenosis			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral embolism			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Temporal arteritis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombophlebitis superficial			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombosis			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma gastric			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
B-cell lymphoma			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Basal cell carcinoma			
subjects affected / exposed	5 / 972 (0.51%)	4 / 948 (0.42%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 5	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign gastrointestinal neoplasm			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer recurrent			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder neoplasm			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bladder transitional cell carcinoma subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone neoplasm subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Bronchial carcinoma subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carcinoma in situ of penis subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemangioma subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon neoplasm subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal adenocarcinoma subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colorectal cancer subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung adenocarcinoma stage IV subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung cancer metastatic subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lung carcinoma cell type unspecified stage I subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphocytic leukaemia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lymphoma			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mantle cell lymphoma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to bone			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to liver			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metastases to lung			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to spine			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelofibrosis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-Hodgkin's lymphoma			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Non-small cell lung cancer recurrent			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Plasma cell myeloma			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	6 / 972 (0.62%)	3 / 948 (0.32%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal adenocarcinoma			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal cancer stage 0			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cell carcinoma			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal neoplasm			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin cancer			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small cell lung cancer			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of the tongue			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Testicular neoplasm			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma recurrent			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour ulceration			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary bladder adenoma			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	0 / 972 (0.00%)	5 / 948 (0.53%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac death			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Chest discomfort			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	14 / 972 (1.44%)	15 / 948 (1.58%)	15 / 758 (1.98%)
occurrences causally related to treatment / all	0 / 14	0 / 15	0 / 17
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Death			
subjects affected / exposed	8 / 972 (0.82%)	5 / 948 (0.53%)	6 / 758 (0.79%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 6
deaths causally related to treatment / all	0 / 8	0 / 5	0 / 6

Device related thrombosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug effect increased			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gait disturbance			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired healing			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implant site haematoma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injection site haematoma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Localised oedema			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Medical device site haematoma subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple organ dysfunction syndrome subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain subjects affected / exposed	3 / 972 (0.31%)	1 / 948 (0.11%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	1 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Puncture site haemorrhage subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden cardiac death subjects affected / exposed	4 / 972 (0.41%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2

deaths causally related to treatment / all	0 / 4	0 / 1	0 / 2
Sudden death			
subjects affected / exposed	2 / 972 (0.21%)	7 / 948 (0.74%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 7	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 7	0 / 1
Ulcer			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ulcer haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent occlusion			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent restenosis			
subjects affected / exposed	5 / 972 (0.51%)	3 / 948 (0.32%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent stenosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular stent thrombosis			
subjects affected / exposed	25 / 972 (2.57%)	17 / 948 (1.79%)	10 / 758 (1.32%)
occurrences causally related to treatment / all	4 / 25	2 / 17	2 / 10
deaths causally related to treatment / all	0 / 4	0 / 3	1 / 2
Psychiatric disorders			
Alcohol abuse			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anxiety disorder			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hallucination, visual			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paranoia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient psychosis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatitis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vaginal haemorrhage			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arterial bypass occlusion			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain contusion			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chemical burn			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clavicle fracture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Concussion			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusion postoperative			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery restenosis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	4 / 972 (0.41%)	5 / 948 (0.53%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 6	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Head injury			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iatrogenic injury			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint injury			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laceration			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ligament injury			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Near drowning			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	0 / 972 (0.00%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic fracture			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periprosthetic fracture			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural complication			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haemorrhage subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural myocardial infarction subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative fever subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative renal failure subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thrombosis subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural complication subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pubis fracture subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture subjects affected / exposed	1 / 972 (0.10%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Road traffic accident			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fracture			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skull fractured base			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Splenic injury			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid haemorrhage			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haemorrhage			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	2 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic intracranial haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Upper limb fracture			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 972 (0.10%)	3 / 948 (0.32%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular graft occlusion			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wound dehiscence			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Wrist fracture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Anticoagulation drug level above therapeutic			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure abnormal			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure increased			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood urine			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood urine present			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematocrit decreased			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoglobin decreased			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	0 / 0	1 / 2	2 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
International normalised ratio increased			
subjects affected / exposed	0 / 972 (0.00%)	9 / 948 (0.95%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	8 / 9	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Occult blood positive			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Troponin increased			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 972 (0.10%)	4 / 948 (0.42%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction subjects affected / exposed	20 / 972 (2.06%)	15 / 948 (1.58%)	14 / 758 (1.85%)
occurrences causally related to treatment / all	1 / 21	0 / 16	2 / 14
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Acute right ventricular failure subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris subjects affected / exposed	20 / 972 (2.06%)	18 / 948 (1.90%)	18 / 758 (2.37%)
occurrences causally related to treatment / all	1 / 22	0 / 20	1 / 21
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable subjects affected / exposed	26 / 972 (2.67%)	13 / 948 (1.37%)	15 / 758 (1.98%)
occurrences causally related to treatment / all	2 / 31	0 / 17	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease mixed subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve incompetence subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve stenosis subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Arrhythmia supraventricular subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arteriosclerosis coronary artery subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter subjects affected / exposed	18 / 972 (1.85%)	6 / 948 (0.63%)	8 / 758 (1.06%)
occurrences causally related to treatment / all	0 / 20	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation subjects affected / exposed	44 / 972 (4.53%)	34 / 948 (3.59%)	36 / 758 (4.75%)
occurrences causally related to treatment / all	0 / 51	0 / 41	0 / 44
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial thrombosis subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrioventricular block second degree subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradyarrhythmia subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bradycardia			
subjects affected / exposed	5 / 972 (0.51%)	6 / 948 (0.63%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	0 / 5	0 / 6	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	4 / 972 (0.41%)	5 / 948 (0.53%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 4	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 2	1 / 4	0 / 1
Cardiac asthma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	48 / 972 (4.94%)	46 / 948 (4.85%)	30 / 758 (3.96%)
occurrences causally related to treatment / all	0 / 56	0 / 57	0 / 41
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 2
Cardiac failure acute			
subjects affected / exposed	7 / 972 (0.72%)	4 / 948 (0.42%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	0 / 7	0 / 4	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Cardiac failure chronic			
subjects affected / exposed	7 / 972 (0.72%)	3 / 948 (0.32%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 8	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	14 / 972 (1.44%)	19 / 948 (2.00%)	13 / 758 (1.72%)
occurrences causally related to treatment / all	0 / 18	0 / 30	0 / 26
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 1
Cardiac flutter			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac tamponade			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiogenic shock			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	6 / 972 (0.62%)	7 / 948 (0.74%)	6 / 758 (0.79%)
occurrences causally related to treatment / all	0 / 6	0 / 7	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery insufficiency			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery occlusion			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	4 / 972 (0.41%)	3 / 948 (0.32%)	12 / 758 (1.58%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 14
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart valve incompetence			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0

Intracardiac thrombus			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Left ventricular failure			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Microvascular coronary artery disease			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve prolapse			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	5 / 972 (0.51%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial fibrosis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	3 / 972 (0.31%)	5 / 948 (0.53%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 3	1 / 5	0 / 1
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Myocardial infarction			

subjects affected / exposed	17 / 972 (1.75%)	8 / 948 (0.84%)	8 / 758 (1.06%)
occurrences causally related to treatment / all	2 / 17	1 / 8	1 / 8
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Palpitations			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis constrictive			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericarditis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Right ventricular failure			
subjects affected / exposed	0 / 972 (0.00%)	3 / 948 (0.32%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Silent myocardial infarction			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus bradycardia			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus node dysfunction			
subjects affected / exposed	5 / 972 (0.51%)	3 / 948 (0.32%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 5	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systolic dysfunction			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trifascicular block			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricle rupture			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Ventricular extrasystoles			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular arrhythmia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	7 / 972 (0.72%)	3 / 948 (0.32%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	0 / 8	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Generalised resistance to thyroid hormone			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Phimosi			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Venous angioma of brain			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	4 / 972 (0.41%)	2 / 948 (0.21%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	1 / 972 (0.10%)	3 / 948 (0.32%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Asthma			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiectasis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchospasm			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 972 (0.51%)	6 / 948 (0.63%)	6 / 758 (0.79%)
occurrences causally related to treatment / all	0 / 7	0 / 8	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic respiratory failure			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	11 / 972 (1.13%)	17 / 948 (1.79%)	10 / 758 (1.32%)
occurrences causally related to treatment / all	0 / 16	0 / 18	0 / 11

deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Dyspnoea at rest			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	3 / 972 (0.31%)	9 / 948 (0.95%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	2 / 3	9 / 11	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	4 / 972 (0.41%)	5 / 948 (0.53%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	3 / 4	5 / 5	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemothorax			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Interstitial lung disease			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Laryngeal oedema			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung disorder			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	8 / 972 (0.82%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 10	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleurisy			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Pneumothorax			
subjects affected / exposed	3 / 972 (0.31%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary fibrosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	2 / 758 (0.26%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	7 / 972 (0.72%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 8	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Sleep apnoea syndrome			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 972 (0.62%)	7 / 948 (0.74%)	7 / 758 (0.92%)
occurrences causally related to treatment / all	4 / 6	3 / 7	4 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia macrocytic			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iron deficiency anaemia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphadenopathy			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to	0 / 1	0 / 0	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Normochromic normocytic anaemia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Basal ganglia stroke			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain injury			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Brain oedema			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem infarction			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid arteriosclerosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery occlusion			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid artery stenosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carotid sinus syndrome			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebellar haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	2 / 2	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral ischaemia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cerebrovascular accident			
subjects affected / exposed	3 / 972 (0.31%)	4 / 948 (0.42%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	0 / 3	1 / 4	3 / 4
deaths causally related to treatment / all	0 / 1	0 / 1	1 / 1
Dementia			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diplegia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disturbance in attention			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
subjects affected / exposed	2 / 972 (0.21%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness postural			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drop attacks			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalomalacia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalopathy			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Facial paresis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Headache			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiplegia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	4 / 972 (0.41%)	1 / 948 (0.11%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	1 / 4	0 / 1	1 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lateral medullary syndrome			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental impairment			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Movement disorder			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post herpetic neuralgia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Quadriparesis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Sciatica			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal claudication			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	9 / 972 (0.93%)	7 / 948 (0.74%)	10 / 758 (1.32%)
occurrences causally related to treatment / all	1 / 9	0 / 7	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tension headache			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	4 / 972 (0.41%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	1 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness transient			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			

subjects affected / exposed	2 / 972 (0.21%)	3 / 948 (0.32%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glaucoma			
subjects affected / exposed	3 / 972 (0.31%)	2 / 948 (0.21%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neovascular age-related macular degeneration			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	1 / 972 (0.10%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular disorder			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vertigo			

subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic gastritis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dental cyst			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric polyps			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis erosive			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis haemorrhagic			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	9 / 972 (0.93%)	13 / 948 (1.37%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	9 / 9	13 / 14	7 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal tract irritation			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gingival bleeding			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematemesis			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	2 / 972 (0.21%)	2 / 948 (0.21%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	1 / 2	2 / 2	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hiatus hernia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incarcerated inguinal hernia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 972 (0.10%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Melaena			
subjects affected / exposed	4 / 972 (0.41%)	4 / 948 (0.42%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	3 / 4	3 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophagitis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	4 / 972 (0.41%)	4 / 948 (0.42%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	4 / 4	4 / 4	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Rectal ulcer haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal haematoma			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomach mass			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	15 / 972 (1.54%)	6 / 948 (0.63%)	14 / 758 (1.85%)
occurrences causally related to treatment / all	2 / 15	0 / 6	1 / 18
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Acute prerenal failure			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Calculus bladder			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis haemorrhagic			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematuria			
subjects affected / exposed	3 / 972 (0.31%)	7 / 948 (0.74%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	2 / 3	7 / 7	4 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage urinary tract			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cyst			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	6 / 972 (0.62%)	2 / 948 (0.21%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	1 / 6	0 / 3	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	3 / 972 (0.31%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	1 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal infarct			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal mass			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary bladder haemorrhage subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract obstruction subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Bile duct obstruction subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary cirrhosis primary subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Biliary colic subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis subjects affected / exposed	4 / 972 (0.41%)	4 / 948 (0.42%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cholelithiasis subjects affected / exposed	4 / 972 (0.41%)	3 / 948 (0.32%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			

subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gallbladder perforation			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cirrhosis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis toxic			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatomegaly			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dermatitis allergic			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage subcutaneous			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pemphigoid			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psoriasis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin ulcer			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stasis dermatitis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis			

subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chondropathy			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bursitis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exostosis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemarthrosis			
subjects affected / exposed	0 / 972 (0.00%)	3 / 948 (0.32%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint swelling			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle haemorrhage			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal pain			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myalgia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	7 / 972 (0.72%)	2 / 948 (0.21%)	4 / 758 (0.53%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteochondrosis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plica syndrome			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Polymyalgia rheumatica			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rheumatoid arthritis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sacroiliitis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal column stenosis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 972 (0.21%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	3 / 972 (0.31%)	4 / 948 (0.42%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 3	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperhomocysteinaemia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	2 / 972 (0.21%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	3 / 972 (0.31%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypovolaemia			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Metabolic disorder			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic syndrome			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone abscess			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	2 / 972 (0.21%)	2 / 948 (0.21%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Candida infection			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	1 / 972 (0.10%)	3 / 948 (0.32%)	6 / 758 (0.79%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dengue fever			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device related infection			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis intestinal haemorrhagic			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocarditis			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia sepsis			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fungal oesophagitis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis viral			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis C			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Helicobacter infection			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infected cyst			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 972 (0.10%)	2 / 948 (0.21%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious pleural effusion			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	2 / 972 (0.21%)	3 / 948 (0.32%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Labyrinthitis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver abscess			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Lung infection			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	1 / 972 (0.10%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	3 / 972 (0.31%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	20 / 972 (2.06%)	19 / 948 (2.00%)	15 / 758 (1.98%)
occurrences causally related to treatment / all	0 / 22	0 / 19	1 / 19
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudomonas infection			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary sepsis			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	0 / 758 (0.00%)

occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal abscess			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhinovirus infection			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal abscess			
subjects affected / exposed	2 / 972 (0.21%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	5 / 972 (0.51%)	4 / 948 (0.42%)	5 / 758 (0.66%)
occurrences causally related to treatment / all	0 / 5	0 / 4	1 / 5

deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 972 (0.00%)	2 / 948 (0.21%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin bacterial infection			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Systemic infection			
subjects affected / exposed	1 / 972 (0.10%)	0 / 948 (0.00%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	6 / 972 (0.62%)	4 / 948 (0.42%)	3 / 758 (0.40%)
occurrences causally related to treatment / all	0 / 6	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Urinary tract infection bacterial subjects affected / exposed	0 / 972 (0.00%)	0 / 948 (0.00%)	1 / 758 (0.13%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis subjects affected / exposed	3 / 972 (0.31%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis subjects affected / exposed	2 / 972 (0.21%)	0 / 948 (0.00%)	2 / 758 (0.26%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection subjects affected / exposed	0 / 972 (0.00%)	1 / 948 (0.11%)	0 / 758 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Dabigatran Etexilate 110mg	Warfarin	Dabigatran Etexilate 150mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	128 / 972 (13.17%)	229 / 948 (24.16%)	126 / 758 (16.62%)
Vascular disorders			
Haematoma			
subjects affected / exposed	27 / 972 (2.78%)	60 / 948 (6.33%)	24 / 758 (3.17%)
occurrences (all)	30	74	28
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	62 / 972 (6.38%)	61 / 948 (6.43%)	60 / 758 (7.92%)
occurrences (all)	80	89	77
Epistaxis			
subjects affected / exposed	52 / 972 (5.35%)	146 / 948 (15.40%)	59 / 758 (7.78%)
occurrences (all)	71	218	81

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 September 2015	This amendment introduced several changes to facilitate patient recruitment and to operationally simplify trial procedures. The time windows for Visit 1 and for drug administration post PCI were prolonged (Visit 1 prolonged by 2 d and first drug administration prolonged by 48 h to a maximum of 120 h after PCI). It was allowed to use of blood samples taken by standard of care local laboratory up to 7 d prior to screening to verify eligibility. The physical examination was streamlined. A possibility to switch the antiplatelet therapy to ASA (≤ 100 mg once daily) after Month 12 as per investigator discretion was introduced as well. Inclusion/exclusion criteria were modified to allow inclusion of patients with atrial fibrillation secondary to a reversible disorder if they were candidates for long term oral anticoagulation; patients on cytotoxic/myelosuppressive therapy were no longer excluded. A clarification regarding the definition of active liver disease was added to the exclusion criterion 13. The use of the reversal agent for dabigatran was introduced as well as the allowance to collect the information regarding its use. The restriction of ASA use during the on-treatment period and recording of concomitant therapy throughout the trial were clarified. Subclassifications of myocardial infarction were introduced and the definitions of fatal and disabling stroke were added. Finally, the need for monitoring of drug-induced liver injury (AESIs) was removed as there were no signs of dabigatran-related hepatotoxicity during the clinical development and post-marketing period.
05 April 2016	This amendment revised the trial design due to insufficient patient recruitment rate. The trial focused on safety and was powered to test the non-inferiority of each of the dabigatran etexilate doses (110 mg and 150 mg bid) in a dual antithrombotic regimen versus warfarin in a triple antithrombotic regimen in respect to bleeding events (time to first ISTH major bleeding or clinically relevant non-major bleeding event). Efficacy parameters (e.g. all death, myocardial infarction, stroke/systemic embolism), including the original co-primary endpoint (DTE), were to be evaluated as secondary endpoints. A definition of unplanned revascularisation was added as well. Regarding hypothesis testing, a hierarchical approach replaced the original Benjamini-Hochberg procedure as the Type I error rate control method. The change of trial design led to the reduction of total number of entered patients from 8520 to 2502 and from 2840 entered patients per treatment arm to 834. Moreover, an unblinded interim analysis was removed to reflect the changes in trial design. Following the changes introduced by Global Amendment 1, the guideline on using the reversal agent was updated to reflect current approval status of idarucizumab. Finally, the amendment introduced that warfarin tablets were also supplied as blister packs.
21 July 2016	This amendment introduced that repeated revascularisation by PCI/CABG had to be adjudicated by the IAC as requested by the DMC. This change in administrative aspect did not require approval by the IRB/IEC/competent authority.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

1 subject with missing information for number of enrolled subjects has been included in age range 'Elderly 85 years and over' as the missing category is not available.

Notes:

