Clinical trial results:
A Prospective, Randomized, Open Label, Multi-center Study of the Safety and Pharmacokinetics of Apixaban versus Vitamin K Antagonist or LMWH in Pediatric Subjects with Congenital or Acquired Heart Disease Requiring Chronic Anticoagulation for Thromboembolism Prevention

Summary

EudraCT number	2016-001247-39
Trial protocol	DE GB IT FI AT ES
Global end of trial date	18 October 2021

Results information

Result version number	v1 (current)
This version publication date	25 April 2022
First version publication date	25 April 2022

Trial information

Trial identification

Sponsor protocol code	CV185-362

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02981472
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000183-PIP01-08
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	15 November 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of apixaban, compared to VKA or subcutaneous LMWH and to evaluate apixaban PK in pediatric subjects with congenital or acquired heart disease requiring chronic anticoagulation for thromboprophylaxis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 January 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	Australia: 21
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Finland: 6
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Mexico: 16
Country: Number of subjects enrolled	Russian Federation: 2
Country: Number of subjects enrolled	United Kingdom: 13
Country: Number of subjects enrolled	United States: 70
Worldwide total number of subjects	192
EEA total number of subjects	53

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)	11
Children (2-11 years)	134
Adolescents (12-17 years)	47
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

192 participants were randomized and 188 were treated for up to 12 months or until anticoagulation is no longer needed, whichever is shorter

Period 1

Period 1 title	Pre-treatment Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Apixaban

Arm description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants weighing between >/= 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2mg and 4 mg depending on body weight. Children randomized to the apixaban arm of the study weighing >/= 35 kg will be administered apixaban 5 mg twice daily (BID).

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	BMS-562247-01
Pharmaceutical forms	Capsule, Film-coated tablet, Oral solution
Routes of administration	Oral use, Nasogastric use , Gastric use

Dosage and administration details:

Children between 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2 mg and 4 mg depending on body weight with the 0.1 capsules, 0.5 mg mini-tablets, or oral solution. Children randomized to the apixaban arm of the study weighing >/=35 kg will be administered apixaban 5 mg twice daily (BID) as a tablet or solution.

Arm title	LMWH/VKA

Arm description:

Participants receive thromboprophylaxis with Vitamin K Antagonists (VKA) or Low Molecular Weight Heparin (LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants who receive LMWH are allowed to switch to VKA at any time during the study; conversely, participants having difficulty with VKA may switch to LMWH.

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

Dosage and administration details:

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL.

Investigational medicinal product name	Enoxaparin sodium (Clexane)
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL.

Investigational medicinal product name	Enoxaparin sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL.

Number of subjects in period 1	Apixaban	LMWH/VKA
Started	129	63
Completed	126	62
Not completed	3	1
Participant withdrew consent	2	1
Participant no longer meets study criteria	1	-

Period 2

Period 2 title	Treatment Period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Apixaban

Arm description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants weighing between >/= 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2mg and 4 mg depending on body weight. Children randomized to the apixaban arm of the study weighing >/= 35 kg will be administered apixaban 5 mg twice daily (BID).

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	BMS-562247-01
Pharmaceutical forms	Capsule, Film-coated tablet, Oral solution
Routes of administration	Oral use, Nasogastric use , Gastric use

Dosage and administration details:

Children between 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2 mg and 4 mg depending on body weight with the 0.1 capsules, 0.5 mg mini-tablets, or oral solution. Children randomized to the apixaban arm of the study weighing >/=35 kg will be administered apixaban 5 mg twice daily (BID) as a tablet or solution.

Arm title	LMWH/VKA

Arm description:

Participants receive thromboprophylaxis with Vitamin K Antagonists (VKA) or Low Molecular Weight Heparin (LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants who receive LMWH are allowed to switch to VKA at any time during the study; conversely, participants having difficulty with VKA may switch to LMWH.

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

Dosage and administration details:

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. . The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL.

Investigational medicinal product name	Enoxaparin sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. . The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL.

Investigational medicinal product name	Enoxaparin sodium (Clexane)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Use of VKA or LMWH will follow the local standard of care that is aligned with the ACCP guidelines. . The dose of VKA is recommended to be titrated to achieve a target international normalized ratio (INR) of 2.0 to 3.0, and the dose of LMWH is recommended to target an anti-Xa level between 0.5 and 1.0 units/mL.

Number of subjects in period 2	Apixaban	LMWH/VKA
Started	126	62
Completed	119	60
Not completed	7	2
Participant withdrew consent	1	-
Adverse event	6	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Apixaban
Reporting group description:	
Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants weighing between >/= 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2mg and 4 mg depending on body weight. Children randomized to the apixaban arm of the study weighing >/= 35 kg will be administered apixaban 5 mg twice daily (BID).	
Reporting group title	LMWH/VKA
Reporting group description:	
Participants receive thromboprophylaxis with Vitamin K Antagonists (VKA) or Low Molecular Weight Heparin (LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants who receive LMWH are allowed to switch to VKA at any time during the study; conversely, participants having difficulty with VKA may switch to LMWH.	

Reporting group values	Apixaban	LMWH/VKA	Total
Number of subjects	129	63	192
Age Categorical Units: Participants			
28 DAYS - < 2 YEARS	8	3	11
2 YEARS - < 6 YEARS	40	22	62
6 YEARS - < 12 YEARS	49	23	72
12 YEARS - < 18 YEARS	32	15	47
Age Continuous Units: Years			
arithmetic mean	7.96	7.56	
standard deviation	± 4.553	± 4.408	-
Sex: Female, Male Units: Participants			
Female	67	23	90
Male	62	40	102
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	6	4	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	2	9
White	109	51	160
More than one race	0	0	0
Unknown or Not Reported	6	6	12
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	20	14	34
Not Hispanic or Latino	105	47	152
Unknown or Not Reported	4	2	6

End points

End points reporting groups

Reporting group title	Apixaban

Reporting group description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants weighing between >/= 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2mg and 4 mg depending on body weight. Children randomized to the apixaban arm of the study weighing >/= 35 kg will be administered apixaban 5 mg twice daily (BID).

Reporting group title	LMWH/VKA

Reporting group description:

Participants receive thromboprophylaxis with Vitamin K Antagonists (VKA) or Low Molecular Weight Heparin (LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants who receive LMWH are allowed to switch to VKA at any time during the study; conversely, participants having difficulty with VKA may switch to LMWH.

Reporting group title	Apixaban

Reporting group description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants weighing between >/= 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2mg and 4 mg depending on body weight. Children randomized to the apixaban arm of the study weighing >/= 35 kg will be administered apixaban 5 mg twice daily (BID).

Reporting group title	LMWH/VKA

Reporting group description:

Participants receive thromboprophylaxis with Vitamin K Antagonists (VKA) or Low Molecular Weight Heparin (LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants who receive LMWH are allowed to switch to VKA at any time during the study; conversely, participants having difficulty with VKA may switch to LMWH.

Subject analysis set title	Participants Weight Range 6 to < 9 kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first.

Participants weighing between 6 to < 9 kg will be administered 1mg apixaban twice daily (BID).

Subject analysis set title	Participants Weight Range 9 to < 12 kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first.

Participants weighing between 9 to < 12 kg will be administered 1.5mg apixaban twice daily (BID).

Subject analysis set title	Participants Weight Range 12 to < 18 kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first.

Participants weighing between 12 to < 18 kg will be administered 2mg apixaban twice daily (BID).

Subject analysis set title	Participants Weight Range 18 to < 25 kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first.

Participants weighing between 18 to < 25 kg will be administered 3mg apixaban twice daily (BID).

Subject analysis set title	Participants Weight Range 25 to < 35 kg

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first.

Participants weighing between 25 to < 35 kg will be administered 4mg apixaban twice daily (BID).

Subject analysis set title	Participants Weight Range ≥ 35 kg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first.

Participants weighing between ≥ 35 kg will be administered 5mg apixaban twice daily (BID).

Primary: Composite of Adjudicated Major or Clinically Relevant Non-Major (CRNM) Bleeding Events

End point title	Composite of Adjudicated Major or Clinically Relevant Non-Major (CRNM) Bleeding Events[1]

End point description:

The number of participants with adjudicated major or CRNM bleeding events per the Perinatal and Paediatric Haemostasis Subcommittee of International Society on Thrombosis and Haemostasis (ISTH) criteria. Events are adjudicated by a blinded, independent events adjudication committee (EAC).

Major bleeding satisfies one or more of the following criteria: fatal bleeding, clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (i.e., 2 g/dL) in a 24-hour period, bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS, or bleeding that requires surgical intervention in an operating suite, including interventional radiology.
CRNM bleeding satisfies one or both of the following criteria: overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition or bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room.

End point type	Primary

End point timeframe:

From first dose to 2 days after last dose (Up to approximately 12 months)

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: Only summary statistics planned for this endpoint

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Participants	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Thrombotic Events and Thromboembolic Event-Related Death

End point title	The Number of Participants with Thrombotic Events and Thromboembolic Event-Related Death

End point description:

The number of participants with thromboembolic events (intra-cardiac, shunt, inside Fontan pathway, pulmonary embolism (PE), stroke, other arterial or venous thromboembolic events, etc.) and thromboembolic event-related death detected by imaging or clinical diagnosis.

Death and thromboembolic events are adjudicated by a blinded, independent events adjudication committee (EAC)

End point type	Secondary

End point timeframe:

From randomization to 2 days after last dose (Up to approximately 12 months)

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	63		
Units: Participants				
Thromboembolic events	0	0		
Thromboembolic event-related death	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Adjudicated Major Bleeding

End point title	The Number of Participants with Adjudicated Major Bleeding

End point description:

The number of participants with adjudicated major bleeding events per the Perinatal and Paediatric Haemostasis Subcommittee of International Society on Thrombosis and Haemostasis (ISTH) criteria. Major bleeding events are adjudicated by a blinded, independent events adjudication committee (EAC).

Major bleeding is defined as bleeding that satisfies one or more of the following criteria:
-fatal bleeding
-clinically overt bleeding associated with a decrease in hemoglobin of at least 20 g/L (i.e., 2 g/dL) in a 24-hour period
-bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS
-bleeding that requires surgical intervention in an operating suite, including interventional radiology

End point type	Secondary

End point timeframe:

From first dose to 2 days after last dose (Up to approximately 12 months)

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Participants	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with All Adjudicated Bleeding

End point title	The Number of Participants with All Adjudicated Bleeding

End point description:

The number of participants with all adjudicated bleeding events

End point type	Secondary

End point timeframe:

From first dose to 2 days after last dose (Up to approximately 12 months)

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Participants	47	23		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Adjudicated CRNM bleeding

End point title	The Number of Participants with Adjudicated CRNM bleeding

End point description:

The number of participants with adjudicated clinically relevant non-major (CRNM) bleeding events per the Perinatal and Paediatric Haemostasis Subcommittee of International Society on Thrombosis and Haemostasis (ISTH) criteria. CRNM bleeding events are adjudicated by a blinded, independent events adjudication committee (EAC).

CRNM bleeding is defined as bleeding that satisfies one or both of the following criteria:
-overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition
-bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room

End point type	Secondary

End point timeframe:

From first dose to 2 days after last dose (Up to approximately 12 months)

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Participants	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Drug Discontinuation Due to Adverse Effects, Intolerability, or Bleeding

End point title	The Number of Participants with Drug Discontinuation Due to Adverse Effects, Intolerability, or Bleeding

End point description:

The number of participants with drug discontinuation due to adverse effects, intolerability, or bleeding.

End point type	Secondary

End point timeframe:

From first dose to 2 days after last dose (Up to approximately 12 months)

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Participants	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-FXa Activity

End point title	Anti-FXa Activity

End point description:

Anti-FXa Activity was measured to assess participant plasma apixaban levels.

End point type	Secondary

End point timeframe:

From first dose up to 6 months after first dose

End point values	Apixaban			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: ng/mL				
arithmetic mean (standard error)				
Day 1 (4 HRS POSTDOSE)	147.69 (± 7.243)			
Week 2 (PREDOSE)	86.24 (± 7.652)			
Week 2 (2 HRS POSTDOSE)	242.34 (± 18.966)			
Month 3 (2 HRS POSTDOSE)	228.88 (± 14.263)			
Month 6 (PREDOSE)	66.93 (± 6.532)			

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participant Deaths in the Study

End point title	The Number of Participant Deaths in the Study

End point description:

The number of participant deaths in the study.

End point type	Secondary

End point timeframe:

From first dose to 2 days after last dose (Up to approximately 12 months)

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	126	62		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Chromogenic FX Assay (apparent FX level)

End point title	Chromogenic FX Assay (apparent FX level)

End point description:

Chromogenic FX was measured to assess (apparent) FX levels in participants and inhibition of FXa by apixaban.

End point type	Secondary

End point timeframe:

From first dose up to 6 months after first dose

End point values	Apixaban			
Subject group type	Reporting group			
Number of subjects analysed	125			
Units: Percent				
arithmetic mean (standard error)				
Day 1 (PREDOSE)	58.87 (± 2.368)			

Day 1 (4 HRS POSTDOSE)	18.90 (± 1.205)			
Week 2 (PREDOSE)	35.88 (± 1.973)			
Week 2 (2 HRS POSTDOSE)	21.26 (± 1.680)			
Month 3 (2 HRS POSTDOSE)	18.25 (± 0.970)			
Month 6 (PREDOSE)	36.57 (± 1.943)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax)

End point title	Maximum Observed Concentration (Cmax)

End point description:

Maximum observed concentration (Cmax) was measured to assess the pharmacokinetics of apixaban

End point type	Secondary

End point timeframe:

From first dose up to 6 months after first dose

End point values	Participants Weight Range 6 to < 9 kg	Participants Weight Range 9 to < 12 kg	Participants Weight Range 12 to < 18 kg	Participants Weight Range 18 to < 25 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	28	29
Units: ng/mL				
geometric mean (geometric coefficient of variation)	185 (± 48.8)	218 (± 23.4)	222 (± 39.6)	244 (± 30.7)

End point values	Participants Weight Range 25 to < 35 kg	Participants Weight Range ≥ 35 kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	35		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	249 (± 37.7)	203 (± 35.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Observed Concentration (Cmin)

End point title	Trough Observed Concentration (Cmin)

End point description:

Trough observed concentration (Cmin) was measured to assess the pharmacokinetics of apixaban

End point type	Secondary

End point timeframe:

From first dose up to 6 months after first dose

End point values	Participants Weight Range 6 to < 9 kg	Participants Weight Range 9 to < 12 kg	Participants Weight Range 12 to < 18 kg	Participants Weight Range 18 to < 25 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	28	29
Units: ng/mL				
geometric mean (geometric coefficient of variation)	57.9 (± 90.3)	82.7 (± 21.5)	64.3 (± 69.5)	67.4 (± 58.9)

End point values	Participants Weight Range 25 to < 35 kg	Participants Weight Range ≥ 35 kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	35		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	73.1 (± 64.7)	72.7 (± 46.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve in One Dosing Interval (AUC (TAU))

End point title	Area Under the Concentration-Time Curve in One Dosing Interval (AUC (TAU))

End point description:

Area under the concentration-time curve in one dosing interval (AUC (TAU)) was measured to assess the pharmacokinetics of apixaban

End point type	Secondary

End point timeframe:

From first dose up to 6 months after first dose

End point values	Participants Weight Range 6 to < 9 kg	Participants Weight Range 9 to < 12 kg	Participants Weight Range 12 to < 18 kg	Participants Weight Range 18 to < 25 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	28	29
Units: ng • h/mL				
geometric mean (geometric coefficient of variation)	1460 (± 61.2)	1840 (± 20.7)	1610 (± 49.6)	1760 (± 38.3)

End point values	Participants Weight Range 25 to < 35 kg	Participants Weight Range ≥ 35 kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	35		
Units: ng • h/mL				
geometric mean (geometric coefficient of variation)	1840 (± 43.3)	1630 (± 37.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time of Maximum Observed Concentration (Tmax)

End point title	Time of Maximum Observed Concentration (Tmax)

End point description:

Time of maximum observed concentration (Tmax) was measured to assess the pharmacokinetics of apixaban

End point type	Secondary

End point timeframe:

From first dose up to 6 months after first dose

End point values	Participants Weight Range 6 to < 9 kg	Participants Weight Range 9 to < 12 kg	Participants Weight Range 12 to < 18 kg	Participants Weight Range 18 to < 25 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	6	2	28	29
Units: hours				
median (full range (min-max))	2.24 (1.41 to 2.83)	2.47 (2.23 to 2.71)	1.72 (0.938 to 3.35)	1.74 (0.775 to 2.18)

End point values	Participants Weight Range 25 to < 35 kg	Participants Weight Range ≥ 35 kg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	24	35		

Units: hours				
median (full range (min-max))	1.65 (1.26 to 2.85)	1.85 (1.47 to 2.93)		

Statistical analyses

No statistical analyses for this end point

Secondary: The Child and Parent Reports of Pediatric Quality of Life Inventory (PedsQL)

End point title	The Child and Parent Reports of Pediatric Quality of Life Inventory (PedsQL)

End point description:

Subjects' quality of life was measured using the PedsQL instrument administered only to English-speaking children/parents. Only subjects who completed the questionnaires at both baseline and post-baseline visits were included in the analyses.

PedsQL consists of 23 items scored on a 5-point Likert scale from 0 (never) to 4 (almost always) or for the child report for younger children ages 5-7, a 3-point Likert scale: 0 (Not at all), 2 (Sometimes), and 4 (A lot).

Scores are reverse scored and transformed to a 0-100 scale as follows: 0=100, 1=75, 3=25, 4=0. Higher scores indicate a better HRQOL and/or lower problems.

End point type	Secondary

End point timeframe:

from randomization up to 12 months after randomization

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	129	63		
Units: Score on a scale				
arithmetic mean (standard deviation)				
GENERAL-SPECIFIC MODULE BY CHILD - BASELINE	69.64 (± 15.512)	60.71 (± 17.374)		
GENERAL-SPECIFIC MODULE BY CHILD - MONTH 12	73.37 (± 19.998)	64.81 (± 22.327)		
GENERAL-SPECIFIC MODULE BY PARENT - BASELINE	65.61 (± 16.625)	65.42 (± 18.000)		
GENERAL-SPECIFIC MODULE BY PARENT - MONTH 12	70.00 (± 19.560)	70.32 (± 21.949)		
HEART PROBLEMS AND TREATMENT BY CHILD - BASELINE	65.34 (± 22.130)	64.70 (± 18.465)		
HEART PROBLEMS AND TREATMENT BY CHILD - MONTH 12	69.46 (± 21.119)	63.44 (± 19.836)		
TREATMENT II BY CHILD - BASELINE	87.39 (± 22.994)	85.68 (± 15.857)		
TREATMENT II BY CHILD - MONTH 12	91.77 (± 10.896)	86.27 (± 16.400)		
PERCEIVED PHYSICAL APPEARANCE BY CHILD - BASELINE	75.51 (± 27.477)	78.44 (± 23.390)		
PERCEIVED PHYSICAL APPEARANCE BY CHILD - MONTH 12	80.56 (± 22.408)	81.37 (± 30.689)		

TREATMENT ANXIETY BY CHILD - BASELINE	80.52 (± 23.420)	60.31 (± 34.162)		
TREATMENT ANXIETY BY CHILD - MONTH 12	80.71 (± 25.480)	60.31 (± 38.333)		
COGNITIVE PROBLEMS BY CHILD - BASELINE	69.85 (± 20.871)	53.24 (± 20.382)		
COGNITIVE PROBLEMS BY CHILD - MONTH 12	68.24 (± 24.367)	53.53 (± 26.796)		
COMMUNICATION BY CHILD - BASELINE	66.15 (± 30.000)	63.55 (± 28.998)		
COMMUNICATION BY CHILD - MONTH 12	70.31 (± 26.681)	57.28 (± 38.948)		
HEART PROBLEMS AND TREATMENT BY PARENT - BASELINE	63.68 (± 20.727)	67.71 (± 22.668)		
HEART PROBLEMS AND TREATMENT BY PARENT - MONTH 12	66.37 (± 20.811)	69.00 (± 23.688)		
TREATMENT II BY PARENT - BASELINE	91.41 (± 11.557)	85.27 (± 17.325)		
TREATMENT II BY PARENT - MONTH 12	90.30 (± 12.381)	83.80 (± 18.915)		
PERCEIVED PHYSICAL APPEARANCE BY PARENT - BASELINE	79.16 (± 22.571)	79.66 (± 22.958)		
PERCEIVED PHYSICAL APPEARANCE BY PARENT - MONTH 12	79.38 (± 21.012)	74.33 (± 26.998)		
TREATMENT ANXIETY BY PARENT - BASELINE	61.44 (± 30.804)	56.27 (± 33.997)		
TREATMENT ANXIETY BY PARENT - MONTH 12	64.03 (± 29.567)	57.77 (± 34.199)		
COGNITIVE PROBLEMS BY PARENT - BASELINE	60.29 (± 29.558)	61.60 (± 25.807)		
COGNITIVE PROBLEMS BY PARENT - MONTH 12	58.69 (± 29.560)	58.53 (± 33.432)		
COMMUNICATION BY PARENT - BASELINE	65.57 (± 27.342)	67.33 (± 28.257)		
COMMUNICATION BY PARENT - MONTH 12	68.20 (± 24.037)	66.17 (± 28.067)		

Statistical analyses

No statistical analyses for this end point

Secondary: Kids Informed Decrease Complications Learning on Thrombosis (KIDCLOT) IMPACT Score

End point title	Kids Informed Decrease Complications Learning on Thrombosis (KIDCLOT) IMPACT Score

End point description:

Subjects' quality of life was measured using the KIDCLOT instrument administered only to English-speaking children/parents. Only subjects who completed the questionnaires at both baseline and post-baseline visits were included in the analyses.

KIDCLOT Parent inventory uses a 5 point Likert scale from 1 (N/A), 2 (Never), 3 (Rarely), 4 (Now and then), 5 (Often). Child inventory uses a 4 point Likert scale 1 (N/A), 2 (Never), 3 (Now and then), 5 (Always). Values are scores as follows 1=0, 2=1, 3=2, 4=3, 5=4. Score interpretation is 0 to 100 percent IMPACT of anticoagulation on a child's life therefore, higher scores indicates a more negative effect.

End point type	Secondary

End point timeframe:

from randomization up to 12 months after randomization

End point values	Apixaban	LMWH/VKA		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	30		
Units: Score on a scale				
arithmetic mean (standard deviation)				
BASELINE CHILD REPORTED - 6 MONTHS	24.35 (± 12.887)	26.45 (± 12.114)		
POST BASELINE CHILD REPORTED - 6 MONTHS	22.81 (± 13.380)	22.57 (± 16.049)		
BASELINE CHILD REPORTED - 12 MONTHS	22.50 (± 11.787)	25.32 (± 11.719)		
POST BASELINE CHILD REPORTED - 12 MONTHS	21.52 (± 13.251)	18.01 (± 10.408)		
BASELINE PARENT REPORTED - 6 MONTHS	37.97 (± 20.493)	39.02 (± 17.932)		
POST BASELINE PARENT REPORTED - 6 MONTHS	32.32 (± 17.060)	37.94 (± 20.626)		
BASELINE PARENT REPORTED - 12 MONTHS	38.37 (± 18.874)	39.36 (± 16.057)		
POST BASELINE PARENT REPORTED - 12 MONTHS	31.10 (± 16.021)	33.61 (± 17.943)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs collected from first dose to last dose + 2 days/ SAEs collected from first dose until last dose date + 30 days (Up to approximately 13 months) All Cause Mortality was assessed from first dose to study completion (up to approximately 57 months)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	VKA/LMWH

Reporting group description:

Participants receive thromboprophylaxis with Vitamin K Antagonists (VKA) or Low Molecular Weight Heparin (LMWH) for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants who receive LMWH are allowed to switch to VKA at any time during the study; conversely, participants having difficulty with VKA may switch to LMWH.

Reporting group title	APIXABAN

Reporting group description:

Participants receive thromboprophylaxis with open-label apixaban for up to 12 months or until the need for anticoagulant is resolved, whichever occurs first. Participants weighing between >/= 3 and < 35 kg will be administered apixaban twice daily (BID) in doses between 0.2mg and 4 mg depending on body weight. Children randomized to the apixaban arm of the study weighing >/= 35 kg will be administered apixaban 5 mg twice daily (BID).

Serious adverse events	VKA/LMWH	APIXABAN	
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 62 (20.97%)	26 / 126 (20.63%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Generalised oedema			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
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			
Penile haematoma			

subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
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 / 62 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax spontaneous			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
International normalised ratio increased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracardiac pressure increased			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary arterial pressure increased			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 62 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect dose administered			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			

subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 62 (0.00%)	2 / 126 (1.59%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
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			
Congenital cystic kidney disease			

subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoplastic left heart syndrome			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	1 / 62 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial septal defect acquired			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac dysfunction			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			

subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gingival bleeding			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Protein-losing gastroenteropathy			
subjects affected / exposed	1 / 62 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (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			
COVID-19			
subjects affected / exposed	1 / 62 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dengue fever			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 62 (1.61%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia viral			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 62 (0.00%)	1 / 126 (0.79%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 62 (1.61%)	0 / 126 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	VKA/LMWH	APIXABAN	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 62 (83.87%)	101 / 126 (80.16%)	
Investigations			
International normalised ratio increased			
subjects affected / exposed	4 / 62 (6.45%)	0 / 126 (0.00%)	
occurrences (all)	4	0	
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	5 / 62 (8.06%)	9 / 126 (7.14%)	
occurrences (all)	5	15	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 62 (1.61%)	8 / 126 (6.35%)	
occurrences (all)	1	8	
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 62 (6.45%)	4 / 126 (3.17%)	
occurrences (all)	6	6	
Headache			
subjects affected / exposed	3 / 62 (4.84%)	19 / 126 (15.08%)	
occurrences (all)	3	34	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	8 / 62 (12.90%)	20 / 126 (15.87%)	
occurrences (all)	12	27	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 62 (6.45%)	12 / 126 (9.52%)	
occurrences (all)	7	17	
Vomiting			
subjects affected / exposed	9 / 62 (14.52%)	20 / 126 (15.87%)	
occurrences (all)	14	39	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	4 / 62 (6.45%)	8 / 126 (6.35%)	
occurrences (all)	4	12	
Epistaxis			
subjects affected / exposed	6 / 62 (9.68%)	20 / 126 (15.87%)	
occurrences (all)	10	38	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	4 / 62 (6.45%)	7 / 126 (5.56%)	
occurrences (all)	4	8	
Upper respiratory tract infection			

subjects affected / exposed	4 / 62 (6.45%)	14 / 126 (11.11%)	
occurrences (all)	5	26	
Nasopharyngitis			
subjects affected / exposed	8 / 62 (12.90%)	13 / 126 (10.32%)	
occurrences (all)	11	19	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 December 2017	Added to exclusion criteria confirmed diagnosis of a GI ulcer. Adjusted QOL assessment based on initiation of anticoagulation therapy. Opened up the younger age group to allow enrollment of children >/= 3 months of age and indicated that only children > 6 kg can be enrolled. Changed apixaban dosing scheme from a mg/kg dosing to a fixed-dose, body weight-tiered regimen.
07 June 2019	Exclusion criteria was revised for those patients with a known inherited or acquired thrombotic disorder
27 January 2020	Open enrollment to patients 28 days to < 3 months and >/= 3 kg. Update exclusion criteria for subjects with known inherited bleeding disorders, coagulopathies, and antiphospholipid syndrome
16 July 2020	Neonates (subjects < 28 days of age) will no longer be included in the study, Subjects < 3 kg are excluded.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported