Clinical trial results:
A PHASE 3, OPEN-LABEL, RANDOMIZED, MULTICENTER, CONTROLLED TRIAL TO EVALUATE THE PHARMACOKINETICS AND PHARMACODYNAMICS OF EDOXABAN AND TO COMPARE THE EFFICACY AND SAFETY OF EDOXABAN WITH STANDARD OF CARE ANTICOAGULANT THERAPY IN PEDIATRIC SUBJECTS FROM BIRTH TO LESS THAN 18 YEARS OF AGE WITH CONFIRMED VENOUS THROMBOEMBOLISM (VTE)

Summary

EudraCT number	2016-000991-49
Trial protocol	CZ PT HU DE ES SI DK NL HR BG NO PL FR
Global end of trial date	24 May 2022

Results information

Result version number	v1 (current)
This version publication date	14 December 2022
First version publication date	14 December 2022

Trial information

Trial identification

Sponsor protocol code	DU176b-D-U312

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02798471
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Daiichi Sankyo
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	24 May 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 May 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective is to demonstrate the non-inferiority of edoxaban to standard of care (SOC; including low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors) in the treatment and secondary prevention of VTE in pediatric subjects with regard to the composite efficacy endpoint (ie, symptomatic recurrent VTE, death as result of VTE, and no change or extension of thrombotic burden) 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	27 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	Netherlands: 6
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Spain: 10
Country: Number of subjects enrolled	Croatia: 6
Country: Number of subjects enrolled	Bulgaria: 4
Country: Number of subjects enrolled	Czechia: 13
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 23
Country: Number of subjects enrolled	Singapore: 6
Country: Number of subjects enrolled	United States: 41

Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Thailand: 15
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	El Salvador: 5
Country: Number of subjects enrolled	Panama: 1
Country: Number of subjects enrolled	Brazil: 11
Country: Number of subjects enrolled	Guatemala: 9
Country: Number of subjects enrolled	Chile: 2
Country: Number of subjects enrolled	Ukraine: 4
Country: Number of subjects enrolled	India: 8
Country: Number of subjects enrolled	Lebanon: 9
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Turkey: 30
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	Israel: 13
Country: Number of subjects enrolled	Colombia: 11
Worldwide total number of subjects	290
EEA total number of subjects	90

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)	44
Children (2-11 years)	75
Adolescents (12-17 years)	171
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 290 participants who met all inclusion criteria and no exclusion criteria were randomized to receive either edoxaban or standard of care treatment; 286 patients received at least 1 dose of study drug (modified intent-to-treat population).

Pre-assignment

Screening details:

Pre-randomization treatment was provided by the Investigator or diagnosing clinic of the index VTE. Initial treatment using LMWH, SP Xa inhibitor, or UFH for index VTE prior to randomization was within 5-15 days and up to 20 days with approval. If VKA are administrated prior randomization, INR prior to randomization is recommended to be ≤2.5.

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

Arm description:

Pediatric patients who were randomized to edoxaban treatment. Edoxaban was administered as 15 or 30 mg tablets for participants 12 years of age to <18, and 60 mg edoxaban suspension for oral administration to participants under 12 years of age.

Arm type	Experimental
Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Edoxaban was supplied as tablets (15- and/or 30-mg strength) or granules for oral suspension 60 mg (6 mg/mL). Patients were instructed to take edoxaban (tablets or granules) 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

Arm description:

Pediatric patients who were randomized to standard of care (SOC) treatment. Standard of care may have included low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors.

Arm type	Active comparator
Investigational medicinal product name	Standard of care: Enoxaparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Solution for injection

Dosage and administration details:

Enoxaparin (LMWH) was provided as a solution for subcutaneous injection in prefilled syringes with 40 mg/0.4mL, 60 mg/0.6mL, 80 mg/0.8mL, and 100 mg/1.0 mL concentration for injection, or as multiple-dose vials (for patients <10 kg) for injection where allowed per standard clinical practice.

Investigational medicinal product name	Standard of care: Fondaparinux (SP Xa inhibitor)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Oral use

Dosage and administration details:

Fondaparinux (SP Xa inhibitor) was supplied as solution for subcutaneous injection in prefilled syringes (2.5 mg/0.5 mL, 5.0 mg/0.4 mL, 7.5 mg/0.6 mL, 10.0 mg/0.8 mL, and [where available] 1.5 mg/0.3 mL).

Investigational medicinal product name	Standard of care: Warfarin (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet, Suspension for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Warfarin (VKA) was supplied as tablets (0.5 mg, 1.0 mg, and 3.0 mg) and Warfarin suspension (1 mg/mL oral suspension). Various doses were available for international normalized ratio maintenance in the therapeutic range of ≥2.0 and ≤3.0.

Number of subjects in period 1	Edoxaban	Standard of Care
Started	147	143
Completed	128	119
Not completed	19	24
Physician decision	3	7
Consent withdrawn by subject	-	6
Adverse event, non-fatal	7	2
Death	2	3
Not specified	5	5
Data entry error (study completion + discontinued)	2	-
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Edoxaban
Reporting group description:	
Pediatric patients who were randomized to edoxaban treatment. Edoxaban was administered as 15 or 30 mg tablets for participants 12 years of age to <18, and 60 mg edoxaban suspension for oral administration to participants under 12 years of age.	
Reporting group title	Standard of Care
Reporting group description:	
Pediatric patients who were randomized to standard of care (SOC) treatment. Standard of care may have included low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors.	

Reporting group values	Edoxaban	Standard of Care	Total
Number of subjects	147	143	290
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)	22	22	44
Children (2-11 years)	38	37	75
Adolescents (12-17 years)	87	84	171
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	10.9	11.1	
standard deviation	± 5.99	± 6.03	-
Gender categorical Units: Subjects			
Female	70	70	140
Male	77	73	150

End points

End points reporting groups

Reporting group title	Edoxaban
Reporting group description:	
Pediatric patients who were randomized to edoxaban treatment. Edoxaban was administered as 15 or 30 mg tablets for participants 12 years of age to <18, and 60 mg edoxaban suspension for oral administration to participants under 12 years of age.	
Reporting group title	Standard of Care
Reporting group description:	
Pediatric patients who were randomized to standard of care (SOC) treatment. Standard of care may have included low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors.	

Primary: Number of Patients With Symptomatic Recurrent Venous Thromboembolism During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With Symptomatic Recurrent Venous Thromboembolism During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)
End point description:	
Diagnosis of recurrent venous thromboembolism (VTE) requires the confirmation by diagnostic imaging and at least one of the symptoms of VTE from such areas as lower or upper extremity, catheter-related thrombosis, pulmonary embolism, or sinovenous thrombosis. Symptomatic recurrent VTE was assessed in the modified intent-to-treat population (mITT).	
End point type	Primary
End point timeframe:	
Randomization to Month 3	

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Symptomatic Recurrent Venous Thromboembolism	5	2		

Statistical analyses

Statistical analysis title	Composite primary efficacy endpoint
Comparison groups	Edoxaban v Standard of Care

Number of subjects included in analysis	286
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.9694
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.594
upper limit	1.719

Notes:

[1] - The edoxaban-to-comparator hazard ratio will be computed with 95% confidence interval (CI) (two-sided) based on this model. Edoxaban will be considered non-inferior to comparator if the upper limit of the 95% CI is ≤1.5.

Primary: Number of Patients Who Died as a Result of VTE During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients Who Died as a Result of VTE During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)[2]

End point description:

Death from venous thromboembolism (VTE) is based on objective diagnostic testing, autopsy or death which cannot be attributed to documented cause for which VTE cannot be ruled out. Death was assessed in the modified intent-to-treat population (mITT).

End point type	Primary

End point timeframe:

Randomization to Month 3

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 statistics were used to assess this outcome measure.

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Pulmonary embolism with or without DVT	0	1		
Fatal pulmonary embolism	0	0		
Non-fatal pulmonary embolism	0	1		
Deep vein thrombosis (DVT) only	5	1		
Fatal DVT	0	0		
Non-fatal DVT	4	0		
Unexplained death which VTE cannot be ruled out	1	1		

Statistical analyses

No statistical analyses for this end point

Primary: Number of Patients With No Change or Extension of Thrombotic Burden During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With No Change or Extension of Thrombotic Burden During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)[3]

End point description:

No change or extension of thrombotic burden as assessed by quantitative diagnostic imaging of the index qualifying VTE thrombus at baseline and at Month 3. Change in thrombotic burden was assessed in the modified intent-to-treat population (mITT).

End point type	Primary

End point timeframe:

Randomization to Month 3

Notes:

[3] - 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 statistics were used to assess this outcome.

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
No Change or Extension of Thrombotic Burden	21	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Symptomatic Recurrent Venous Thromboembolism During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With Symptomatic Recurrent Venous Thromboembolism During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point description:

Diagnosis of recurrent venous thromboembolism (VTE) requires the confirmation by diagnostic imaging and at least one of the symptoms of VTE from such areas as lower or upper extremity, catheter related thrombosis, pulmonary embolism, or sinovenous thrombosis. Symptomatic VTE was assessed in the modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

From randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Symptomatic Recurrent Venous Thromboembolism	7	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Symptomatic Recurrent VTE During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Individual Component of Primary Efficacy Endpoint)

End point title	Number of Patients With Symptomatic Recurrent VTE During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Individual Component of Primary Efficacy Endpoint)

End point description:

Diagnosis of recurrent venous thromboembolism (VTE) requires the confirmation by diagnostic imaging and at least one of the symptoms of VTE from such areas as lower or upper extremity, catheter related thrombosis, pulmonary embolism (PE), or sinovenous thrombosis. Symptomatic recurrent VTE was assessed in the modified intent-to-treat population (mITT).

End point type	Secondary

End point timeframe:

Randomization to Month 3

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Symptomatic VTE	4	1		
Pulmonary embolism with or without DVT	0	1		
Deep vein thrombosis (DVT) only	4	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Died as a Result of VTE During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients Who Died as a Result of VTE During the

	Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point description:

Death from venous thromboembolism (VTE) is based on objective diagnostic testing, autopsy or death which cannot be attributed to documented cause for which VTE cannot be ruled out. Death was assessed in the modified intent-to-treat population (mITT).

End point type	Secondary

End point timeframe:

From randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Pulmonary embolism (PE) with or without DVT	1	1		
Fatal PE	0	0		
Non-fatal PE	1	1		
Deep vein thrombosis (DVT) only	6	1		
Fatal DVT	0	0		
Non-fatal DVT	5	0		
Unexplained death which VTE cannot be ruled out	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Who Died as a Result of VTE During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Individual Component of Primary Efficacy Endpoint)

End point title	Number of Patients Who Died as a Result of VTE During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Individual Component of Primary Efficacy Endpoint)

End point description:

Death from venous thromboembolism (VTE) is based on objective diagnostic testing, autopsy or death which cannot be attributed to documented cause for which VTE cannot be ruled out. Death was assessed in the modified intent-to-treat population (mITT).

End point type	Secondary

End point timeframe:

Randomization to Month 3

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Death as a result of VTE	1	1		
Unexplained death which VTE cannot be ruled out	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With No Change or Extension of Thrombotic Burden During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With No Change or Extension of Thrombotic Burden During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point description:

No change or extension of thrombotic burden as assessed by quantitative diagnostic imaging of the index qualifying VTE thrombus at baseline and at Month 3. Change in thrombotic burden was assessed in the modified intent-to-treat population (mITT).

End point type	Secondary

End point timeframe:

Randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
No Change or Extension of Thrombotic Burden	35	47		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With No Change or Extension of Thrombotic Burden During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Individual Component of Primary Efficacy Endpoint)

End point title	Number of Patients With No Change or Extension of Thrombotic Burden During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Individual

	Component of Primary Efficacy Endpoint)

End point description:

No change or extension of thrombotic burden as assessed by quantitative diagnostic imaging of the index qualifying VTE thrombus at baseline and at Month 3. Change in thrombotic burden was assessed in the modified intent-to-treat population (mITT).

End point type	Secondary

End point timeframe:

Randomization to Month 3

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
No Change or Extension of Thrombotic Burden	21	29		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients Reporting All-Cause Mortality During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated)

End point title	Number of Patients Reporting All-Cause Mortality During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated)

End point description:

All-cause mortality is defined as death due to any cause. All-cause mortality was assessed in the modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

Randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Participants with all-cause mortality	2	3		
Venous thromboembolism (VTE)-related death	1	1		
Unexplained death which VTE cannot be ruled out	1	1		
Other known causes of death	1	2		
Cancer	0	1		

Infectious disease	0	1		
Other	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Deep Vein Thrombosis, Catheter-related Thrombosis, Sino-venous Thrombosis, and Pulmonary Embolism During the Main, Extension, and Overall Treatment Periods Following Edoxaban or Standard of Care Treatment

End point title	Number of Patients With Deep Vein Thrombosis, Catheter-related Thrombosis, Sino-venous Thrombosis, and Pulmonary Embolism During the Main, Extension, and Overall Treatment Periods Following Edoxaban or Standard of Care Treatment

End point description:

Deep vein thrombosis was assessed by ultrasonography or magnetic resonance venography (MRV), catheter-related thrombosis was assessed by ultrasonography or echocardiography, sino-venous thrombosis was assessed by brain MRI, and pulmonary embolism was assessed by nuclear ventilation/perfusion (V/Q) scanning. Deep vein thrombosis, catheter-related thrombosis, sino-venous thrombosis, and pulmonary embolism were assessed in the modified intent-to-treat (mITT) population.

End point type	Secondary

End point timeframe:

Randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Main Treatment: DVT only	4	0		
Main Treatment: Catheter-related thrombosis	1	0		
Main Treatment: Cerebral sinovenous DVT thrombosis	0	0		
Main Treatment: PE with or without DVT	0	1		
Extension Treatment: DVT	1	0		
Extension Treatment: Catheter-related thrombosis	0	0		
Extension Treatment: Sino-venous DVT thrombosis	1	0		
Extension Treatment: PE	1	0		
Overall Treatment: DVT	5	0		
Overall Treatment: Catheter-related thrombosis	1	0		
Overall Treatment: Sino-venous DVT thrombosis	1	0		
Overall Treatment: PE	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Major and Clinically Relevant Non-Major Bleeding Events (On Treatment) During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With Major and Clinically Relevant Non-Major Bleeding Events (On Treatment) During the Main Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point description:

Any bleeding event defined as major and clinically relevant non-major bleeding (CRNM) events was reported. Major bleeding was defined as defined as a composite of any of the following: fatal bleeding; and/or symptomatic bleeding in critical area or organ such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pulmonary, or pericardial, or intramuscular with compartment syndrome; and/or bleeding that causes a decrease in hemoglobin of at least 2 g/dL or more, or leading to transfusion of the equivalent of two or more units of whole blood or red blood cells. CRNM was defined as 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; a physician-guided medical or surgical treatment for bleeding or a change in antithrombotic therapy (including interruption or discontinuation of study drug). [Safety Analysis]

End point type	Secondary

End point timeframe:

Randomization to Month 3

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Major and CRNM	3	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With All Bleeding Events (On Treatment) During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With All Bleeding Events (On Treatment) During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point description:

All bleeding events included major bleeding defined as a composite of any of the following: fatal bleeding; and/or symptomatic bleeding in critical area or organ such as intracranial, intra-spinal, intraocular, retroperitoneal, intraarticular, pulmonary, or pericardial, or intramuscular with compartment syndrome; and/or bleeding that causes a decrease in hemoglobin of at least 2 g/dL or more, or leading to transfusion of the equivalent of two or more units of whole blood or red blood cells (RBCs), clinically relevant non-major bleeding defined as 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; a physician-guided medical or surgical treatment for bleeding or a change in antithrombotic therapy (including interruption or discontinuation of study drug), nuisance bleeding, or a combination of bleeding events. [Safety Analysis Set

End point type	Secondary

End point timeframe:

Randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
All Bleeding Events	25	24		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients With Major and Clinically Relevant Non-Major Bleeding Events (On Treatment) During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point title	Number of Patients With Major and Clinically Relevant Non-Major Bleeding Events (On Treatment) During the Overall Treatment Period Following Edoxaban or Standard of Care Treatment (Adjudicated Composite)

End point description:

Any bleeding event defined as major and clinically relevant non-major bleeding (CRNM) events was reported. Major bleeding was defined as defined as a composite of any of the following: fatal bleeding; and/or symptomatic bleeding in critical area or organ such as intracranial, intra-spinal, intraocular, retroperitoneal, intra-articular, pulmonary, or pericardial, or intramuscular with compartment syndrome; and/or bleeding that causes a decrease in hemoglobin of at least 2 g/dL or more, or leading to transfusion of the equivalent of two or more units of whole blood or red blood cells. CRNM was defined as 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; a physician-guided medical or surgical treatment for bleeding or a change in antithrombotic therapy (including interruption or discontinuation of study drug). [Safety Analysis]

End point type	Secondary

End point timeframe:

Randomization to the date of last study drug plus 30 days, up to approximately 5 years 2 months

End point values	Edoxaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	145	141		
Units: Count of patients				
number (not applicable)				
Major and CRNM	8	5		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events were collected from the date the Informed Consent Form was signed up to 30 days after the last dose of study drug, up to approximately 5 years 2 months.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Edoxaban

Reporting group description:

Pediatric patients who were randomized to edoxaban treatment. Edoxaban was administered as 15 or 30 mg tablets for participants 12 years of age to <18, and 60 mg edoxaban suspension for oral administration to participants under 12 years of age.

Reporting group title	Standard of Care

Reporting group description:

Pediatric patients who were randomized to standard of care (SOC) treatment. Standard of care may have included low molecular weight heparin (LMWH), vitamin K antagonist (VKA), or synthetic pentasaccharide (SP) Xa inhibitors.

Serious adverse events	Edoxaban	Standard of Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	44 / 145 (30.34%)	37 / 141 (26.24%)	
number of deaths (all causes)	3	3	
number of deaths resulting from adverse events	3	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Anaplastic astrocytoma			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to spine			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Embolism venous			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post thrombotic syndrome			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava occlusion			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venoocclusive disease			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site rash			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Non-cardiac chest pain			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic inflammatory response syndrome			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menometrorrhagia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchomalacia			

subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoventilation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiogenic pulmonary oedema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oropharyngeal pain			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
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	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	2 / 145 (1.38%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			

subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric decompensation			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	2 / 145 (1.38%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Liver function test increased			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma complication			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Chronic granulomatous disease			

subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	1 / 145 (0.69%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Cerebral venous sinus thrombosis			
subjects affected / exposed	2 / 145 (1.38%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervicobrachial syndrome			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	2 / 145 (1.38%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic intracranial hypertension			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	2 / 145 (1.38%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord paralysis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 145 (4.14%)	6 / 141 (4.26%)	
occurrences causally related to treatment / all	0 / 12	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypereosinophilic syndrome			

subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anemia with crisis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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	2 / 145 (1.38%)	3 / 141 (2.13%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric perforation			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
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 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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	2 / 145 (1.38%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Liver disorder			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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 / 145 (0.69%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthropathy			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Chest wall haematoma			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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			
Anal abscess			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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 / 145 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Enterovirus infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis viral			

subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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 / 145 (0.69%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	4 / 145 (2.76%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			

subjects affected / exposed	0 / 145 (0.00%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcutaneous abscess			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 145 (2.07%)	0 / 141 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 145 (0.69%)	0 / 141 (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 / 145 (0.69%)	2 / 141 (1.42%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipoedema			
subjects affected / exposed	0 / 145 (0.00%)	1 / 141 (0.71%)	
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	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	51 / 145 (35.17%)	46 / 141 (32.62%)	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 145 (13.79%)	14 / 141 (9.93%)	
occurrences (all)	35	21	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	12 / 145 (8.28%)	11 / 141 (7.80%)	
occurrences (all)	18	12	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	16 / 145 (11.03%)	9 / 141 (6.38%)	
occurrences (all)	21	12	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	12 / 145 (8.28%)	10 / 141 (7.09%)	
occurrences (all)	44	13	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	8 / 145 (5.52%)	3 / 141 (2.13%)	
occurrences (all)	9	3	
Upper respiratory tract infection			
subjects affected / exposed	9 / 145 (6.21%)	8 / 141 (5.67%)	
occurrences (all)	14	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2018	Update the sample size for PK evaluation, updated exclusion criteria, and revised dose administration procedures.
07 June 2019	Revised dose administration procedures, updated exclusion criteria, clarified bleeding definitions, revised screening and re-screening procedures, updated reporting requirements for AEs, and revised echocardiogram assessment procedures.
08 June 2021	Updated dosing requirements for patients ≤28 days old, revised anticoagulation treatment, increased sample size, and updated procedures for renal function monitoring and radiologic VTE imaging.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported