



Clinical trial results:

A Prospective, Randomized, Open-Label, Blinded Endpoint Evaluation (PROBE) Parallel Group Study Comparing Edoxaban vs. VKA in Subjects Undergoing Catheter Ablation of Non-valvular Atrial Fibrillation (ELIMINATE-AF)

Summary

EudraCT number	2016-003069-25
Trial protocol	CZ DE GB HU ES BE PL IT
Global end of trial date	24 September 2018

Results information

Result version number	v1 (current)
This version publication date	02 January 2020
First version publication date	02 January 2020

Trial information

Trial identification

Sponsor protocol code	DSE-EDO-01-16-EU
-----------------------	------------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02942576
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo Europe GmbH
Sponsor organisation address	Zielstattstrasse 48, Munich, Germany, 81379
Public contact	Global Medical Affairs Edoxaban, Daiichi Sankyo Europe GmbH, +49 89 78080508, Heiko.Rauer@daiichi-sankyo.eu
Scientific contact	Global Medical Affairs Edoxaban, Daiichi Sankyo Europe GmbH, +49 89 78080508, Heiko.Rauer@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	24 September 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 September 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary efficacy objective:

To compare descriptively the incidence of the composite of all-cause death, stroke (ischemic, hemorrhagic, or undetermined) and Major Bleeding (International Society on Thrombosis and Hemostasis [ISTH] definition) in the edoxaban group against the vitamin K antagonist (VKA) group in subjects undergoing catheter ablation of atrial fibrillation (AF) in the period from the end of the catheter ablation procedure to Day 90/end-of-treatment (EOT).

Primary safety objective:

To compare descriptively the incidence of Major Bleeding (ISTH definition) in the edoxaban group against the VKA group in the period from date of first intake of study medication to Day 90/EOT.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized to receive study treatment.

Background therapy:

After Screening and randomization, eligible subjects received 21 days (+7) anticoagulation before being assessed for suitability for the catheter ablation procedure. Subjects received 90 days anticoagulation post-procedure and were followed for an additional 30 days.

Evidence for comparator: -

Actual start date of recruitment	21 March 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	Poland: 78
Country: Number of subjects enrolled	Spain: 33
Country: Number of subjects enrolled	United Kingdom: 60
Country: Number of subjects enrolled	Belgium: 9
Country: Number of subjects enrolled	Czech Republic: 109
Country: Number of subjects enrolled	Germany: 44
Country: Number of subjects enrolled	Hungary: 75
Country: Number of subjects enrolled	Canada: 53
Country: Number of subjects enrolled	Korea, Republic of: 39
Country: Number of subjects enrolled	Taiwan: 39
Country: Number of subjects enrolled	Italy: 63
Worldwide total number of subjects	602
EEA total number of subjects	471

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)	392
From 65 to 84 years	210
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 614 subjects who met the inclusion and none of the exclusion criteria were randomized; 602 received the study drug.

Pre-assignment

Screening details:

Subjects were required to have completed between 21 to 28 days of anticoagulation with study treatment prior to the catheter ablation visit/periprocedural visit (Day 0).

Period 1

Period 1 title	Overall period (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-based Regimen

Arm description:

Edoxaban-based regimen for 21 days pre- and 90 days post-ablation period.

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

Dosage and administration details:

Edoxaban 60 mg once-daily or 30 mg once-daily in selected subjects.

Arm title	VKA-based Regimen
------------------	-------------------

Arm description:

VKA-based regimen for 21 days pre- and 90 days post-ablation period (control regimen)

Arm type	Active comparator
Investigational medicinal product name	Vitamin K antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

VKA-Based Regimen: Dosed at International Normalised Ratio (INR) levels, which is a test of how long it takes for blood to clot. Standard of Care treatment in Canada, Italy, Poland, Hungary, Czech Republic, UK, Taiwan and Korea.

VKA-Based Regimen: Dosed at INR levels. Standard of Care treatment in Germany and Belgium.

VKA-Based Regimen: Dosed at INR levels. Standard of Care treatment in Spain.

Number of subjects in period 1	Edoxaban-based Regimen	VKA-based Regimen
Started	405	197
Completed	359	174
Not completed	46	23
Consent withdrawn by subject	7	5
Physician decision	1	4
Adverse event, non-fatal	28	6
Not specified	10	8

Baseline characteristics

Reporting groups

Reporting group title	Edoxaban-based Regimen
Reporting group description: Edoxaban-based regimen for 21 days pre- and 90 days post-ablation period.	
Reporting group title	VKA-based Regimen
Reporting group description: VKA-based regimen for 21 days pre- and 90 days post-ablation period (control regimen)	

Reporting group values	Edoxaban-based Regimen	VKA-based Regimen	Total
Number of subjects	405	197	602
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)	262	130	392
From 65-84 years	143	67	210
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	59.5	59.6	
standard deviation	± 10.2	± 10.0	-
Gender categorical Units: Subjects			
Female	118	51	169
Male	287	146	433

End points

End points reporting groups

Reporting group title	Edoxaban-based Regimen
Reporting group description: Edoxaban-based regimen for 21 days pre- and 90 days post-ablation period.	
Reporting group title	VKA-based Regimen
Reporting group description: VKA-based regimen for 21 days pre- and 90 days post-ablation period (control regimen)	

Primary: Number of Subjects Who Experienced the Composite of All-cause Death, Stroke (VARC-2), and Major Bleeding (ISTH) in the Edoxaban Group Compared With Vitamin K Antagonist (VKA) Group in Subjects Undergoing Catheter Ablation (Adjudicated Data)

End point title	Number of Subjects Who Experienced the Composite of All-cause Death, Stroke (VARC-2), and Major Bleeding (ISTH) in the Edoxaban Group Compared With Vitamin K Antagonist (VKA) Group in Subjects Undergoing Catheter Ablation (Adjudicated Data) ^[1]
-----------------	---

End point description:

Stroke (ischemic, hemorrhagic, or undetermined) was defined by Valve Academic Research Consortium-2 (VARC-2) as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury following hemorrhage or infarction. A stroke event was based on any of the following: duration of neurological dysfunction >24 hours (h), duration of neurological dysfunction <24 h in case of imaging-documented new hemorrhage or infarction, and a neurological dysfunction resulting in death.

Major bleeding was defined by the International Society on Thrombosis and Hemostasis (ISTH) as fatal bleeding and/or bleeding that is symptomatic and occurs in a critical area or organ and/or extrasurgical site bleeding causing a fall in hemoglobin level of >2 g/dL or leads to blood transfusion, surgical site bleeding that requires a second intervention, causes hemarthrosis that delays mobilization or wound healing, or causes hemodynamic instability.

End point type	Primary
----------------	---------

End point timeframe:

Day 1 to Day 90

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 drug(s) administered for this outcome.

End point values	Edoxaban-based Regimen	VKA-based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	101		
Units: Number of subjects				
number (not applicable)				
All-cause death, stroke, and major bleeding	1	2		

Statistical analyses

Primary: Number of Subjects Who Experienced Major Bleeding (International Society on Thrombosis and Hemostasis [ISTH]) in the Edoxaban Group Compared With VKA Group Among Participants Undergoing Catheter Ablation (Adjudicated Data)

End point title	Number of Subjects Who Experienced Major Bleeding (International Society on Thrombosis and Hemostasis [ISTH]) in the Edoxaban Group Compared With VKA Group Among Participants Undergoing Catheter Ablation (Adjudicated Data) ^[2]
-----------------	---

End point description:

Major bleeding was defined by the International Society on Thrombosis and Hemostasis (ISTH) as fatal bleeding and/or bleeding that is symptomatic and occurs in a critical area or organ and/or extrasurgical site bleeding causing a fall in hemoglobin level of >2 g/dL or leads to blood transfusion, surgical site bleeding that requires a second intervention, causes hemarthrosis that delays mobilization or wound healing, or causes hemodynamic instability.

End point type	Primary
----------------	---------

End point timeframe:

Day 1 to Day 90

Notes:

[2] - 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 drug(s) administered for this outcome.

End point values	Edoxaban-based Regimen	VKA-based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	405	197		
Units: Number of subjects				
number (not applicable)				
Major bleeding	10	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced the Composite of All-cause Death, Stroke (Alternative), and Major Bleeding (ISTH) in the Edoxaban Group Compared With VKA Group Among Subjects Undergoing Catheter Ablation (Adjudicated Data)

End point title	Number of Subjects Who Experienced the Composite of All-cause Death, Stroke (Alternative), and Major Bleeding (ISTH) in the Edoxaban Group Compared With VKA Group Among Subjects Undergoing Catheter Ablation (Adjudicated Data)
-----------------	---

End point description:

An alternative definition characterized stroke (ischemic, hemorrhagic, or undetermined) as an abrupt onset, over minutes to hours, of a focal neurological deficit in the distribution of a single brain artery that was not due to an identifiable nonvascular cause (ie, brain tumor or trauma), and that either lasted at least 24 hours or resulted in death within 24 hours of onset.

Major bleeding was defined by the International Society on Thrombosis and Hemostasis (ISTH) as fatal bleeding and/or bleeding that is symptomatic and occurs in a critical area or organ and/or extrasurgical site bleeding causing a fall in hemoglobin level of >2 g/dL or leads to blood transfusion, surgical site bleeding that requires a second intervention, causes hemarthrosis that delays mobilization or wound healing, or causes hemodynamic instability.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Day 90

End point values	Edoxaban-based Regimen	VKA-based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	101		
Units: Number of subjects				
number (not applicable)				
All-cause death, stroke, and major bleeding	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Experienced the Composite of Stroke (VARC-2), Systemic Embolic Events (SEE), and Cardiovascular (CV) Mortality in the Edoxaban Group Compared With VKA Group Among Participants Undergoing Catheter Ablation (Adjudicated Data)

End point title	Number of Subjects Who Experienced the Composite of Stroke (VARC-2), Systemic Embolic Events (SEE), and Cardiovascular (CV) Mortality in the Edoxaban Group Compared With VKA Group Among Participants Undergoing Catheter Ablation (Adjudicated Data)
-----------------	--

End point description:

Stroke (ischemic, hemorrhagic, or undetermined) was defined by Valve Academic Research Consortium-2 (VARC-2) as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury following hemorrhage or infarction. A stroke event was based on any of the following: duration of neurological dysfunction >24 hours (h), duration of neurological dysfunction <24 h in case of imaging-documented new hemorrhage or infarction, and a neurological dysfunction resulting in death.

SEE was defined as an arterial embolism resulting in clinical ischemia, excluding the central nervous system, coronary, and pulmonary arterial circulation.

CV mortality was defined as cardiac or vascular death according to Academic Research Consortium.

End point type	Secondary
----------------	-----------

End point timeframe:

Day 1 to Day 90

End point values	Edoxaban-based Regimen	VKA-based Regimen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	316	101		
Units: Number of subjects				
number (not applicable)				
Stroke, systemic embolic events, CV mortality	1	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from the first dose of the study drug to 30 days after last dose of study drug.

Adverse event reporting additional description:

Adverse events that emerge (or worsen) from the first dose of the study drug to the last dose of the study drug.

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	19.1
--------------------	------

Reporting groups

Reporting group title	Edoxaban-based Regimen
-----------------------	------------------------

Reporting group description:

Edoxaban-based regimen for 21 days pre- and 90 days post-ablation period.

Reporting group title	VKA-based Regimen
-----------------------	-------------------

Reporting group description:

VKA-based regimen for 21 days pre- and 90 days post-ablation period (control regimen)

Serious adverse events	Edoxaban-based Regimen	VKA-based Regimen	
Total subjects affected by serious adverse events			
subjects affected / exposed	40 / 405 (9.88%)	15 / 197 (7.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon adenoma			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Ateriovenous fistula			
subjects affected / exposed	2 / 405 (0.49%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery stenosis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (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 edema			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (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			
Foot fracture			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural complication			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	15 / 405 (3.70%)	6 / 197 (3.05%)	
occurrences causally related to treatment / all	0 / 15	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	3 / 405 (0.74%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial tachycardia			
subjects affected / exposed	0 / 405 (0.00%)	2 / 197 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial thrombosis			
subjects affected / exposed	1 / 405 (0.25%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac thrombus			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular dysfunction			

subjects affected / exposed	2 / 405 (0.49%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (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	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (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			
Anemia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (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	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenal perforation			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retroperitoneal mass			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urethral obstruction			
subjects affected / exposed	1 / 405 (0.25%)	0 / 197 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 405 (0.00%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 405 (0.49%)	1 / 197 (0.51%)	
occurrences causally related to treatment / all	0 / 2	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-based Regimen	VKA-based Regimen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	210 / 405 (51.85%)	99 / 197 (50.25%)	
Vascular disorders			
Arteriovenous fistula			
subjects affected / exposed	3 / 405 (0.74%)	2 / 197 (1.02%)	
occurrences (all)	3	2	
Hypertension			
subjects affected / exposed	8 / 405 (1.98%)	3 / 197 (1.52%)	
occurrences (all)	8	3	
Hypotension			
subjects affected / exposed	8 / 405 (1.98%)	2 / 197 (1.02%)	
occurrences (all)	8	2	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 405 (1.23%)	3 / 197 (1.52%)	
occurrences (all)	5	3	
Non-cardiac chest pain			

subjects affected / exposed occurrences (all)	5 / 405 (1.23%) 5	2 / 197 (1.02%) 2	
Pyrexia subjects affected / exposed occurrences (all)	19 / 405 (4.69%) 19	3 / 197 (1.52%) 3	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	6 / 405 (1.48%) 6	3 / 197 (1.52%) 3	
Dyspnea subjects affected / exposed occurrences (all)	14 / 405 (3.46%) 14	1 / 197 (0.51%) 1	
Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all)	5 / 405 (1.23%) 5	0 / 197 (0.00%) 0	
Injury, poisoning and procedural complications Post procedural complication subjects affected / exposed occurrences (all)	3 / 405 (0.74%) 3	2 / 197 (1.02%) 2	
Procedural pain subjects affected / exposed occurrences (all)	4 / 405 (0.99%) 4	2 / 197 (1.02%) 2	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	41 / 405 (10.12%) 41	21 / 197 (10.66%) 21	
Atrial flutter subjects affected / exposed occurrences (all)	15 / 405 (3.70%) 15	8 / 197 (4.06%) 8	
Atrial tachycardia subjects affected / exposed occurrences (all)	3 / 405 (0.74%) 3	5 / 197 (2.54%) 5	
Atrial thrombosis subjects affected / exposed occurrences (all)	2 / 405 (0.49%) 2	2 / 197 (1.02%) 2	

Atrioventricular block first degree subjects affected / exposed occurrences (all)	3 / 405 (0.74%) 3	2 / 197 (1.02%) 2	
Bradycardia subjects affected / exposed occurrences (all)	0 / 405 (0.00%) 0	2 / 197 (1.02%) 2	
Cardiac flutter subjects affected / exposed occurrences (all)	4 / 405 (0.99%) 4	5 / 197 (2.54%) 5	
Palpitations subjects affected / exposed occurrences (all)	12 / 405 (2.96%) 12	4 / 197 (2.03%) 4	
Pericarditis subjects affected / exposed occurrences (all)	6 / 405 (1.48%) 6	2 / 197 (1.02%) 2	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	8 / 405 (1.98%) 8	3 / 197 (1.52%) 3	
Headache subjects affected / exposed occurrences (all)	8 / 405 (1.98%) 8	5 / 197 (2.54%) 5	
Phrenic nerve paralysis subjects affected / exposed occurrences (all)	1 / 405 (0.25%) 1	2 / 197 (1.02%) 2	
Blood and lymphatic system disorders			
Leukocytosis subjects affected / exposed occurrences (all)	0 / 405 (0.00%) 0	2 / 197 (1.02%) 2	
Gastrointestinal disorders			
Abdominal pain upper subjects affected / exposed occurrences (all)	5 / 405 (1.23%) 5	1 / 197 (0.51%) 1	
Diarrhea subjects affected / exposed occurrences (all)	3 / 405 (0.74%) 3	3 / 197 (1.52%) 3	
Flatulence			

subjects affected / exposed occurrences (all)	2 / 405 (0.49%) 2	2 / 197 (1.02%) 2	
Nausea subjects affected / exposed occurrences (all)	6 / 405 (1.48%) 6	1 / 197 (0.51%) 1	
Vomiting subjects affected / exposed occurrences (all)	5 / 405 (1.23%) 5	2 / 197 (1.02%) 2	
Hepatobiliary disorders Liver disorder subjects affected / exposed occurrences (all)	1 / 405 (0.25%) 1	2 / 197 (1.02%) 2	
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	2 / 405 (0.49%) 2	2 / 197 (1.02%) 2	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 405 (0.49%) 2	2 / 197 (1.02%) 2	
Back pain subjects affected / exposed occurrences (all)	6 / 405 (1.48%) 6	1 / 197 (0.51%) 1	
Pain in extremity subjects affected / exposed occurrences (all)	5 / 405 (1.23%) 5	1 / 197 (0.51%) 1	
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)	4 / 405 (0.99%) 4	3 / 197 (1.52%) 3	
Nasopharyngitis subjects affected / exposed occurrences (all)	9 / 405 (2.22%) 9	1 / 197 (0.51%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	2 / 405 (0.49%) 2	2 / 197 (1.02%) 2	

Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 405 (0.00%)	2 / 197 (1.02%)	
occurrences (all)	0	2	
Hypokalaemia			
subjects affected / exposed	2 / 405 (0.49%)	5 / 197 (2.54%)	
occurrences (all)	2	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 February 2017	Analyses relating to anticoagulation under "other objectives" as well as any other reference to anticoagulation markers in the protocol were deleted; administration of study drug and active comparator were clarified; eligibility criteria were updated; and the method of treatment allocation section was revised
27 July 2017	Administration of the study drug was further clarified; the method of assessing regimen compliance section was updated; and the list of hematology analyses required prior to randomization and protocol for assessing these markers were updated

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported