Clinical trial results:
An Open-label, Randomised, Parallel-group, Multicentre, Observational Trial to Evaluate Safety and Efficacy of Edoxaban Tosylate in Children From 38 Weeks Gestational Age to Less Than 18 Years of Age With Cardiac Diseases At Risk of Thromboembolic Events

Summary

EudraCT number	2017-000475-90
Trial protocol	GB HU DE ES AT FR PL HR IT
Global end of trial date	03 December 2020

Results information

Result version number	v1 (current)
This version publication date	18 June 2022
First version publication date	18 June 2022

Trial information

Trial identification

Sponsor protocol code	DU176b-C-U313

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03395639
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo, Inc.
Sponsor organisation address	211 Mount Airy Rd., Basking Ridge, United States, 07920
Public contact	Clinical Trial Information Contact, Daiichi Sankyo Inc, +1 908-992-6400, CTRinfo@dsi.com
Scientific contact	Clinical Trial Information Contact, Daiichi Sankyo Inc, +1 908-992-6400, CTRinfo@dsi.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000788-PIP02-11
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	03 December 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to compare the safety of edoxaban with the SOC in pediatric subjects with cardiac diseases at risk of thromboembolic complications who need primary or secondary anticoagulant prophylaxis with regard to the combination of major and clinically relevant non-major (CRNM) bleedings per International Society on Thrombosis and Haemostasis [ISTH] definition occurring on treatment (ie, during treatment or within 3 days of completing, interrupting or stopping study treatment during the first 3-month treatment period).

Protection of trial subjects:

The study protocol, amendments (if any), the informed consent form(s) (ICFs), and information sheets were approved by the appropriate and applicable Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs). This 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 for Good Clinical Practice (GCP) (CPMP/ICH/135/95), and applicable regulatory requirement(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 February 2018
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	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 8
Country: Number of subjects enrolled	Austria: 15
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Egypt: 37
Country: Number of subjects enrolled	India: 4
Country: Number of subjects enrolled	Israel: 11
Country: Number of subjects enrolled	Lebanon: 7
Country: Number of subjects enrolled	United States: 34
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Croatia: 1
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Russian Federation: 3
Country: Number of subjects enrolled	Turkey: 10

Country: Number of subjects enrolled	Ukraine: 6
Worldwide total number of subjects	168
EEA total number of subjects	52

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)	16
Children (2-11 years)	108
Adolescents (12-17 years)	44
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 168 participants who met all inclusion criteria and no exclusion criteria were randomized to treatment; 167 participants received treatment and were included in the modified Intent to Treat and Safety Populations.

Pre-assignment

Screening details:

All subjects at the Screening Visit were assessed for international normalized ratio (INR) and activated partial thromboplastin time (aPTT) and evaluated at the local laboratory.

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:

Open label

Arms

Are arms mutually exclusive?	Yes
Arm title	Edoxaban

Arm description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

Arm type	Experimental
Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	Lixiana, Savaysa
Pharmaceutical forms	Granules for oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Tablets (15- and/or 30-mg strength) or granules for oral suspension (60 mg, 6 mg/mL) were administered orally once a day, at the same time every day, with or without food. Tablets were to be swallowed with a glass of water.

Arm title	Standard of Care (SOC)

Arm description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site’s SOC treatment regimen.

Arm type	Active comparator
Investigational medicinal product name	Standard of Care (SOC)
Investigational medicinal product code	
Other name	Warfarin/heparin, Vitamin K antagonist
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Standard of care (SOC) was administered according to the clinical site’s SOC treatment regimen.

Number of subjects in period 1	Edoxaban	Standard of Care (SOC)
Started	110	58
Completed	106	55
Not completed	4	3
Consent withdrawn by subject	2	2
Participant discontinued at Principal Investigator	-	1
Adverse event, non-fatal	1	-
Did not receive study drug	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Edoxaban
Reporting group description:	
Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.	
Reporting group title	Standard of Care (SOC)
Reporting group description:	
Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.	

Reporting group values	Edoxaban	Standard of Care (SOC)	Total
Number of subjects	110	58	168
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)	8	8	16
Children (2-11 years)	74	34	108
Adolescents (12-17 years)	28	16	44
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	7.7	7.3	
standard deviation	± 4.8	± 5.1	-
Gender categorical Units: Subjects			
Female	38	21	59
Male	72	37	109

End points

End points reporting groups

Reporting group title	Edoxaban

Reporting group description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

Reporting group title	Standard of Care (SOC)

Reporting group description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.

Subject analysis set title	Edoxaban (Extension Period)
Subject analysis set type	Safety analysis

Subject analysis set description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral
suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

Primary: Number of Participants With Adjudicated Bleeding Events Within the Main Treatment Period

End point title	Number of Participants With Adjudicated Bleeding Events Within the Main Treatment Period

End point description:

Adjudicated bleeding events included major and clinically-relevant non-major (CRNM) bleeding events per International Society on Thrombosis and Haemostasis (ISTH) definition occurring within the main treatment period. Based on modified ISTH recommendations, major bleeding is defined as a composite (ie, any) of the following: fatal bleeding; and/or symptomatic bleeding in a critical area or organ; and/or bleeding causing a decrease in hemoglobin level of >2 g/dL, or leading to transfusion of the equivalent of ≥2 units of whole blood or red cells. A CRNM bleed is an acute or sub-acute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in that it leads to at least one of the following: a hospital admission for bleeding, or a physician guided medical or surgical treatment for bleeding, or a change in antithrombotic therapy. Minor bleeding is any other overt bleeding event that does not meet criteria for either major or CRNM bleeding

End point type	Primary

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study treatment was discontinued, whichever was earlier

End point values	Edoxaban	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	58		
Units: participants				
number (not applicable)				
Major or CRNM bleeding events	1	1		
Major bleeding events	0	0		

All bleeding events (Major, CRNM, minor)	4	2		

Statistical analyses

Statistical analysis title	Edoxaban vs Standard of Care (SOC)
Comparison groups	Edoxaban v Standard of Care (SOC)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Annualized rate difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.18
upper limit	0.12

Notes:

[1] - Difference in adjudicated major or CRNM bleeding rates were assessed.

Statistical analysis title	Edoxaban vs Standard of Care (SOC)
Comparison groups	Edoxaban v Standard of Care (SOC)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Annualized rate difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0

Notes:

[2] - Difference in adjudicated major bleeding rates were assessed.

Statistical analysis title	Edoxaban vs Standard of Care (SOC)
Comparison groups	Edoxaban v Standard of Care (SOC)
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Annualized rate difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.25

Notes:

[3] - Difference in all adjudicated bleeding (major, CRNM, minor) rates were assessed.

Secondary: Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways Within the Main Treatment Period

End point title	Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways Within the Main Treatment Period

End point description:

Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI).

End point type	Secondary

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study treatment was discontinued, whichever was earlier

End point values	Edoxaban	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	58		
Units: participants				
number (not applicable)				
Thromboembolic event, Any Event	0	1		
Deep vein thrombosis	0	1		
Pulmonary embolism	0	1		
Stroke	0	0		
Systemic embolic event	0	0		
Intracardiac thrombus	0	0		
Myocardial infarction	0	0		
Asymptomatic intracardiac thrombus-cardiac imaging	0	0		
Death as a result of TE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Thromboembolic Event Within the Main Treatment Period

End point title	Number of Participants Who Died as a Result of Thromboembolic Event Within the Main Treatment Period

End point description:

Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI).

End point type	Secondary

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study

treatment was discontinued, whichever was earlier

End point values	Edoxaban	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	58		
Units: participants				
number (not applicable)				
Died as a result of TE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) Within the Main Treatment Period

End point title	Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) Within the Main Treatment Period

End point description:

Death due to any cause (all-cause mortality) was assessed.

End point type	Secondary

End point timeframe:

Date of first dose of study drug up to the Month 4 or to the date of last dose of study drug if study treatment was discontinued, whichever was earlier

End point values	Edoxaban	Standard of Care (SOC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	109	58		
Units: participants				
number (not applicable)				
All-cause mortality	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Adjudicated Bleeding Events During the Extension Period

End point title	Number of Participants With Adjudicated Bleeding Events During the Extension Period

End point description:

Adjudicated bleeding events included major and clinically-relevant non-major (CRNM) bleeding events

per International
Society on Thrombosis and Haemostasis (ISTH) definition occurring within the main treatment period. Based on
modified ISTH recommendations, major bleeding is defined as a composite (ie, any) of the following: fatal bleeding;
and/or symptomatic bleeding in a critical area or organ; and/or bleeding causing a decrease in hemoglobin level of
>2 g/dL, or leading to transfusion of the equivalent of ≥2 units of whole blood or red cells. A CRNM bleed is an acute
or sub-acute clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, in
that it leads to at least one of the following: a hospital admission for bleeding, or a physician guided medical or surgical
treatment for bleeding, or a change in antithrombotic therapy. Minor bleeding is any other overt bleeding event that does not meet criteria for either major or CRNM bl

End point type	Secondary

End point timeframe:

End of Month 3 up to Month 13

End point values	Edoxaban (Extension Period)			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: participants				
number (not applicable)				
Major or CRNM bleeding events	1			
Major bleeding events	1			
All bleeding events (Major, CRNM, minor)	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways During the Extension Period

End point title	Number of Participants With Symptomatic Thromboembolic Events (TE) in the Systemic Arterial or Venous Pathways During the Extension Period

End point description:

Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI).

End point type	Secondary

End point timeframe:

End of Month 3 up to Month 13

End point values	Edoxaban (Extension Period)			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: participants				
number (not applicable)				
Thromboembolic event, Any Event	4			
Deep vein thrombosis	0			
Pulmonary embolism	0			
Stroke	2			
Systemic embolic event	0			
Intracardiac thrombus	0			
Myocardial infarction	2			
Asymptomatic intracardiac thrombus-cardiac imaging	0			
Death as a result of TE	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Thromboembolic Event During the Extension Period

End point title	Number of Participants Who Died as a Result of Thromboembolic Event During the Extension Period

End point description:

Symptomatic thromboembolic events (TE) in the systemic arterial or venous pathways include deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, intracardiac thrombus, and myocardial infarction (MI).

End point type	Secondary

End point timeframe:

End of Month 3 up to Month 13

End point values	Edoxaban (Extension Period)			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: participant				
number (not applicable)				
Died as a result of TE	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) During the Extension Period

End point title	Number of Participants Who Died as a Result of Any Cause (All-Cause Mortality) During the Extension Period

End point description:

Death due to any cause (all-cause mortality) was assessed.

End point type	Secondary

End point timeframe:

End of Month 3 up to Month 13

End point values	Edoxaban (Extension Period)			
Subject group type	Subject analysis set			
Number of subjects analysed	144			
Units: participants				
number (not applicable)				
All-cause mortality	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from the time of signing the informed consent form up to 30 days after the last dose of study drug, up to 13 months.

Adverse event reporting additional description:

Adverse events (AEs) were defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Edoxaban

Reporting group description:

Participants who were randomized to edoxaban solution or tablets orally once a day. Participants 12 to <18 years of age were administered 30 mg, 45 mg, or 60 mg edoxaban tablets or offered granules for oral suspension if they did not have the capacity to swallow. Participants under 12 years of age were administered edoxaban granules (dosed as mg/kg), with maximum dose of 45 mg for 6 months to <12 years, maximum dose of 12 mg for >28 days to <6 months, and maximum dose of 6 mg for 38 weeks gestation to ≤28 days.

Reporting group title	Standard of Care (SOC)

Reporting group description:

Participants who were randomized to SOC regimen which may have included low molecular weight heparin (LMWH) and/or Vitamin K antagonist (VKA) according to the clinical site's SOC treatment regimen.

Serious adverse events	Edoxaban	Standard of Care (SOC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 109 (21.10%)	3 / 58 (5.17%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (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			
Non-cardiac chest pain			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 109 (1.83%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary artery stenosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 109 (0.00%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 109 (1.83%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Pulmonary arterial pressure increased			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (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			
Skin laceration			

subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue injury			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic liver injury			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Coarctation of the aorta			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (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 thrombosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorder			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 109 (1.83%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Coronary artery thrombosis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (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			
Cerebellar infarction			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (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 / 109 (0.92%)	0 / 58 (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			

Haemolysis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune thrombocytopenia			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gingival bleeding			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucous stools			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 109 (0.92%)	1 / 58 (1.72%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (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	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abscess limb			

subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 109 (0.92%)	0 / 58 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 109 (0.00%)	1 / 58 (1.72%)	
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	Standard of Care (SOC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 109 (44.04%)	12 / 58 (20.69%)	
Nervous system disorders			
Headache			
subjects affected / exposed	13 / 109 (11.93%)	2 / 58 (3.45%)	
occurrences (all)	19	2	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	17 / 109 (15.60%)	1 / 58 (1.72%)	
occurrences (all)	19	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	7 / 109 (6.42%)	1 / 58 (1.72%)	
occurrences (all)	11	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	14 / 109 (12.84%)	2 / 58 (3.45%)	
occurrences (all)	18	2	
Epistaxis			

subjects affected / exposed	8 / 109 (7.34%)	2 / 58 (3.45%)	
occurrences (all)	14	2	
Rhinorrhoea			
subjects affected / exposed	8 / 109 (7.34%)	1 / 58 (1.72%)	
occurrences (all)	10	1	
Infections and infestations			
Influenza			
subjects affected / exposed	6 / 109 (5.50%)	0 / 58 (0.00%)	
occurrences (all)	6	0	
Nasopharyngitis			
subjects affected / exposed	8 / 109 (7.34%)	3 / 58 (5.17%)	
occurrences (all)	8	3	
Upper respiratory tract infection			
subjects affected / exposed	9 / 109 (8.26%)	2 / 58 (3.45%)	
occurrences (all)	16	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 October 2017	Risk/Benefit section was added, eligibility criteria were updated, drug formulation and administration procedures were clarified, study assessment procedures were clarified, and vendors were updated.
27 March 2018	Timeframe for primary/secondary objectives was updated and the secondary objectives, primary/secondary endpoints, statistical analysis, drug administration, and study design were revised
03 June 2019	Drug administration and study procedures were clarified and eligibility criteria were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported