Clinical trial results:
A prospective, randomised, open-label, blinded endpoint evaluation (PROBE) parallel group study comparing edoxaban (DU-176b) with enoxaparin/warfarin followed by warfarin alone in subjects undergoing planned electrical cardioversion of nonvalvular atrial fibrillation

Summary

EudraCT number	2013-003148-21
Trial protocol	SE BE DE GB HU IT DK ES AT CZ NL RO BG PL
Global end of trial date	04 February 2016

Results information

Result version number	v1 (current)
This version publication date	27 January 2017
First version publication date	27 January 2017

Trial information

Trial identification

Sponsor protocol code	DU176b-F-E308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02072434
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	399 Thornall Avenue, Edison, NJ, United States, 08837
Public contact	Clinical Trial Information, Daiichi Sankyo Development Ltd, +44 1753482800, euregaffairs@dsd-eu.com
Scientific contact	Clinical Trial Information, Daiichi Sankyo Development Ltd, +44 1753482800, euregaffairs@dsd-eu.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 June 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 February 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Efficacy Objective:
Compare the incidences of the composite endpoints of stroke, systemic embolic event (SEE), myocardial infarction (MI) and cardiovascular (CV) mortality between the edoxaban group and the enoxaparin/warfarin group from randomization to end of follow up (FU).

Primary Safety Objective:
Compare the incidence of the composite endpoints of major and clinically-relevant non-major (CRNM) bleeding between the edoxaban group and the enoxaparin/warfarin group from the first administration of study drug to end of treatment + 3 days.

Protection of trial subjects:

This study was conducted in compliance with the protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Conference on Harmonization (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirements.

Subjects, after having the study explained to them by the investigator or designee, gave voluntary and signed informed consent before participating in any study-specific procedures. For subjects in the United States (US), consent required for the Health Insurance Portability and Accountability Act (HIPAA) was included in the single, main informed consent form (ICF).

The study protocol, amendments (if any), the informed consent/assent form(s), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs).

An independent Data Monitoring committee (DMC) was created to further protect the rights, safety, and well-being of subjects who were participating in this study by monitoring their progress and results. The independent DMC was comprised of qualified scientists, who were not Investigators in the study and not otherwise directly associated with the Sponsor.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 March 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	Netherlands: 47
Country: Number of subjects enrolled	Poland: 54
Country: Number of subjects enrolled	Romania: 122
Country: Number of subjects enrolled	Spain: 142
Country: Number of subjects enrolled	Sweden: 14

Country: Number of subjects enrolled	United Kingdom: 159
Country: Number of subjects enrolled	Austria: 32
Country: Number of subjects enrolled	Belgium: 41
Country: Number of subjects enrolled	Bulgaria: 125
Country: Number of subjects enrolled	Czech Republic: 173
Country: Number of subjects enrolled	Denmark: 57
Country: Number of subjects enrolled	France: 39
Country: Number of subjects enrolled	Germany: 123
Country: Number of subjects enrolled	Hungary: 179
Country: Number of subjects enrolled	Italy: 69
Country: Number of subjects enrolled	Russian Federation: 216
Country: Number of subjects enrolled	Ukraine: 430
Country: Number of subjects enrolled	Israel: 82
Country: Number of subjects enrolled	United States: 95
Worldwide total number of subjects	2199
EEA total number of subjects	1376

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)	1064
From 65 to 84 years	1097
85 years and over	38

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of 2199 patients enrolled in 19 countries worldwide, 2149 received study drug.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Edoxaban

Arm description:

Patients randomized to receive edoxaban

Arm type	Experimental
Investigational medicinal product name	Edoxaban
Investigational medicinal product code	SUB32701
Other name	DU176-b
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Edoxaban was supplied in 30 mg tablets (yellow) in child resistant blister wallets of 42 tablets. Subjects taking the full dose of edoxaban for the study will take 60 mg QD (two 30 mg tablets once daily). Subjects with a dose reduction took 30 mg (one 30 mg tablet once daily) when required by the protocol dose reduction criteria. All dispensing was done via the IXRS. In addition 15 mg tablets of edoxaban (orange or yellow) were supplied in child resistant blister wallets of 42 tablets to be used as transition kits when necessary.

Arm title	Warfarin

Arm description:

Patients randomised to receive the comparator product.

Arm type	Active comparator
Investigational medicinal product name	Warfarin
Investigational medicinal product code	SUB12396MIG
Other name	Warfarin Sodium Clathrate, Warfarin Teva 1 mg Tablet
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Warfarin, was the active control and was provided by the Sponsor in dosage strengths of 1.0 mg (brown) and 2.5 mg (green). Individual doses were made by combining the strengths provided. Investigators determined the dose strength(s) of warfarin necessary to achieve the prescribed dose, and the quantity dispensed was determined by the dose. Subjects randomized to the warfarin treatment group were dispensed active warfarin. These subjects could also have been dispensed enoxaparin. All dispensing was done via
the IXRS. Should a dose change be required between visits, additional quantity and/or strengths were dispensed via the IXRS.

Number of subjects in period 1	Edoxaban	Warfarin
Started	1095	1104
Intention to Treat Analysis Set	1095	1104
Received Study Drug	1067	1082
Safety Analysis Set	1067	1082
Completed	1041	1014
Not completed	54	90
Adverse event, serious fatal	1	6
Physician decision	5	10
Consent withdrawn by subject	17	29
Adverse event, non-fatal	7	6
Lost to follow-up	-	1
Protocol deviation	10	9
No reason provided	14	29

Baseline characteristics

Reporting groups	
Reporting group title	Edoxaban
Reporting group description: Patients randomized to receive edoxaban	
Reporting group title	Warfarin
Reporting group description: Patients randomised to receive the comparator product.	

Reporting group values	Edoxaban	Warfarin	Total
Number of subjects	1095	1104	2199
Age categorical Units: Subjects			
Adults <75 Years of Age	923	917	1840
Adults >= 75 Years of Age	172	187	359
Age continuous Units: years			
arithmetic mean	64.3	64.2	
standard deviation	± 10.34	± 10.75	-
Gender categorical Units: Subjects			
Female	374	382	756
Male	721	722	1443

End points

End points reporting groups

Reporting group title	Edoxaban
Reporting group description:	
Patients randomized to receive edoxaban	
Reporting group title	Warfarin
Reporting group description:	
Patients randomised to receive the comparator product.	
Subject analysis set title	Edoxaban Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients randomized to and treated with edoxaban.	
Subject analysis set title	Warfarin Safety Analysis Set
Subject analysis set type	Safety analysis
Subject analysis set description:	
Patients randomized to and treated with warfarin.	

Primary: Percentage of patients with composite endpoint of stroke, systemic embolic stroke(SEE), myocardial infarction (MI) and cardiovascular (CV) mortality from randomization to end of follow up (FU)

End point title	Percentage of patients with composite endpoint of stroke, systemic embolic stroke(SEE), myocardial infarction (MI) and cardiovascular (CV) mortality from randomization to end of follow up (FU)
End point description:	
End point type	Primary
End point timeframe:	
Randomization to end of follow up	

End point values	Edoxaban	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1095	1104		
Units: Percentage of Patients				
number (not applicable)	0.5	1		

Statistical analyses

Statistical analysis title	Odds Ratio
Comparison groups	Edoxaban v Warfarin

Number of subjects included in analysis	2199
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Odds ratio (OR)
Point estimate	0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.12
upper limit	1.43

Notes:

[1] - Exact

Primary: Percentage of patients with composite endpoints of major and clinically-relevant non-major (CRNM) bleeding

End point title	Percentage of patients with composite endpoints of major and clinically-relevant non-major (CRNM) bleeding

End point description:

End point type	Primary

End point timeframe:

from first administration of study drug to end of treatment + 3 days

End point values	Edoxaban Safety Analysis Set	Warfarin Safety Analysis Set		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1067	1082		
Units: Percentage of Patients				
number (not applicable)	1.5	1		

Statistical analyses

Statistical analysis title	Odds Ratio
Comparison groups	Edoxaban Safety Analysis Set v Warfarin Safety Analysis Set
Number of subjects included in analysis	2149
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Odds ratio (OR)
Point estimate	1.48
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	3.55

Notes:
[2] - exact

Secondary: Percentage of patients with composite endpoints of stroke, SEE MI, CV mortality and major bleeding

End point title	Percentage of patients with composite endpoints of stroke, SEE MI, CV mortality and major bleeding

End point description:

End point type	Secondary

End point timeframe:
from randomization to end of follow up

End point values	Edoxaban	Warfarin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1095	1104		
Units: Percentage of patients				
number (not applicable)	0.7	1.4		

Statistical analyses

Statistical analysis title	Difference in Percent
Comparison groups	Edoxaban v Warfarin
Number of subjects included in analysis	2199
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Mean difference (final values)
Point estimate	-0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.59
upper limit	0.15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were defined as events that started on or after the first dose of study drug or start prior to but then worsen after the first dose of study drug, through 30 days after the last dose of study drug.

Adverse event reporting additional description:

This table includes counts of patients in the safety analysis set. Patients who experienced more than one episode of an adverse event are counted only once within a preferred term. Patients who experienced more than one adverse event within a system organ class are counted once for each preferred term, but only once for the system organ class.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Edoxaban Safety Analysis Set

Reporting group description:

Patients randomized to and treated with edoxaban.

Reporting group title	Warfarin Safety Analysis Set

Reporting group description:

Patients randomized to and treated with warfarin.

Serious adverse events	Edoxaban Safety Analysis Set	Warfarin Safety Analysis Set	
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 1067 (7.97%)	83 / 1082 (7.67%)	
number of deaths (all causes)	1	5	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-small cell lung cancer			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal carcinoma			

subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 1067 (0.09%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm rupture	Additional description: Aneurysm with Rupture Abdominal Aorta		
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Deep vein thrombosis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemodynamic instability			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery thrombosis			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: General Disorder Death		
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Drug effect increased			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injection site bruising			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary oedema			
subjects affected / exposed	2 / 1067 (0.19%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 1067 (0.09%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	2 / 1067 (0.19%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute respiratory distress syndrome			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinal cyst			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
International normalised ratio increased			
subjects affected / exposed	4 / 1067 (0.37%)	10 / 1082 (0.92%)	
occurrences causally related to treatment / all	1 / 4	9 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	2 / 1067 (0.19%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urine present			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coagulation test abnormal			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
International normalised ratio fluctuation			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemorrhage			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	20 / 1067 (1.87%)	14 / 1082 (1.29%)	
occurrences causally related to treatment / all	0 / 20	0 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Decompensated heart failure		
subjects affected / exposed	3 / 1067 (0.28%)	6 / 1082 (0.55%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure congestive	Additional description: Acute, congestive heart failure		
subjects affected / exposed	5 / 1067 (0.47%)	3 / 1082 (0.28%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Atrial flutter			
subjects affected / exposed	3 / 1067 (0.28%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sick sinus syndrome			
subjects affected / exposed	2 / 1067 (0.19%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 1067 (0.09%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	2 / 1067 (0.19%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	3 / 1067 (0.28%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve incompetence			

subjects affected / exposed	2 / 1067 (0.19%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 1067 (0.09%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	2 / 1067 (0.19%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 1067 (0.00%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	2 / 1067 (0.19%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest	Additional description: Cardiac arrest, ventricular fibrillation		
subjects affected / exposed	0 / 1067 (0.00%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block second degree			

subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chordae tendinae rupture			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Torsade de pointes			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia			

subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 1067 (0.09%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 1067 (0.19%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 1067 (0.09%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 1067 (0.19%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypocoagulable state			

subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	0 / 1067 (0.00%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 1067 (0.19%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoidal haemorrhage			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			

subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haematoma			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal haemorrhage			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spigelian hernia			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	3 / 1067 (0.28%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	1 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 1067 (0.09%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis haemorrhagic			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Hyperadrenocorticism			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (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			
Haemarthrosis			
subjects affected / exposed	0 / 1067 (0.00%)	2 / 1082 (0.18%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	4 / 1067 (0.37%)	4 / 1082 (0.37%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 1067 (0.09%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 1067 (0.09%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Arthritis bacterial			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective aneurysm			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver abscess			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			

subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia haemophilus			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (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			
Dehydration			
subjects affected / exposed	1 / 1067 (0.09%)	0 / 1082 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 1067 (0.00%)	1 / 1082 (0.09%)	
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 / 1067 (0.00%)	1 / 1082 (0.09%)	
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: 5 %

Non-serious adverse events	Edoxaban Safety Analysis Set	Warfarin Safety Analysis Set	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 1067 (4.97%)	53 / 1082 (4.90%)	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	53 / 1067 (4.97%)	53 / 1082 (4.90%)	
occurrences (all)	53	53	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2014	To clarify that all patients transitioning from edoxaban to other anticoagulants receive an edoxaban transition kit

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 October 2014	For approval of substantial protocol amendment - restart dates were dependent on the date each health authority approved the amendment	-

Notes:

Limitations and caveats

None reported