Clinical trial results:
A Phase 1, Open-Label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics and Pharmacodynamics of Edoxaban in Pediatric Patients

Summary

EudraCT number	2015-005732-18
Trial protocol	ES FR IT
Global end of trial date	16 September 2021

Results information

Result version number	v1 (current)
This version publication date	02 April 2022
First version publication date	02 April 2022

Trial information

Trial identification

Sponsor protocol code	DU176b-A-U157

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02303431
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 Director, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo@dsi.com
Scientific contact	Clinical Director, Daiichi Sankyo, Inc., +1 908-992-6400, CTRinfo@dsi.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 September 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To characterize the PK of Edoxaban in pediatric patients following oral single-dose administration.

Protection of trial subjects:

The protocol, amendments, informed consent forms, and information sheets were approved by the appropriate and applicable Independent Ethics Committee (IECs) or Institutional Review Boards (IRBs). Prior to study participation, written informed consent was provided by the patient's parent or legal guardian. This study was conducted in compliance with the study protocol, the ethical principles that have their origin in the Declaration of Helsinki, the International Council of Harmonisation (ICH) consolidated Guideline E6 for Good Clinical Practice (GCP)(Committee for Proprietary Medicinal Products/ICH/135/95), and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	India: 11
Country: Number of subjects enrolled	Jordan: 5
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Czechia: 1
Worldwide total number of subjects	66
EEA total number of subjects	11

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	25
Children (2-11 years)	26
Adolescents (12-17 years)	15
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 66 participants who met all inclusion criteria and no exclusion criteria were enrolled in the study and received treatment at 32 clinical sites in the United States, Canada, France, India, Italy, Jordan, Lebanon, Spain, Turkey, and the United Kingdom.

Pre-assignment

Screening details:

Participants were asked to fast for at least 4 hrs before dosing and for an additional 2 hrs after dosing. If this was not feasible because of the patient's age, (unflavored) milk, or an equivalent substitute liquid (but not fruit juices), was allowed until 1 hr before and starting at 1 hr postdose (total volume of liquids not to exceed 240 mL).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1a: 30 mg Edoxaban

Arm description:

Participants who were 12 to < 18 years of age and received a single-dose, oral tablet of 30 mg edoxaban.

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:

Single-dose, oral tablet

Arm title	Cohort 1b: 60 mg Edoxaban

Arm description:

Participants who were 12 to < 18 years of age and received a single dose, oral tablet of 60 mg edoxaban.

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:

Single-dose, oral tablet

Arm title	Cohort 2a: 24 mg Edoxaban

Arm description:

Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 24 mg edoxaban.

Arm type	Experimental

Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 2b: 45 mg Edoxaban

Arm description:

Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 45 mg edoxaban.

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

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 3a: 0.7 mg/kg Edoxaban

Arm description:

Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 0.7 mg/kg (cap 24 mg) edoxaban.

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

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 3b: 1.4 mg/kg Edoxaban

Arm description:

Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 1.4 mg/kg (cap 45 mg) edoxaban.

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

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 4a: 0.75 mg/kg Edoxaban

Arm description:

Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 0.75 mg/kg edoxaban.

Arm type	Experimental

Investigational medicinal product name	Edoxaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 4b: 1.5 mg/kg Edoxaban

Arm description:

Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 1.5 mg/kg edoxaban.

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

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 5a: 0.4 mg/kg Edoxaban

Arm description:

Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.4 mg/kg edoxaban.

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

Dosage and administration details:

Single-dose, oral suspension

Arm title	Cohort 5b: 0.8 mg/kg Edoxaban

Arm description:

Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.8 mg/kg edoxaban.

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

Dosage and administration details:

Single-dose, oral suspension

Number of subjects in period 1	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban
Started	8	7	7
Completed	8	7	7

Number of subjects in period 1	Cohort 2b: 45 mg Edoxaban	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban
Started	6	7	6
Completed	6	7	6

Number of subjects in period 1	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban	Cohort 5a: 0.4 mg/kg Edoxaban
Started	7	6	6
Completed	7	6	6

Number of subjects in period 1	Cohort 5b: 0.8 mg/kg Edoxaban
Started	6
Completed	6

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1a: 30 mg Edoxaban
Reporting group description:	
Participants who were 12 to < 18 years of age and received a single-dose, oral tablet of 30 mg edoxaban.	
Reporting group title	Cohort 1b: 60 mg Edoxaban
Reporting group description:	
Participants who were 12 to < 18 years of age and received a single dose, oral tablet of 60 mg edoxaban.	
Reporting group title	Cohort 2a: 24 mg Edoxaban
Reporting group description:	
Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 24 mg edoxaban.	
Reporting group title	Cohort 2b: 45 mg Edoxaban
Reporting group description:	
Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 45 mg edoxaban.	
Reporting group title	Cohort 3a: 0.7 mg/kg Edoxaban
Reporting group description:	
Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 0.7 mg/kg (cap 24 mg) edoxaban.	
Reporting group title	Cohort 3b: 1.4 mg/kg Edoxaban
Reporting group description:	
Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 1.4 mg/kg (cap 45 mg) edoxaban.	
Reporting group title	Cohort 4a: 0.75 mg/kg Edoxaban
Reporting group description:	
Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 0.75 mg/kg edoxaban.	
Reporting group title	Cohort 4b: 1.5 mg/kg Edoxaban
Reporting group description:	
Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 1.5 mg/kg edoxaban.	
Reporting group title	Cohort 5a: 0.4 mg/kg Edoxaban
Reporting group description:	
Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.4 mg/kg edoxaban.	
Reporting group title	Cohort 5b: 0.8 mg/kg Edoxaban
Reporting group description:	
Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.8 mg/kg edoxaban.	

Reporting group values	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban
Number of subjects	8	7	7
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	7
Adolescents (12-17 years)	8	7	0
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	15.9	15.3	9.6
standard deviation	± 1.1	± 1.3	± 1.1
Gender categorical			
Units: Subjects			
Female	5	4	3
Male	3	3	4

Reporting group values	Cohort 2b: 45 mg Edoxaban	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban
Number of subjects	6	7	6
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)	6	7	6
Adolescents (12-17 years)	0	0	0
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	9.5	4.3	4.3
standard deviation	± 1.9	± 1.6	± 1.4
Gender categorical			
Units: Subjects			
Female	4	3	1
Male	2	4	5

Reporting group values	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban	Cohort 5a: 0.4 mg/kg Edoxaban
Number of subjects	7	6	6
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)	7	6	6
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0

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	1.2	1.0	0.2
standard deviation	± 0.5	± 0.5	± 0.2
Gender categorical			
Units: Subjects			
Female	3	3	2
Male	4	3	4

Reporting group values	Cohort 5b: 0.8 mg/kg Edoxaban	Total	
Number of subjects	6	66	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	6	25	
Children (2-11 years)	0	26	
Adolescents (12-17 years)	0	15	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	0.3		
standard deviation	± 0.2	-	
Gender categorical			
Units: Subjects			
Female	3	31	
Male	3	35	

End points

End points reporting groups

Reporting group title	Cohort 1a: 30 mg Edoxaban
Reporting group description: Participants who were 12 to < 18 years of age and received a single-dose, oral tablet of 30 mg edoxaban.	
Reporting group title	Cohort 1b: 60 mg Edoxaban
Reporting group description: Participants who were 12 to < 18 years of age and received a single dose, oral tablet of 60 mg edoxaban.	
Reporting group title	Cohort 2a: 24 mg Edoxaban
Reporting group description: Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 24 mg edoxaban.	
Reporting group title	Cohort 2b: 45 mg Edoxaban
Reporting group description: Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 45 mg edoxaban.	
Reporting group title	Cohort 3a: 0.7 mg/kg Edoxaban
Reporting group description: Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 0.7 mg/kg (cap 24 mg) edoxaban.	
Reporting group title	Cohort 3b: 1.4 mg/kg Edoxaban
Reporting group description: Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 1.4 mg/kg (cap 45 mg) edoxaban.	
Reporting group title	Cohort 4a: 0.75 mg/kg Edoxaban
Reporting group description: Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 0.75 mg/kg edoxaban.	
Reporting group title	Cohort 4b: 1.5 mg/kg Edoxaban
Reporting group description: Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 1.5 mg/kg edoxaban.	
Reporting group title	Cohort 5a: 0.4 mg/kg Edoxaban
Reporting group description: Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.4 mg/kg edoxaban.	
Reporting group title	Cohort 5b: 0.8 mg/kg Edoxaban
Reporting group description: Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.8 mg/kg edoxaban.	
Subject analysis set title	All Patients
Subject analysis set type	Sub-group analysis
Subject analysis set description: All participants included in the study (Cohorts 1a, 1b, 2a, 2b, 3a, 3b, 4a, 4b, 5a, and 5b) in the Population Pharmacokinetic (PopPK) Analysis Set.	

Primary: Pharmacokinetic Parameter of Apparent Systemic Clearance (CL/F)

End point title	Pharmacokinetic Parameter of Apparent Systemic Clearance (CL/F)[1]
End point description: A population pharmacokinetic (PK) method was used to estimate systemic clearance (CL/F). Due to sparse PK samples being collected, the median PK estimate is reported in all participants at a total of 5	

blood samplings.

End point type	Primary

End point timeframe:

0.25 to 1 hours, 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post-dose

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 statistics were used to assess this outcome in the cohorts reported.

End point values	All Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: L/h				
median (confidence interval 90%)				
CL/F	42.9 (40.3 to 45.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Pharmacokinetic Parameter of Apparent Volume of Distribution (V/F)

End point title	Pharmacokinetic Parameter of Apparent Volume of Distribution (V/F)[2]

End point description:

A population pharmacokinetic (PK) method was used to estimate apparent volume of distribution (V/F). Due to sparse PK samples being collected, the median PK estimate is reported in all participants at a total of 5 blood samplings.

End point type	Primary

End point timeframe:

0.25 to 1 hours, 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post-dose

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 in the cohorts reported.

End point values	All Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	64			
Units: Liters				
median (confidence interval 90%)				
V/F	198 (180 to 219)			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Parameter Mean Prothrombin Time (PT)

End point title	Pharmacodynamic Parameter Mean Prothrombin Time (PT)

End point description:

Descriptive statistics were used to assess Mean Prothrombin Time (PT) by cohort at a total of 6 blood samplings.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25 to 1 hours (except for Cohorts 4a, 4b, 5a, and 5b, 0.5 to 2 hours), 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post-dose

End point values	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban	Cohort 2b: 45 mg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	6	5[3]
Units: seconds				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hours (n= 6,7,4,4,5,4,4,4,6,5)	13.3 (± 1.1)	13.5 (± 0.5)	14.0 (± 0.4)	13.9 (± 0.5)
Postdose: 0.25 to 1 hours (n= 6,7,4,4,5,4,4,4,6,5)	15.0 (± 1.8)	17.3 (± 4.1)	19.1 (± 3.1)	21.3 (± 7.0)
Predose: 1.5 to 3 hours (n= 7,7,5,5,6,4,1,0,0,0)	13.3 (± 1.0)	13.5 (± 0.5)	14.0 (± 0.4)	14.9 (± 2.2)
Postdose: 1.5 to 3 hours (n= 7,7,5,5,6,4,1,0,0,0)	17.6 (± 2.5)	23.0 (± 3.8)	26.8 (± 14.9)	25.3 (± 5.9)
Predose: 3.5 to 6 hours (n= 6,5,1,0,0,0,0,0,0,0)	13.4 (± 1.1)	13.6 (± 0.6)	13.4 (± 13.4)	0 (± 0)
Postdose: 3.5 to 6 hours (n= 6,5,1,0,0,0,0,0,0,0)	17.9 (± 4.6)	20.1 (± 2.0)	16.5 (± 16.5)	0 (± 0)
Predose: 4 to 8 hours (n= 1,2,3,4,6,4,1,0,0,0)	12.9 (± 12.9)	13.4 (± 0.1)	14.2 (± 0.2)	13.9 (± 0.5)
Postdose: 4 to 8 hours (n= 1,2,3,4,6,4,1,0,0,0)	15.9 (± 15.9)	17.5 (± 2.3)	17.9 (± 1.3)	18.0 (± 2.2)
Predose: 6.5 to 8 hours (n= 6,4,2,0,0,0,0,0,0,0)	13.4 (± 1.1)	13.6 (± 0.7)	13.7 (± 0.4)	0 (± 0)
Postdose: 6.5 to 8 hours (n= 6,4,2,0,0,0,0,0,0,0)	14.7 (± 1.4)	16.7 (± 1.5)	15.8 (± 1.1)	0 (± 0)
Predose: 9 to 14 hours (n= 1,2,3,5,6,4,1,0,0,0)	12.9 (± 12.9)	13.4 (± 0.1)	14.4 (± 0.5)	14.9 (± 2.2)
Postdose: 9 to 14 hours (n= 1,2,3,5,6,4,1,0,0,0)	13.9 (± 13.9)	15.9 (± 1.6)	15.8 (± 1.1)	17.7 (± 5.1)
Predose: 24 to 36 hours (n= 6,7,6,4,6,4,1,0,0,0)	13.4 (± 1.1)	13.5 (± 0.5)	14.2 (± 0.5)	13.9 (± 0.5)
Postdose: 24 to 36 hours (n= 6,7,6,4,6,4,1,0,0,0)	13.1 (± 1.0)	13.8 (± 0.7)	14.5 (± 0.6)	14.5 (± 0.9)

Notes:

[3] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

End point values	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[4]	4[5]	4[6]	4[7]
Units: seconds				
arithmetic mean (standard deviation)				

Predose: 0.25 to 1 hours (n= 6,7,4,4,5,4,4,4,6,5)	14.6 (± 1.3)	13.7 (± 0.5)	13.6 (± 0.7)	13.8 (± 1.6)
Postdose: 0.25 to 1 hours (n= 6,7,4,4,5,4,4,4,6,5)	18.7 (± 2.0)	22.0 (± 0.8)	21.4 (± 2.4)	26.5 (± 7.6)
Predose: 1.5 to 3 hours (n= 7,7,5,5,6,4,1,0,0,0)	14.7 (± 1.3)	13.7 (± 0.5)	14.3 (± 14.3)	0 (± 0)
Postdose: 1.5 to 3 hours (n= 7,7,5,5,6,4,1,0,0,0)	21.0 (± 2.5)	21.3 (± 2.3)	20.0 (± 20.0)	0 (± 0)
Predose: 3.5 to 6 hours (n= 6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Postdose: 3.5 to 6 hours (n= 6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Predose: 4 to 8 hours (n= 1,2,3,4,6,4,1,0,0,0)	14.7 (± 1.3)	13.7 (± 0.5)	14.3 (± 14.3)	0 (± 0)
Postdose: 4 to 8 hours (n= 1,2,3,4,6,4,1,0,0,0)	17.3 (± 0.8)	16.1 (± 2.0)	17.4 (± 17.4)	0 (± 0)
Predose: 6.5 to 8 hours (n= 6,4,2,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Postdose: 6.5 to 8 hours (n= 6,4,2,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Predose: 9 to 14 hours (n= 1,2,3,5,6,4,1,0,0,0)	14.7 (± 1.3)	13.7 (± 0.5)	14.3 (± 14.3)	0 (± 0)
Postdose: 9 to 14 hours (n= 1,2,3,5,6,4,1,0,0,0)	16.1 (± 1.2)	16.0 (± 2.5)	16.7 (± 16.7)	0 (± 0)
Predose: 24 to 36 hours (n= 6,7,6,4,6,4,1,0,0,0)	14.7 (± 1.3)	13.7 (± 0.5)	14.3 (± 14.3)	0 (± 0)
Postdose: 24 to 36 hours (n= 6,7,6,4,6,4,1,0,0,0)	15.5 (± 0.9)	14.9 (± 1.1)	14.1 (± 14.1)	0 (± 0)

Notes:

[4] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[5] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[6] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[7] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

End point values	Cohort 5a: 0.4 mg/kg Edoxaban	Cohort 5b: 0.8 mg/kg Edoxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[8]	5[9]		
Units: seconds				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hours (n= 6,7,4,4,5,4,4,4,6,5)	16.3 (± 4.0)	15.3 (± 1.8)		
Postdose: 0.25 to 1 hours (n= 6,7,4,4,5,4,4,4,6,5)	18.3 (± 3.0)	21.8 (± 4.1)		
Predose: 1.5 to 3 hours (n= 7,7,5,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 1.5 to 3 hours (n= 7,7,5,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 3.5 to 6 hours (n= 6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 3.5 to 6 hours (n= 6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 4 to 8 hours (n= 1,2,3,4,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 4 to 8 hours (n= 1,2,3,4,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 6.5 to 8 hours (n= 6,4,2,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		

Postdose: 6.5 to 8 hours (n= 6,4,2,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 9 to 14 hours (n= 1,2,3,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 9 to 14 hours (n= 1,2,3,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 24 to 36 hours (n= 6,7,6,4,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 24 to 36 hours (n= 6,7,6,4,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		

Notes:

[8] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

[9] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Parameter Mean Activated Partial Thromboplastin Time (aPTT)

End point title	Pharmacodynamic Parameter Mean Activated Partial Thromboplastin Time (aPTT)

End point description:

Descriptive statistics were used to assess Mean Activated Partial Thromboplastin Time by cohort for a total of 6 blood samplings.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25 to 1 hours (except for Cohorts 4a, 4b, 5a, and 5b, 0.5 to 2 hours), 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post-dose

End point values	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban	Cohort 2b: 45 mg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	5	5[10]
Units: seconds				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hours (n=6,7,3,5,4,4,4,4,6,5)	24.1 (± 1.5)	26.0 (± 1.6)	33.9 (± 6.4)	32.7 (± 2.8)
Postdose: 0.25 to 1 hours (n=6,7,5,5,4,4,4,4,6,5)	26.6 (± 2.0)	28.4 (± 4.8)	57.9 (± 26.3)	42.4 (± 9.9)
Predose: 1.5 to 3 hours (n=7,7,5,5,6,4,1,0,0,0)	24.1 (± 1.4)	26.0 (± 1.6)	34.6 (± 5.8)	32.7 (± 2.8)
Postdose: 1.5 to 3 hours (n=7,7,5,5,6,4,1,0,0,0)	27.7 (± 1.1)	32.8 (± 3.0)	62.5 (± 35.7)	43.0 (± 3.9)
Predose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	23.8 (± 1.1)	26.1 (± 1.9)	32.2 (± 32.2)	0 (± 0)
Postdose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	26.9 (± 1.4)	30.8 (± 1.5)	39.0 (± 39.0)	0 (± 0)
Predose: 4 to 8 hours (n=1,2,5,4,6,4,1,0,0,0)	26.2 (± 26.2)	25.5 (± 0.7)	33.9 (± 6.4)	32.8 (± 3.2)
Postdose: 4 to 8 hours (n=1,2,5,4,6,4,1,0,0,0)	24.4 (± 24.2)	28.9 (± 1.0)	35.5 (± 4.9)	38.8 (± 5.7)
Predose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	23.8 (± 1.1)	26.7 (± 1.7)	32.2 (± 32.2)	0 (± 0)

Postdose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	26.4 (± 1.2)	30.2 (± 2.3)	34.5 (± 34.5)	0 (± 0)
Predose: 9 to 14 hours (n=1,2,2,5,6,4,1,0,0,0)	26.2 (± 26.2)	25.5 (± 0.7)	35.8 (± 7.6)	32.7 (± 2.8)
Postdose: 9 to 14 hours (n=1,2,2,5,6,4,1,0,0,0)	23.7 (± 23.7)	27.7 (± 0.3)	35.3 (± 2.8)	35.9 (± 5.7)
Predose: 23 to 36 hours (n=6,7,5,5,5,4,1,0,0,0)	24.4 (± 1.3)	26.0 (± 1.6)	32.0 (± 5.6)	32.7 (± 2.8)
Postdose: 23 to 36 hours (n=6,7,5,5,5,4,1,0,0,0)	24.8 (± 0.9)	25.8 (± 1.9)	29.0 (± 2.2)	38.2 (± 10.7)

Notes:

[10] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

End point values	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[11]	4[12]	4[13]	4[14]
Units: seconds				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hours (n=6,7,3,5,4,4,4,4,6,5)	34.3 (± 4.1)	40.7 (± 21.0)	32.9 (± 5.3)	34.9 (± 8.2)
Postdose: 0.25 to 1 hours (n=6,7,5,5,4,4,4,4,6,5)	39.4 (± 6.4)	45.3 (± 20.1)	45.4 (± 6.3)	46.0 (± 10.9)
Predose: 1.5 to 3 hours (n=7,7,5,5,6,4,1,0,0,0)	30.10 (± 7.2)	40.7 (± 21.0)	37.4 (± 37.4)	0 (± 0)
Postdose: 1.5 to 3 hours (n=7,7,5,5,6,4,1,0,0,0)	38.1 (± 8.9)	45.5 (± 7.9)	40.9 (± 40.9)	0 (± 0)
Predose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Postdose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Predose: 4 to 8 hours (n=1,2,5,4,6,4,1,0,0,0)	30.1 (± 7.2)	40.7 (± 21.0)	37.4 (± 37.4)	0 (± 0)
Postdose: 4 to 8 hours (n=1,2,5,4,6,4,1,0,0,0)	36.7 (± 10.1)	35.7 (± 4.6)	35.8 (± 35.8)	0 (± 0)
Predose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Postdose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Predose: 9 to 14 hours (n=1,2,2,5,6,4,1,0,0,0)	30.1 (± 7.2)	40.7 (± 21.0)	37.4 (± 37.4)	0 (± 0)
Postdose: 9 to 14 hours (n=1,2,2,5,6,4,1,0,0,0)	33.8 (± 7.4)	35.1 (± 7.3)	35.0 (± 35.0)	0 (± 0)
Predose: 23 to 36 hours (n=6,7,5,5,5,4,1,0,0,0)	29.9 (± 8.1)	40.7 (± 21.0)	37.4 (± 37.4)	0 (± 0)
Postdose: 23 to 36 hours (n=6,7,5,5,5,4,1,0,0,0)	32.9 (± 5.2)	86.1 (± 112.6)	32.5 (± 32.5)	0 (± 0)

Notes:

[11] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[12] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[13] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[14] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

End point values	Cohort 5a: 0.4 mg/kg Edoxaban	Cohort 5b: 0.8 mg/kg Edoxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[15]	5[16]		

Units: seconds				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hours (n=6,7,3,5,4,4,4,4,6,5)	41.0 (± 17.9)	47.7 (± 13.0)		
Postdose: 0.25 to 1 hours (n=6,7,5,5,4,4,4,4,6,5)	39.5 (± 3.8)	52.6 (± 18.1)		
Predose: 1.5 to 3 hours (n=7,7,5,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 1.5 to 3 hours (n=7,7,5,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 4 to 8 hours (n=1,2,5,4,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 4 to 8 hours (n=1,2,5,4,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 9 to 14 hours (n=1,2,2,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 9 to 14 hours (n=1,2,2,5,6,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 23 to 36 hours (n=6,7,5,5,5,4,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 23 to 36 hours (n=6,7,5,5,5,4,1,0,0,0)	0 (± 0)	0 (± 0)		

Notes:

[15] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

[16] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacodynamic Parameter Mean Anti-Factor Xa (FXa)

End point title	Pharmacodynamic Parameter Mean Anti-Factor Xa (FXa)

End point description:

Descriptive statistics were used to assess Mean Anti-Factor Xa (FXa) by cohort for a total of 6 blood samplings.

End point type	Secondary

End point timeframe:

Pre-dose and 0.25 to 1 hours (except for Cohorts 4a, 4b, 5a, and 5b, 0.5 to 2 hours), 1.5 to 3 hours, 4 to 8 hours, 9 to 14 hours, and 24 to 36 hours post-dose

End point values	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban	Cohort 2b: 45 mg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	7	5	5[17]
Units: IU/mL				
arithmetic mean (standard deviation)				

Predose: 0.25 to 1 hour (n=6,7,5,5,5,5,4,4,6,5)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)
Postdose: 0.25 to 1 hour (n=6,7,5,5,5,5,4,4,6,5)	0.5 (± 0.4)	1.0 (± 1.0)	1.8 (± 0.3)	1.6 (± 0.8)
Predose: 1.5 to 3 hours (n=7,7,5,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)
Postdose: 1.5 to 3 hours (n=7,7,5,5,6,5,1,0,0,0)	1.3 (± 0.4)	2.6 (± 1.0)	1.3 (± 0.7)	1.9 (± 0.1)
Predose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0.1)	0 (± 0)
Postdose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0.9 (± 0.4)	1.7 (± 0.4)	1.4 (± 1.4)	0 (± 0)
Predose: 4 to 8 hours (n=1,2,3,5,6,5,1,0,0,0)	0.1 (± 0.1)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)
Postdose: 4 to 8 hours (n=1,2,3,5,6,5,1,0,0,0)	1.0 (± 1.0)	1.2 (± 0.7)	0.8 (± 0.3)	1.5 (± 0.3)
Predose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0.1)	0 (± 0)
Postdose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0.4 (± 0.1)	0.9 (± 0.4)	0.8 (± 0.8)	0 (± 0)
Predose: 9 to 14 hours (n=1,2,2,5,6,5,1,0,0,0)	0.1 (± 0.1)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)
Postdose: 9 to 14 hours (n=1,2,2,5,6,5,1,0,0,0)	0.4 (± 0.4)	0.6 (± 0.3)	0.3 (± 0.1)	0.8 (± 0.5)
Predose: 24 to 36 hours (n=6,7,5,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)	0.1 (± 0)
Postdose: 24 to 36 hours (n=6,7,5,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0.1)	0.1 (± 0)	0.2 (± 0.1)

Notes:

[17] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

End point values	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	6[18]	5[19]	4[20]	4[21]
Units: IU/mL				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hour (n=6,7,5,5,5,5,4,4,6,5)	0.1 (± 0)	0.1 (± 0.1)	0.1 (± 0)	0.5 (± 0.3)
Postdose: 0.25 to 1 hour (n=6,7,5,5,5,5,4,4,6,5)	1.2 (± 0.6)	1.9 (± 0.2)	2.0 (± 0)	2.0 (± 0)
Predose: 1.5 to 3 hours (n=7,7,5,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0.1)	0.1 (± 0.1)	0 (± 0)
Postdose: 1.5 to 3 hours (n=7,7,5,5,6,5,1,0,0,0)	1.7 (± 0.3)	1.9 (± 0.2)	2.0 (± 2.0)	0 (± 0)
Predose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Postdose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Predose: 4 to 8 hours (n=1,2,3,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0.1)	0.1 (± 0.1)	0 (± 0)
Postdose: 4 to 8 hours (n=1,2,3,5,6,5,1,0,0,0)	0.7 (± 0.2)	0.8 (± 0.6)	1.2 (± 1.2)	0 (± 0)
Predose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Postdose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)	0 (± 0)	0 (± 0)
Predose: 9 to 14 hours (n=1,2,2,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0.1)	0.1 (± 0.1)	0 (± 0)

Postdose: 9 to 14 hours (n=1,2,2,5,6,5,1,0,0,0)	0.2 (± 0.1)	0.4 (± 0.2)	0.3 (± 0.3)	0 (± 0)
Predose: 24 to 36 hours (n=6,7,5,5,6,5,1,0,0,0)	0.1 (± 0)	0.1 (± 0.1)	0.1 (± 0.1)	0 (± 0)
Postdose: 24 to 36 hours (n=6,7,5,5,6,5,1,0,0,0)	0.3 (± 0.5)	0.4 (± 0.7)	0.1 (± 0.1)	0 (± 0)

Notes:

[18] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[19] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[20] - No subjects were analyzed at Predose and Postdose at 3.5 to 6 hours and at 6.5 to 8 hours.

[21] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

End point values	Cohort 5a: 0.4 mg/kg Edoxaban	Cohort 5b: 0.8 mg/kg Edoxaban		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6[22]	5[23]		
Units: IU/mL				
arithmetic mean (standard deviation)				
Predose: 0.25 to 1 hour (n=6,7,5,5,5,5,4,4,6,5)	0.1 (± 0.1)	0.4 (± 0.4)		
Postdose: 0.25 to 1 hour (n=6,7,5,5,5,5,4,4,6,5)	1.1 (± 0.8)	1.7 (± 0.7)		
Predose: 1.5 to 3 hours (n=7,7,5,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 1.5 to 3 hours (n=7,7,5,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 3.5 to 6 hours (n=6,5,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 4 to 8 hours (n=1,2,3,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 4 to 8 hours (n=1,2,3,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 6.5 to 8 hours (n=6,4,1,0,0,0,0,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 9 to 14 hours (n=1,2,2,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 9 to 14 hours (n=1,2,2,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Predose: 24 to 36 hours (n=6,7,5,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		
Postdose: 24 to 36 hours (n=6,7,5,5,6,5,1,0,0,0)	0 (± 0)	0 (± 0)		

Notes:

[22] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

[23] - No subjects were analyzed beyond Predose and Postdose at 0.25 to 1 hour.

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Palatability Score for the Liquid Formulation on a 100 mm Visual Analog Scale (VAS)

End point title	Mean Palatability Score for the Liquid Formulation on a 100 mm Visual Analog Scale (VAS)[24]

End point description:

Bitterness, sweetness, and overall taste or aroma was assessed by participants (or guardians) receiving the liquid oral suspension using a 100 mm visual analog scale (VAS), where 0 corresponded to a sad face and indicated a low palatability score (eg, patients not pleased) and 100 corresponded to a happy face and indicated a high palatability score (eg, patients were pleased). Patients who were old enough scored the VAS themselves. For younger children, the parents provided this information, if possible. For the youngest children, there was free text input available to provide information on whether the patient spat it out or may not have liked the flavor, etc.

End point type	Other pre-specified

End point timeframe:

Baseline up to 30 minutes post-dose

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Descriptive statistics were used to assess this outcome in the cohorts reported.

End point values	Cohort 2a: 24 mg Edoxaban	Cohort 2b: 45 mg Edoxaban	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	7	6
Units: mm				
arithmetic mean (standard deviation)				
Overall palatability (n=7,6,7,6,6,6,6,6)	53.6 (± 35.8)	63.2 (± 48.9)	55.3 (± 40.6)	83.3 (± 20.4)
Bitterness (n=7,5,7,6,6,6,6,6)	66.1 (± 44.5)	53.2 (± 46.3)	40.6 (± 43.5)	66.7 (± 37.6)
Sweetness (n=7,6,7,6,5,6,6,6)	39.1 (± 34.9)	54.3 (± 36.9)	65.9 (± 42.1)	81.7 (± 21.6)
Overall taste (n=7,5,7,6,6,6,6,6)	57.9 (± 42.3)	78.2 (± 43.2)	62.6 (± 44.9)	83.3 (± 25.8)
Aroma (n=7,6,7,6,6,6,6,6)	53.4 (± 38.4)	57.7 (± 34.0)	58.7 (± 39.5)	75.0 (± 27.4)

End point values	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban	Cohort 5a: 0.4 mg/kg Edoxaban	Cohort 5b: 0.8 mg/kg Edoxaban
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	7	6	6	6
Units: mm				
arithmetic mean (standard deviation)				
Overall palatability (n=7,6,7,6,6,6,6,6)	77.3 (± 27.7)	73.0 (± 22.9)	67.3 (± 18.4)	83.2 (± 14.1)
Bitterness (n=7,5,7,6,6,6,6,6)	77.5 (± 27.2)	36.3 (± 41.2)	47.0 (± 32.6)	65.7 (± 36.8)
Sweetness (n=7,6,7,6,5,6,6,6)	86.2 (± 26.1)	76.2 (± 20.2)	68.5 (± 19.0)	86.0 (± 13.3)
Overall taste (n=7,5,7,6,6,6,6,6)	82.8 (± 24.3)	80.5 (± 10.0)	70.8 (± 17.0)	85.2 (± 11.2)
Aroma (n=7,6,7,6,6,6,6,6)	84.5 (± 23.9)	72.3 (± 19.7)	73.2 (± 13.9)	74.2 (± 23.3)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected after the participant (or parent/guardian) signed the informed consent form and through the follow-up visit, up to 10 days after the single dose of edoxaban.

Adverse event reporting additional description:

A TEAE is defined as an adverse event that emerges during treatment, having been absent pretreatment, or worsening relative to the pretreatment state.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Cohort 1a: 30 mg Edoxaban

Reporting group description:

Participants who were 12 to < 18 years of age and received a single-dose, oral tablet of 30 mg edoxaban.

Reporting group title	Cohort 1b: 60 mg Edoxaban

Reporting group description:

Participants who were 12 to < 18 years of age and received a single dose, oral tablet of 60 mg edoxaban.

Reporting group title	Cohort 2a: 24 mg Edoxaban

Reporting group description:

Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 24 mg edoxaban.

Reporting group title	Cohort 2b: 45 mg Edoxaban

Reporting group description:

Participants who were 6 to < 12 years of age and received a single dose, oral suspension of 45 mg edoxaban.

Reporting group title	Cohort 3a: 0.7 mg/kg Edoxaban

Reporting group description:

Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 0.7 mg/kg (cap 24 mg) edoxaban.

Reporting group title	Cohort 3b: 1.4 mg/kg Edoxaban

Reporting group description:

Participants who were 2 to < 6 years of age and received a single dose, oral suspension of 1.4 mg/kg (cap 45 mg) edoxaban.

Reporting group title	Cohort 4a: 0.75 mg/kg Edoxaban

Reporting group description:

Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 0.75 mg/kg edoxaban.

Reporting group title	Cohort 4b: 1.5 mg/kg Edoxaban

Reporting group description:

Participants who were 6 months to <2 years of age and received a single dose, oral suspension of 1.5 mg/kg edoxaban.

Reporting group title	Cohort 5a: 0.4 mg/kg Edoxaban

Reporting group description:

Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.4 mg/kg edoxaban.

Reporting group title	Cohort 5b: 0.8 mg/kg Edoxaban

Reporting group description:

Participants who were 0 to 6 months of age and received a single dose, oral suspension of 0.8 mg/kg

Serious adverse events	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 2b: 45 mg Edoxaban	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban	Cohort 5a: 0.4 mg/kg Edoxaban
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	Cohort 5b: 0.8 mg/kg Edoxaban		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Cohort 1a: 30 mg Edoxaban	Cohort 1b: 60 mg Edoxaban	Cohort 2a: 24 mg Edoxaban
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	2 / 7 (28.57%)	4 / 7 (57.14%)

Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Psychomotor hyperactivity			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 8 (12.50%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	1	1	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	1 / 8 (12.50%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	1	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	1 / 7 (14.29%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 8 (0.00%)	1 / 7 (14.29%)	0 / 7 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 8 (0.00%)	0 / 7 (0.00%)	0 / 7 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 2b: 45 mg Edoxaban	Cohort 3a: 0.7 mg/kg Edoxaban	Cohort 3b: 1.4 mg/kg Edoxaban
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 6 (33.33%)	1 / 7 (14.29%)	0 / 6 (0.00%)
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			

Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Psychomotor hyperactivity			
subjects affected / exposed	0 / 6 (0.00%)	1 / 7 (14.29%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			

Petechiae			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 7 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Cohort 4a: 0.75 mg/kg Edoxaban	Cohort 4b: 1.5 mg/kg Edoxaban	Cohort 5a: 0.4 mg/kg Edoxaban
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 7 (42.86%)	1 / 6 (16.67%)	0 / 6 (0.00%)
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Prothrombin time prolonged			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Psychomotor hyperactivity			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Frequent bowel movements			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 7 (28.57%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Rash			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			

Musculoskeletal chest pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			
subjects affected / exposed	0 / 7 (0.00%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Cohort 5b: 0.8 mg/kg Edoxaban		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)		
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Prothrombin time prolonged			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Psychomotor hyperactivity			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		

Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Frequent bowel movements			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Haematochezia			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Musculoskeletal pain			
subjects affected / exposed	0 / 6 (0.00%)		
occurrences (all)	0		
Infections and infestations			

Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2014	Changed the doses of study drug, clarified the drug formulation that patients <12 years of age would receive, provided a definition of a completer, added a palatability assessment, and clarified the time period in which AEs would be assessed.
21 January 2015	Clarified language for patient eligibility, updated inclusion criteria, and specified patient fasting requirements.
03 November 2015	Updated and further clarified eligibility criteria.
14 July 2016	Added a fifth cohort and increased sample size, revised PK/PD time points and clarified blood collection methods, and updated the study visit schedule.
08 August 2018	Updated the eligibility criteria, revised the PK/PD schedules, and revised the study endpoints.
16 September 2019	Updated requirements for enrollment initiation of Cohort 5 and revised and updated exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported