Clinical trial results:
Evaluation of the Safety and Efficacy of an Edoxaban-based Compared to a Vitamin K Antagonist-based Antithrombotic Regimen in Subjects with Atrial Fibrillation Following Successful Percutaneous Coronary Intervention (PCI) With Stent Placement (ENTRUST AF-PCI)

Summary

EudraCT number	2016-002683-14
Trial protocol	FR IE GB NL DE LT ES AT HU PT BE IT
Global end of trial date	06 June 2019

Results information

Result version number	v1 (current)
This version publication date	27 May 2020
First version publication date	27 May 2020

Trial information

Trial identification

Sponsor protocol code	DSE-EDO-01-15-EU

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02866175
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo Europe, GmbH, a Daiichi Sankyo Company
Sponsor organisation address	Zielstattstrasse 48, Munich, Germany, 81379
Public contact	Late Phase Clinical Operations, Daiichi Sankyo Europe GmbH, +49 89 7808 614, Petra.laeis@daiichi-sankyo.eu
Scientific contact	Late Phase Clinical Operations, Daiichi Sankyo Europe GmbH, +49 89 7808 614, Petra.laeis@daiichi-sankyo.eu

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	07 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare a 12-month antithrombotic regimen of edoxaban in combination with clopidogrel or another P2Y12 antagonist against a regimen of a vitamin K antagonist (VKA) in combination with clopidogrel or another P2Y12 antagonist and at least 1 month acetylsalicylic acid (ASA) in subjects with atrial fibrillation (AF) following successful PCI with stent placement in terms of the incidence of major or clinically relevant non-major International Society on Thrombosis and Hemostasis (ISTH)-defined bleeding (MCRB).

Protection of trial subjects:

The study protocol, amendments, informed consent forms, and information sheets were approved by the appropriate and applicable Independent Ethics Committees or Institutional Review Boards. The study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation (ICH) consolidated Guideline E6(R2) for Good Clinical Practice (GCP) (EMA/CHMP/ICH/135/1995) and applicable regulatory requirements including the following: European Commission Directive (2001/20/EC Apr 2001), and /or European Commission Directive (2005/28/EC Apr 2005), and/or European Data Protection Directive (94/46/EC), and/or General Data Protection Regulation (European Union 2016/679), and/or other applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 February 2017
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	Netherlands: 10
Country: Number of subjects enrolled	Poland: 140
Country: Number of subjects enrolled	Portugal: 24
Country: Number of subjects enrolled	Spain: 115
Country: Number of subjects enrolled	United Kingdom: 15
Country: Number of subjects enrolled	Austria: 26
Country: Number of subjects enrolled	Belgium: 80
Country: Number of subjects enrolled	France: 41
Country: Number of subjects enrolled	Germany: 167
Country: Number of subjects enrolled	Hungary: 103
Country: Number of subjects enrolled	Lithuania: 45
Country: Number of subjects enrolled	Italy: 153
Country: Number of subjects enrolled	Romania: 39

Country: Number of subjects enrolled	Serbia: 28
Country: Number of subjects enrolled	Korea, Republic of: 91
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Taiwan: 78
Country: Number of subjects enrolled	Ukraine: 344
Worldwide total number of subjects	1506
EEA total number of subjects	958

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)	428
From 65 to 84 years	1007
85 years and over	71

Subject disposition

Recruitment

Recruitment details:

A total of 1506 subjects who met all inclusion criteria and no exclusion criteria were enrolled in the study; 1486 subjects received treatment. A total of 20 subjects (5 Edoxaban and 15 Vitamin K antagonist) did not receive treatment.

Pre-assignment

Screening details:

The screening period started after a percutaneous coronary intervention (PCI) with stent placement. Subjects were randomized 1:1 to either a Edoxaban-based or VKA-based regimen within 4 hours and 5 days after a successful PCI.

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:

This was an open-label study with blinded endpoint evaluation.

Arms

Are arms mutually exclusive?	Yes
Arm title	Edoxaban Regimen

Arm description:

Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).

Arm type	Experimental
Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	Savaysa
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

60 mg once-daily or 30 mg once-daily, oral administration

Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	
Other name	Plavix
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Clopidogrel 75 mg once daily

Investigational medicinal product name	Prasugrel
Investigational medicinal product code	
Other name	Effient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Prasugrel 5 mg or 10 mg once daily

Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ticagrelor 90 mg twice daily

Arm title	Vitamin K Antagonist Regimen

Arm description:

Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration.

Arm type	Active comparator
Investigational medicinal product name	Vitamin K antagonist
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

VKA once daily dosing for target international normalized ratio between 2.0 and 3.0, inclusive

Investigational medicinal product name	Clopidogrel
Investigational medicinal product code	
Other name	Plavix
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Clopidogrel 75 mg once daily

Investigational medicinal product name	Prasugrel
Investigational medicinal product code	
Other name	Effient
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Prasugrel 5 mg or 10 mg once daily

Investigational medicinal product name	Ticagrelor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Ticagrelor 90 mg twice daily

Number of subjects in period 1	Edoxaban Regimen	Vitamin K Antagonist Regimen
Started	751	755
Completed	616	580
Not completed	135	175
Consent withdrawn by subject	31	52
Physician decision	3	15

Adverse event, non-fatal	56	54
Death	30	23
Not specified	7	14
Did not receive treatment	5	15
Progressive disease	1	1
Lost to follow-up	2	-
Lack of efficacy	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Edoxaban Regimen
Reporting group description:	
Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).	
Reporting group title	Vitamin K Antagonist Regimen
Reporting group description:	
Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration.	

Reporting group values	Edoxaban Regimen	Vitamin K Antagonist Regimen	Total
Number of subjects	751	755	1506
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	226	202	428
From 65-84 years	489	518	1007
85 years and over	36	35	71
Age continuous Units: years			
arithmetic mean	69.4	70.1	
standard deviation	± 9.74	± 9.51	-
Gender categorical Units: Subjects			
Female	194	192	386
Male	557	563	1120
Region of Enrollment Units: Subjects			
Romania	17	22	39
Hungary	49	54	103
Ukraine	169	175	344
United Kingdom	6	9	15
Portugal	12	12	24
Switzerland	2	5	7
Spain	58	57	115
Austria	18	8	26
Netherlands	3	7	10
South Korea	50	41	91
Belgium	43	37	80

Taiwan	32	46	78
Poland	74	66	140
Italy	69	84	153
France	21	20	41
Lithuania	24	21	45
Serbia	17	11	28
Germany	87	80	167

End points

End points reporting groups

Reporting group title	Edoxaban Regimen

Reporting group description:

Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).

Reporting group title	Vitamin K Antagonist Regimen

Reporting group description:

Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration.

Primary: Number of Participants With Adjudicated Major or Clinically Relevant Non-major Bleeding As First Event Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point title	Number of Participants With Adjudicated Major or Clinically Relevant Non-major Bleeding As First Event Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen[1]

End point description:

Subjects' first major or clinically relevant non-major bleeding (MCRB) events were reported. International Society on Thrombosis and Hemostasis (ISTH) defined bleeding events included: MCRB, major bleeding, including fatal bleeding (intracranial and non-intracranial), symptomatic intracranial hemorrhage, symptomatic bleeding in a critical area or organ, and clinically overt and causing ≥2.0 g/dL adjusted hemoglobin loss, clinically relevant non-major (CRNM) bleeding, minor bleedings, any bleeding (defined as the composite of major, CRNM, and minor bleeding), life-threatening bleeding, provoked (spontaneous, instrumental/traumatic, unknown) bleeding, and spontaneous bleeding.

End point type	Primary

End point timeframe:

Day 1 to 12 months postdose

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive analyses were performed based on the study groups and the study drugs administered for this outcome.

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751	755		
Units: participants				
number (not applicable)				
Composite MCRB	128	152		
Major bleeding	39	44		
Clinically relevant non-major bleeding	89	108		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Major, Clinically Relevant Non-major and Minor Bleeding (All Events) Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist-Based Regimen

End point title	Number of Participants With Adjudicated Major, Clinically Relevant Non-major and Minor Bleeding (All Events) Defined by International Society on Thrombosis and Haemostasis Following Edoxaban-based Regimen Compared With Vitamin K Antagonist-Based Regimen

End point description:

All major, clinically relevant non-major and minor bleeding are reported for the secondary outcome. Subjects may have experiences more than 1 bleeding event, all occurrences are reported. Subjects with International Society on Thrombosis and Hemostasis (ISTH) defined bleeding events included: major or clinically relevant non-major bleeding (MCRB), major bleeding, including fatal bleeding (intracranial and non-intracranial), symptomatic intracranial hemorrhage, symptomatic bleeding in a critical area or organ, and clinically overt and causing ≥2.0 g/dL adjusted hemoglobin loss, clinically relevant non-major (CRNM) bleeding, minor bleedings, any bleeding (defined as the composite of major, CRNM, and minor bleeding), life-threatening bleeding, provoked (spontaneous, instrumental/traumatic, unknown) bleeding, and spontaneous bleeding.

End point type	Secondary

End point timeframe:

Day 1 to 12 months postdose

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751	755		
Units: participants				
number (not applicable)				
Major bleeding	45	48		
Clinically relevant non-major bleeding	97	114		
Minor bleeding	116	125		
Symptomatic intracranial hemorrhage	4	9		
Fatal major bleeding	1	7		
Fatal intracranial hemorrhage	0	4		
Life-threatening bleeding	5	8		
Spontaneous bleeding	184	210		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Major, Minor, and Minimal Bleeding by Thrombolysis in Myocardial Infarction (TIMI) Definition Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point title	Number of Participants With Adjudicated Major, Minor, and

	Minimal Bleeding by Thrombolysis in Myocardial Infarction (TIMI) Definition Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point description:

Thrombolysis in Myocardial Infarction (TIMI) defined bleeding events included: Major bleeding (including fatal bleeding and non-fatal bleeding [fulfilling the TIMI major bleeding definition], major or minor bleeding, minor bleeding, minimal bleeding, and any bleeding (defined as composite of major, minor, and minimal bleeding)

End point type	Secondary

End point timeframe:

Day 1 to 12 months postdose

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751	755		
Units: participants				
number (not applicable)				
Major bleeding	15	24		
Fatal bleeding	1	4		
Major or minor bleeding	124	144		
Minor bleeding	113	126		
Minimal bleeding	117	131		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Bleeding Academic Research Consortium (BARC) Type 1, 2, 3, and 5 Bleeding According to the BARC Definitions Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)- Based Regimen

End point title	Number of Participants With Bleeding Academic Research Consortium (BARC) Type 1, 2, 3, and 5 Bleeding According to the BARC Definitions Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)- Based Regimen

End point description:

Bleeding Academic Research Consortium (BARC) bleeding events included: Bleeding (defined by BARC type 3 or 5), bleeding (defined by BARC type 2, 3, or 5), and any bleeding (defined as the composite of BARC type 1, 2, 3, or 5), where increases in BARC type indicate worse outcome. Type 1: bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consultation; Type 2: any overt, actionable sign of hemorrhage that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation; Type 3: Overt bleeding
plus hemoglobin drop of 3 to ≤5 g/dL (3a), ≥5 g/dl (3b), and intracranial hemorrhage (3c) Type 5: Fatal bleeding

End point type	Secondary

End point timeframe:

Day 1 to 12 months postdose

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751	755		
Units: participants				
number (not applicable)				
Bleeding (BARC Type 3 or 5)	36	42		
Bleeding (BARC Type 2, 3 or 5)	124	144		
Bleeding (BARC Type 1, 2, 3, or 5)	207	242		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs) Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs) Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point description:

Treatment-emergent adverse events (TEAEs) in >1.0% of subjects were defined as events which started on or after first dose of the assigned study drug (edoxaban and VKA) or started prior to but then worsened after the first dose of the assigned study drug.

End point type	Secondary

End point timeframe:

Day 1 to 30 days after the last dose

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	746	740		
Units: participants				
number (not applicable)				
Any TEAE	457	447		
Infections and Infestations	145	140		
Nasopharyngitis	25	22		
Pneumonia	20	22		
Bronchitis	19	20		
Urinary tract infection	14	19		
Respiratory tract infection	12	15		
Influenza	10	7		
Cardiac Disorders	136	134		

Cardiac failure	40	47		
Atrial fibrillation	39	41		
Bradycardia	10	7		
Cardiac failure congestive	8	8		
Ventricular extrasystoles	7	8		
Tachycardia	11	3		
General Disorders & Administration Site Condition	113	98		
Non-cardiac chest pain	30	24		
Oedema peripheral	31	22		
Asthenia	21	14		
Chest pain	7	11		
Fatigue	11	6		
Gastrointestinal Disorders	110	83		
Diarrhea	23	19		
Constipation	11	7		
Abdominal pain upper	6	10		
Gastritis	9	5		
Nausea	8	5		
Dyspepsia	8	3		
Respiratory, Thoracic, and Mediastinal Disorders	87	72		
Dyspnoea	22	26		
Cough	21	11		
Dyspnoea exertional	18	5		
Chronic obstructive pulmonary disease	6	10		
Musculoskeletal and Connective Tissue Disorders	69	83		
Back pain	14	14		
Arthralgia	11	12		
Pain in extremity	5	13		
Myalgia	8	8		
Osteoarthritis	9	5		
Investigations	70	79		
Blood creatinine increased	15	13		
Alanine aminotransferase increased	8	13		
Blood pressure increased	12	8		
Creatinine renal clearance decreased	12	7		
Aspartate aminotransferase increased	7	11		
International normalized ratio increased	0	12		
Nervous System Disorders	83	65		
Dizziness	30	22		
Headache	19	12		
Syncope	8	6		
Vascular Disorders	55	62		
Hypertension	23	23		
Hypotension	14	14		
Hypertensive crisis	11	8		
Renal and Urinary Disorders	49	55		
Renal failure	11	12		
Acute kidney injury	8	13		
Renal impairment	7	8		

Injury, Poisoning, and Procedural Complications	44	44		
Fall	8	12		
Skin and Subcutaneous Tissue Disorders	55	33		
Pruritus	12	7		
Rash	10	9		
Metabolism and Nutrition Disorders	42	42		
Gout	11	4		
Blood and Lymphatic System Disorders	41	35		
Anaemia	19	20		
Psychiatric Disorder	23	20		
Insomnia	8	8		
Ear and Labyrinth Disorders	12	16		
Vertigo	8	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Study Drug-related Treatment-emergent Adverse Events (TEAEs) Experienced by 2 or More Subjects Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point title	Number of Subjects With Study Drug-related Treatment-emergent Adverse Events (TEAEs) Experienced by 2 or More Subjects Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point description:

Study drug-related treatment-emergent adverse events (TEAEs) (experienced by 2 or more subjects) were defined as events which started on or after first dose of the assigned study drug (edoxaban and VKA) or started prior to but then worsened after the first dose of the assigned study drug and were found to be related to treatment by the Investigator.

End point type	Secondary

End point timeframe:

Day 1 to 30 days after the last dose

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	746	740		
Units: participants				
number (not applicable)				
Any Related TEAE	57	48		
Blood and Lymphatic System Disorders	12	11		
Anaemia	9	7		
Haemorrhagic anaemia	0	2		
Normochromic normocytic anaemia	2	0		
Investigations	7	16		
International normalised ratio increased	0	12		

Blood creatinine increased	3	1		
Creatinine renal clearance decreased	2	2		
Haemoglobin decreased	2	0		
Gastrointestinal Disorders	12	4		
Abdominal pain upper	3	1		
Dyspepsia	3	1		
Nausea	2	0		
Skin and Subcutaneous Tissue Disorders	6	5		
Pruritus	2	1		
Rash	1	2		
Injury, Poisoning, and Procedural Complications	1	7		
Overdose	0	4		
Contusion	1	1		
General Disorders & Administration Site Conditions	6	1		
Death	3	0		
Renal and Urinary Disorders	2	2		
Chronic kidney disease	1	1		
Renal failure	1	1		
Nervous System Disorders	3	0		
Dizziness	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Main Efficacy Endpoints For the Overall Study Period Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point title	Number of Participants With Main Efficacy Endpoints For the Overall Study Period Following Edoxaban-based Regimen Compared With Vitamin K Antagonist (VKA)-Based Regimen

End point description:

The main efficacy endpoints were defined as the composite of CV death (ARC), stroke (protocol defined), systemic embolic event (SEE), myocardial infarction (MI), or definite stent thrombosis.

End point type	Secondary

End point timeframe:

Day 1 to 12 months postdose

End point values	Edoxaban Regimen	Vitamin K Antagonist Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	751	755		
Units: participants				
number (not applicable)				
Composite MEE event	49	46		
Cardiovascular death (ARC)	10	12		

Stroke (Protocol definition)	10	11		
Systemic embolic event	0	0		
Myocardial infarction	22	18		
Definite stent thrombosis	7	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from Day 1 to 30 days after last dose, up to 2 years, 4 months.

Adverse event reporting additional description:

Adverse events were reported from the Safety Analysis Set (746 Edoxaban regimen; 740 Vitamin K Antagonist regimen).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups

Reporting group title	Edoxaban Regimen

Reporting group description:

Subjects who were randomized to Edoxaban 60 mg once-daily or 30 mg once-daily and clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used).

Reporting group title	Vitamin K Antagonist Regimen

Reporting group description:

Subjects who were randomized to VKA in combination with clopidogrel 75 mg once-daily (or in the presence of a documented clinical need prasugrel [5 mg or 10 mg once-daily] or ticagrelor [90 mg twice-daily] may be used) and aspirin (100 mg once-daily, for a minimum of 1 month and up to 12 months duration.

Serious adverse events	Edoxaban Regimen	Vitamin K Antagonist Regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	176 / 746 (23.59%)	175 / 740 (23.65%)	
number of deaths (all causes)	46	37	
number of deaths resulting from adverse events	29	24	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical fibroxanthoma			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			

subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder neoplasm			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrosarcoma			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatocellular carcinoma			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oesophageal carcinoma			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatic neoplasm			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectosigmoid cancer			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tongue neoplasm malignant stage unspecified			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extremity necrosis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	4 / 746 (0.54%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 746 (0.13%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery occlusion			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Coronary revascularisation			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Death			
subjects affected / exposed	4 / 746 (0.54%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	2 / 4	0 / 3	
deaths causally related to treatment / all	2 / 4	0 / 3	
Drowning			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	6 / 746 (0.80%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden cardiac death			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Sudden death			
subjects affected / exposed	1 / 746 (0.13%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 1	3 / 3	
deaths causally related to treatment / all	0 / 1	0 / 3	
Vascular stent restenosis			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular stent thrombosis			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 1	1 / 1	
Immune system disorders			

Amyloidosis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	3 / 746 (0.40%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical dysplasia			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian cyst			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatitis			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spermatocele			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary edema			
subjects affected / exposed	2 / 746 (0.27%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	0 / 746 (0.00%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	5 / 746 (0.67%)	9 / 740 (1.22%)	
occurrences causally related to treatment / all	0 / 5	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	2 / 746 (0.27%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea at rest			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	3 / 746 (0.40%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 746 (0.13%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device capturing issue			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	0 / 746 (0.00%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Arterial restenosis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Compression fracture			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Costal cartilage fracture			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hand fracture			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product use issue			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound necrosis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Phimosis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adams-Stokes syndrome			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	20 / 746 (2.68%)	14 / 740 (1.89%)	
occurrences causally related to treatment / all	0 / 20	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 746 (0.40%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	29 / 746 (3.89%)	35 / 740 (4.73%)	
occurrences causally related to treatment / all	0 / 29	4 / 35	
deaths causally related to treatment / all	0 / 1	0 / 4	
Cardiac failure acute			
subjects affected / exposed	2 / 746 (0.27%)	4 / 740 (0.54%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac failure chronic			
subjects affected / exposed	3 / 746 (0.40%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	6 / 746 (0.80%)	5 / 740 (0.68%)	
occurrences causally related to treatment / all	0 / 6	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Cardiogenic shock			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			
subjects affected / exposed	1 / 746 (0.13%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulseless electrical activity			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus arrest			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	2 / 746 (0.27%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachyarrhythmia			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular arrhythmia			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	3 / 746 (0.40%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Carotid artery stenosis			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicogenic headache			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cognitive disorder			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monoparesis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatica			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	3 / 746 (0.40%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 746 (0.54%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypochromic anaemia			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenic purpura			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrogenic anaemia			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Normochromic normocytic anaemia			

subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iridocyclitis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Pancreatitis chronic			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal distension			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	1 / 746 (0.13%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute abdomen			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fissure			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal stenosis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ulcerative			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dental cyst			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal polyp			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary fistula			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			

subjects affected / exposed	3 / 746 (0.40%)	4 / 740 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatorenal syndrome			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cold sweat			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cutaneous lupus erythematosus			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	2 / 746 (0.27%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pemphigoid			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 746 (0.40%)	7 / 740 (0.95%)	
occurrences causally related to treatment / all	0 / 3	1 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Calculus urethral			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nephrolithiasis			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prerenal failure			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal artery stenosis			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	5 / 746 (0.67%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urethral stenosis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chondropathy			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 746 (0.00%)	3 / 740 (0.41%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint swelling			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Monarthritis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal discomfort			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 746 (0.27%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			

subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatic disorder			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Aeromonas infection			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 746 (0.13%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	3 / 746 (0.40%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis infective			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device-related infection			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infectious colitis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	1 / 746 (0.13%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis cryptococcal			

subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal abscess			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	14 / 746 (1.88%)	13 / 740 (1.76%)	
occurrences causally related to treatment / all	0 / 14	0 / 13	
deaths causally related to treatment / all	0 / 3	0 / 3	
Postoperative wound infection			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 746 (0.00%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	2 / 746 (0.27%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Septic shock			
subjects affected / exposed	3 / 746 (0.40%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Sialoadenitis			

subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 746 (0.40%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 746 (0.13%)	0 / 740 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			

subjects affected / exposed	2 / 746 (0.27%)	2 / 740 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic metabolic decompensation			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 746 (0.00%)	1 / 740 (0.14%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Edoxaban Regimen	Vitamin K Antagonist Regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	457 / 746 (61.26%)	447 / 740 (60.41%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 746 (3.08%)	23 / 740 (3.11%)	
occurrences (all)	23	23	
Hypertensive crisis			
subjects affected / exposed	11 / 746 (1.47%)	8 / 740 (1.08%)	
occurrences (all)	11	8	
Hypotension			
subjects affected / exposed	14 / 746 (1.88%)	14 / 740 (1.89%)	
occurrences (all)	14	14	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 746 (2.82%)	14 / 740 (1.89%)	
occurrences (all)	21	14	
Chest pain			
subjects affected / exposed	7 / 746 (0.94%)	11 / 740 (1.49%)	
occurrences (all)	7	11	
Fatigue			

subjects affected / exposed	11 / 746 (1.47%)	6 / 740 (0.81%)	
occurrences (all)	11	6	
Non-cardiac chest pain			
subjects affected / exposed	30 / 746 (4.02%)	24 / 740 (3.24%)	
occurrences (all)	30	24	
Oedema peripheral			
subjects affected / exposed	31 / 746 (4.16%)	22 / 740 (2.97%)	
occurrences (all)	31	22	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	6 / 746 (0.80%)	10 / 740 (1.35%)	
occurrences (all)	6	10	
Cough			
subjects affected / exposed	21 / 746 (2.82%)	11 / 740 (1.49%)	
occurrences (all)	21	11	
Dyspnoea			
subjects affected / exposed	22 / 746 (2.95%)	26 / 740 (3.51%)	
occurrences (all)	22	26	
Dyspnoea exertional			
subjects affected / exposed	18 / 746 (2.41%)	5 / 740 (0.68%)	
occurrences (all)	18	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 746 (1.07%)	8 / 740 (1.08%)	
occurrences (all)	8	8	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 746 (1.07%)	13 / 740 (1.76%)	
occurrences (all)	8	13	
Aspartate aminotransferase increased			
subjects affected / exposed	7 / 746 (0.94%)	11 / 740 (1.49%)	
occurrences (all)	7	11	
Blood creatinine increased			
subjects affected / exposed	15 / 746 (2.01%)	13 / 740 (1.76%)	
occurrences (all)	15	13	

Blood pressure increased			
subjects affected / exposed	12 / 746 (1.61%)	8 / 740 (1.08%)	
occurrences (all)	12	8	
Creatinine renal clearance increased			
subjects affected / exposed	12 / 746 (1.61%)	7 / 740 (0.95%)	
occurrences (all)	12	7	
International normalised ratio increased			
subjects affected / exposed	0 / 746 (0.00%)	12 / 740 (1.62%)	
occurrences (all)	0	12	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	8 / 746 (1.07%)	12 / 740 (1.62%)	
occurrences (all)	8	12	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	39 / 746 (5.23%)	41 / 740 (5.54%)	
occurrences (all)	39	41	
Bradycardia			
subjects affected / exposed	10 / 746 (1.34%)	7 / 740 (0.95%)	
occurrences (all)	10	7	
Cardiac failure			
subjects affected / exposed	40 / 746 (5.36%)	47 / 740 (6.35%)	
occurrences (all)	40	47	
Cardiac failure congestive			
subjects affected / exposed	8 / 746 (1.07%)	8 / 740 (1.08%)	
occurrences (all)	8	8	
Tachycardia			
subjects affected / exposed	11 / 746 (1.47%)	3 / 740 (0.41%)	
occurrences (all)	11	3	
Ventricular extrasystoles			
subjects affected / exposed	7 / 746 (0.94%)	8 / 740 (1.08%)	
occurrences (all)	7	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	30 / 746 (4.02%)	22 / 740 (2.97%)	
occurrences (all)	30	22	

Headache			
subjects affected / exposed	19 / 746 (2.55%)	12 / 740 (1.62%)	
occurrences (all)	19	12	
Syncope			
subjects affected / exposed	8 / 746 (1.07%)	6 / 740 (0.81%)	
occurrences (all)	8	6	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	19 / 746 (2.55%)	20 / 740 (2.70%)	
occurrences (all)	19	20	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	8 / 746 (1.07%)	5 / 740 (0.68%)	
occurrences (all)	8	5	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	6 / 746 (0.80%)	10 / 740 (1.35%)	
occurrences (all)	6	10	
Constipation			
subjects affected / exposed	11 / 746 (1.47%)	7 / 740 (0.95%)	
occurrences (all)	11	7	
Diarrhoea			
subjects affected / exposed	23 / 746 (3.08%)	19 / 740 (2.57%)	
occurrences (all)	23	19	
Dyspepsia			
subjects affected / exposed	8 / 746 (1.07%)	3 / 740 (0.41%)	
occurrences (all)	8	3	
Gastritis			
subjects affected / exposed	9 / 746 (1.21%)	5 / 740 (0.68%)	
occurrences (all)	9	5	
Nausea			
subjects affected / exposed	8 / 746 (1.07%)	5 / 740 (0.68%)	
occurrences (all)	8	5	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	12 / 746 (1.61%)	7 / 740 (0.95%)	
occurrences (all)	12	7	

Rash			
subjects affected / exposed	10 / 746 (1.34%)	9 / 740 (1.22%)	
occurrences (all)	10	9	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	8 / 746 (1.07%)	13 / 740 (1.76%)	
occurrences (all)	8	13	
Renal failure			
subjects affected / exposed	11 / 746 (1.47%)	12 / 740 (1.62%)	
occurrences (all)	11	12	
Renal impairment			
subjects affected / exposed	7 / 746 (0.94%)	8 / 740 (1.08%)	
occurrences (all)	7	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 746 (1.47%)	12 / 740 (1.62%)	
occurrences (all)	11	12	
Back pain			
subjects affected / exposed	14 / 746 (1.88%)	14 / 740 (1.89%)	
occurrences (all)	14	14	
Myalgia			
subjects affected / exposed	8 / 746 (1.07%)	8 / 740 (1.08%)	
occurrences (all)	8	8	
Osteoarthritis			
subjects affected / exposed	9 / 746 (1.21%)	5 / 740 (0.68%)	
occurrences (all)	9	5	
Pain in extremity			
subjects affected / exposed	5 / 746 (0.67%)	13 / 740 (1.76%)	
occurrences (all)	5	13	
Infections and infestations			
Bronchitis			
subjects affected / exposed	19 / 746 (2.55%)	20 / 740 (2.70%)	
occurrences (all)	19	20	
Influenza			
subjects affected / exposed	10 / 746 (1.34%)	7 / 740 (0.95%)	
occurrences (all)	10	7	

Nasopharyngitis			
subjects affected / exposed	25 / 746 (3.35%)	22 / 740 (2.97%)	
occurrences (all)	25	22	
Pneumonia			
subjects affected / exposed	20 / 746 (2.68%)	22 / 740 (2.97%)	
occurrences (all)	20	22	
Respiratory tract infection			
subjects affected / exposed	12 / 746 (1.61%)	15 / 740 (2.03%)	
occurrences (all)	12	15	
Urinary tract infection			
subjects affected / exposed	14 / 746 (1.88%)	19 / 740 (2.57%)	
occurrences (all)	14	19	
Metabolism and nutrition disorders			
Gout			
subjects affected / exposed	11 / 746 (1.47%)	4 / 740 (0.54%)	
occurrences (all)	11	4	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 January 2017	Updated secondary exploratory objectives, study design, and subject eligibility criteria; amended the procedure for removing subjects from therapy; revised procedures prior to and following randomization; clarified assessments to be performed at each site; and included a definition of unexpected adverse events.
28 February 2017	Updated exclusion criteria for subjects with renal impairment and end stage renal disease.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported