



Clinical trial results:

A RANDOMIZED, OPEN-LABEL, ACTIVE CONTROLLED, SAFETY AND DESCRIPTIVE EFFICACY STUDY IN PEDIATRIC SUBJECTS REQUIRING ANTICOAGULATION FOR THE TREATMENT OF A VENOUS THROMBOEMBOLIC EVENT

Summary

EudraCT number	2014-002606-20
Trial protocol	DE Outside EU/EEA AT GB ES PT IT FR
Global end of trial date	30 April 2024

Results information

Result version number	v1 (current)
This version publication date	25 October 2024
First version publication date	25 October 2024

Trial information

Trial identification

Sponsor protocol code	CV185-325/B0661037
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02464969
WHO universal trial number (UTN)	U1111-1160-6336

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussee 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)	EMA-000185-PIP02-12
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	30 April 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the safety and descriptive efficacy of apixaban in pediatric subjects requiring anticoagulation for the treatment of a VTE.

Protection of trial subjects:

Patient Confidentiality, Personal Data Protection and Biomarker Consent.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 November 2015
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: 1
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Spain: 6
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Türkiye: 1
Country: Number of subjects enrolled	Russian Federation: 24
Country: Number of subjects enrolled	Ukraine: 7
Country: Number of subjects enrolled	United Kingdom: 7
Country: Number of subjects enrolled	United States: 161
Worldwide total number of subjects	229
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	16

Infants and toddlers (28 days-23 months)	32
Children (2-11 years)	44
Adolescents (12-17 years)	137
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 11 countries.

Pre-assignment

Screening details:

Of the 243 participants screened for entry into the study, 229 participants were randomized to treatment, and 14 participants did not fulfill all eligibility criteria at screening

Period 1

Period 1 title	Main Phase (Day 1 to Day 84)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Participants receiving Apixaban

Arm description:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet, Chewable tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Arm title	Participants treated with Standard of Care
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Arm description:

Participants treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.

Arm type	Active comparator
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Investigational medicinal product name	Vitamin K antagonist
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Standard of care per local prescribing practices/guidelines	
Investigational medicinal product name	Unfractionated heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
Standard of care per local prescribing practices/guidelines	
Investigational medicinal product name	Low molecular weight heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use
Dosage and administration details:	
Standard of care per local prescribing practices/guidelines	

Number of subjects in period 1	Participants receiving Apixaban	Participants treated with Standard of Care
Started	155	74
Completed	138	65
Not completed	17	9
Adverse event, serious fatal	1	1
Consent withdrawn by subject	1	-
Adverse event, non-fatal	7	-
Other Reasons	4	2
Withdrawal by Parent/Guardian	-	4
Lost to follow-up	3	-
No Longer Meets Eligibility Criteria	-	1
Entrance Criteria	1	1

Period 2

Period 2 title	Extension Phase (Day 85 to Day 168)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Participants receiving Apixaban
Arm description:	
Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥35kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.	
Arm type	Experimental
Investigational medicinal product name	Apixaban
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet, Chewable tablet, Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥35kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Number of subjects in period 2^[1]	Participants receiving Apixaban
Started	53
Completed	50
Not completed	3
Adverse event, non-fatal	1
Other Reasons	1
Withdrawal by Parent/Guardian	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only participants randomized to the apixaban treatment group who subsequently completed the Main Phase of the study on assigned therapy, and then consented to continue their participation, were enrolled in the Extension Phase of the study. Therefore, of the original 155 randomized to apixaban treatment in the Main Phase of the study (152 of them treated), only 53 continued participation into the Extension Phase.

Baseline characteristics

Reporting groups

Reporting group title	Participants receiving Apixaban
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Reporting group description:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Reporting group title	Participants treated with Standard of Care
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Reporting group description:

Participants treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.

Reporting group values	Participants receiving Apixaban	Participants treated with Standard of Care	Total
Number of subjects	155	74	229
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	12	4	16
Infants and toddlers (28 days-23 months)	22	10	32
Children (2-11 years)	30	14	44
Adolescents (12-17 years)	91	46	137
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	11.10	11.68	
standard deviation	± 6.51	± 6.02	-
Sex: Female, Male Units: participants			
Female	85	43	128
Male	70	31	101
Race/Ethnicity, Customized Units: Subjects			
White	120	55	175
Black	22	9	31
Asian	5	4	9
American Indian or Alaska Native	1	0	1
Other	6	5	11

Multiracial	1	1	2
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	12	13	25
Not Hispanic or Latino	143	61	204
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	Participants receiving Apixaban
Reporting group description:	
Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.	
Reporting group title	Participants treated with Standard of Care
Reporting group description:	
Participants treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.	
Reporting group title	Participants receiving Apixaban
Reporting group description:	
Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.	
Subject analysis set title	Participants between age 12 to < 18 years
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants between age 12 to < 18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.	
Subject analysis set title	Participants between age 2 - < 12 years
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants between age 2 - < 12 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter;<35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter;<25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter;<18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter;<12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter;< 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter;<6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter;<5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter;PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same).For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.	
Subject analysis set title	Participants with age 28 days - < 2 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with age 28 days - < 2 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Subject analysis set title	Participants in age group-Birth - ≤ 27 days
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants in age group-Birth - ≤ 27 days were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Subject analysis set title	Participants between age 12 to < 18 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants between age 12 to < 18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Subject analysis set title	Participants between age 2 - < 12 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants between age 2 - < 12 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Subject analysis set title	Participants with age 28 days - < 2 years
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Participants with age 28 days - < 2 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Subject analysis set title	Participants in age group-Birth - ≤ 27 days
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Subject analysis set type	Sub-group analysis
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Subject analysis set description:

Participants in age group-Birth - ≤ 27 days were dosed on a body weight tiered regimen. Subjects ≥35kg received 10mg twice daily(BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; < 9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis ,participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Primary: Percentage of Participants with Composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding (Safety Population)

End point title	Percentage of Participants with Composite of Major and Clinically Relevant Non-Major (CRNM) Bleeding (Safety Population) ^[1]
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End point description:

Bleeding definitions are based on the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria. Major bleeding includes: (i) fatal bleeding; (ii) clinically overt bleeding with a decrease in Hgb of at least 20 g/L (2 g/dL) in 24 hours; (iii) retroperitoneal, pulmonary, intracranial, or central nervous system bleeding; and (iv) bleeding requiring surgical intervention in an operating suite (including interventional radiology). Clinically relevant non-major bleeding includes: (i) overt bleeding requiring a blood product not attributable to the participant's underlying condition; and (ii) bleeding requiring medical or surgical intervention to restore hemostasis, other than in an operating suite.

End point type	Primary
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End point timeframe:

From first dose (Day 1) up to 114 days

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: Study CV185325 was designed as a descriptive efficacy and safety study and so was not powered for any endpoints. As such, formal statistical analyses were not included in the protocol.

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	73		
Units: percentage of participants				
number (confidence interval 95%)	1.3 (0.1 to 5.0)	1.4 (0.0 to 8.1)		

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE) and VTE-Related Mortality

End point title	Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE) and VTE-Related Mortality ^[2]
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End point description:

Recurrent VTE, defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to deep vein thrombosis (DVT), pulmonary embolism (PE) and paradoxical embolism.

95% CI was from the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-protocol amendment 8.

End point type	Primary
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End point timeframe:

From first dose (Day 1) up to 114 days

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: Study CV185325 was designed as a descriptive efficacy and safety study and so was not powered for any endpoints. As such, formal statistical analyses were not included in the protocol.

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: percentage of participants				
number (confidence interval 95%)	2.6 (0.8 to 6.7)	2.7 (0.2 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with VTE-related Mortality

End point title	Percentage of Participants with VTE-related Mortality
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End point description:

Participants were assessed for death due to VTE. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.

End point type	Secondary
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End point timeframe:

From first dose (Day 1) up to 114 days

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Died

End point title	Percentage of Participants who Died
End point description: 95% CI was calculated using the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.	
End point type	Secondary
End point timeframe: From first dose (Day 1) up to 114 days	

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: percentage of participants				
number (confidence interval 95%)	1.3 (0.1 to 4.9)	1.4 (0.0 to 8.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Index VTE Status

End point title	Number of Participants with Index VTE Status
End point description: Index VTE status was defined as the last image obtained during the Main treatment phase for each participant's comparison to baseline imaging. Index VTE status was classified as Recurrence-contiguous; Recurrence-new; Unchanged; Regression; Resolution; Indeterminate/Nondiagnostic. Participants could have multiple concomitant index events such as presence of DVT and PE at baseline. Regression was defined as (ie, unequivocal decrease [$>50\%$] of the total volume/mass of the thrombus compared to the index event). The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8. Participants with a negative or Non-Diagnostic Index Event were excluded.	
End point type	Secondary
End point timeframe: From first dose (Day 1) up to 91 days	

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	65		
Units: participants				
Recurrence-contiguous	2	0		
Recurrence-new	0	0		
Unchanged	8	6		
Regression	25	11		
Resolution	77	36		

Indeterminate/Nondiagnostic	15	7		
Missing Follow-up Imaging	5	8		
Imaging not completed	6	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE)

End point title	Percentage of Participants with Symptomatic and Asymptomatic Recurrent Venous Thromboembolism (VTE)
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End point description:

Recurrent VTE, defined as either contiguous progression or non-contiguous new thrombus and including, but not limited to deep vein thrombosis (DVT), pulmonary embolism (PE) and paradoxical embolism. 95% CI was from the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-protocol amendment 8.

End point type	Secondary
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End point timeframe:

From first dose (Day 1) up to 114 days

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: percentage of participants				
number (confidence interval 95%)	2.6 (0.8 to 6.7)	2.7 (0.2 to 9.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Stroke

End point title	Percentage of Participants with Stroke
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End point description:

Participants were assessed for incidence of stroke. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.

End point type	Secondary
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End point timeframe:

From first dose (Day 1) up to 114 days

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: percentage of participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with New Symptomatic or Asymptomatic Deep Vein Thrombosis (DVT) and New Symptomatic or Asymptomatic Pulmonary Embolism (PE)

End point title	Number of Participants with New Symptomatic or Asymptomatic Deep Vein Thrombosis (DVT) and New Symptomatic or Asymptomatic Pulmonary Embolism (PE)
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End point description:

Participants were assessed for incidence of Symptomatic or Asymptomatic Deep Vein Thrombosis (DVT) and New Symptomatic or Asymptomatic Pulmonary Embolism (PE). The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-PA8.

End point type	Secondary
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End point timeframe:

From first dose (Day 1) up to 114 days

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: participants				
New Symptomatic or Asymptomatic DVT	1	1		
New Symptomatic or Asymptomatic PE	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Clinically Relevant Non-Major (CRNM) Bleeding, Major Bleeding and Minor Bleeding

End point title	Number of Participants with Clinically Relevant Non-Major (CRNM) Bleeding, Major Bleeding and Minor Bleeding
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End point description:

Bleeding definitions are based on the Perinatal and Paediatric Haemostasis Subcommittee of the International Society on Thrombosis and Haemostasis (ISTH) criteria. Major bleeding includes: (i) fatal bleeding; (ii) clinically overt bleeding with a decrease in Hgb of at least 20 g/L (2 g/dL) in 24 hours; (iii)

retroperitoneal, pulmonary, intracranial, or central nervous system bleeding; and (iv) bleeding requiring surgical intervention in an operating suite (including interventional radiology). Clinically relevant non-major bleeding includes: (i) overt bleeding requiring a blood product not attributable to the participant's underlying condition; and (ii) bleeding requiring medical or surgical intervention to restore hemostasis, other than in an operating suite. Minor bleeding was defined as any overt or macroscopic evidence of bleeding that does not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding.

End point type	Secondary
End point timeframe:	
From first dose (Day 1) up to 114 days	

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	152	73		
Units: participants				
Major Bleeding	0	0		
Clinically Relevant Non-major Bleeding	2	1		
Minor Bleeding	54	21		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Other Symptomatic and Asymptomatic Venous Thromboembolism (VTE)

End point title	Percentage of Participants with Other Symptomatic and Asymptomatic Venous Thromboembolism (VTE)
End point description:	
Other VTE included events such as cerebral sinovenous thrombosis, renal vein thrombosis, portal vein thrombosis, catheter-related VTE, and splanchnic thrombosis. If VTE event type was blank, it was included in the Other VTE. 95% CI was from the Agresti-Coull method. The Full Analysis Set contains all randomized participants and also those assigned to apixaban post-protocol amendment 8.	
End point type	Secondary
End point timeframe:	
From first dose (Day 1) up to 114 days	

End point values	Participants receiving Apixaban	Participants treated with Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	155	74		
Units: percentage of participants				
number (confidence interval 95%)	1.9 (0.4 to 5.8)	1.4 (0.0 to 8.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Blood Concentration of Apixaban (ng/mL)

End point title	Blood Concentration of Apixaban (ng/mL)
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End point description:

Blood samples were collected to assess the apixaban concentration at specified timepoints. Day 1 PK concentrations were only collected for participants in the Birth to ≤ 27 days arm. The lower limit of quantification (LLOQ) is 1.0 ng/mL for plasma samples, and 0.5 ng/mL for dried blood samples. 99999 stands for Not applicable as no participants were analyzed for those arms at that specific timepoint. The PK analysis population is defined as all participants randomized to and treated with apixaban who have at least 1 concentration of apixaban. Participants with sample size of quantifiable values ($\geq$ LLOQ) at the specified timepoints were analyzed.

End point type	Secondary
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End point timeframe:

3 hour (H), 12 H, 24 H at Day 3; pre and post dose at Day 14 and Day 42

End point values	Participants between age 12 to < 18 years	Participants between age 2 - < 12 years	Participants with age 28 days - < 2 years	Participants in age group- Birth - ≤ 27 days
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	64	22	15	11
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Hour 3 at Day 1 (n=0,0,0,11)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	30.7 ($\pm$ 12.9)
Hour 12 at Day 1 (n=0,0,0,10)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	13.9 ($\pm$ 5.70)
Hour 24 at Day 1 (n=0,0,0,11)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	99999 ($\pm$ 99999)	23.3 ($\pm$ 10.1)
Pre-dose at Day 14 (n=64,22,15,7)	61.1 ($\pm$ 53.7)	72.7 ($\pm$ 42.5)	56.4 ($\pm$ 65.6)	48.3 ($\pm$ 23.0)
Post-dose at Day 14 (n=61,21,14,6)	152 ($\pm$ 80.2)	189 ($\pm$ 61.0)	203 ($\pm$ 118)	119 ($\pm$ 45.7)
Pre-dose at Day 42 (n=24,5,3,2)	54.5 ($\pm$ 33.7)	67.9 ($\pm$ 33.8)	123 ($\pm$ 123)	50.2 ($\pm$ 34.1)
Post-Dose at Day 42 (n=27,7,4,3)	151 ($\pm$ 79.1)	212 ($\pm$ 89.8)	143 ($\pm$ 88.0)	109 ($\pm$ 56.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Plasma Anti-Factor Xa (ng/mL)

End point title	Concentration of Plasma Anti-Factor Xa (ng/mL)
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End point description:

Blood samples were collected to assess the Anti-Factor Xa concentration at specified timepoints. Day 1 PK concentrations were only collected for participants in the Birth to ≤27 days arm. The lower limit of quantification (LLOQ) is 35.0 ng/mL. 99999 stands for Not applicable where participants analyzed is 0 and 999999 also stands for not applicable where only 1 participant was analyzed and SD could not be analyzed. The PK analysis population is defined as all participants randomized to and treated with apixaban who have at least 1 concentration of apixaban. Participants with sample size of quantifiable values (≥ LLOQ) at the specified timepoints were analyzed.

End point type	Secondary
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End point timeframe:

Pre and post dose at Day 14 and Day 42

End point values	Participants between age 12 to < 18 years	Participants between age 2 - < 12 years	Participants with age 28 days - < 2 years	Participants in age group- Birth - ≤ 27 days
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	60	20	13	3
Units: nanogram per millilitre (ng/mL)				
arithmetic mean (standard deviation)				
Pre-dose at Day 14(n=51,18,10,3)	72.7 (± 60.4)	82.7 (± 41.3)	74.7 (± 69.7)	48.0 (± 1.00)
Post-dose at Day 14(n=60,20,13,3)	147 (± 83.5)	202 (± 75.8)	190 (± 105)	127 (± 4.04)
Pre-dose at Day 42(n=20,4,2,0)	63.9 (± 27.4)	75.3 (± 31.0)	53.5 (± 13.4)	99999 (± 99999)
Post-Dose at Day 42(n=27,7,5,1)	153 (± 84.9)	220 (± 98.4)	156 (± 92.2)	101 (± 999999)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Non-SAEs were collected from first dose Day 1 up to end of treatment visit (Day 168) plus 35 days i.e., up to 203 days. SAEs were collected from Screening (Day -7) to end of treatment visit (Day 168) plus 35 days i.e., up to 210 days.

Adverse event reporting additional description:

SAEs and Non SAEs were collected for safety population who received at least one dose of study drug.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Participants treated with Standard of Care
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Reporting group description:

Participants were treated with unfractionated heparin, low molecular weight heparin, and/or a vitamin K antagonist. For participants under 2 years of age, standard of care was limited to unfractionated heparin or low molecular weight heparin.

Reporting group title	Participants receiving Apixaban
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Reporting group description:

Participants between birth to <18 years were dosed on a body weight tiered regimen. Subjects ≥ 35 kg received 10mg twice daily (BID) for 7 days followed by 5mg BID thereafter; <35kg to 25kg received 8mg BID for 7 days followed by 4mg BID thereafter; <25 to 18kg received 6mg BID for 7 days and then 3mg BID thereafter; <18 to 12kg received 4mg BID for 7 days and then 2mg BID thereafter; <12 to 9kg received 3mg BID for 7 days and then 1.5mg BID thereafter; <9kg to 6kg received 2 mg BID for 7 days and 1mg BID thereafter; <6kg to 5kg received 1mg BID for 7 days and 0.5mg BID thereafter; <5kg to 4kg received 0.6mg twice daily for 7 days and 0.3mg BID thereafter; PK cohort neonates ≥ 2.6 kg received 0.1mg BID. Dose was adjusted as determined by PK measurements (ie, to 0.2mg BID, 0.1mg daily or dose stay the same). For the post PK cohort Neonates 4kg to 2.6kg, if confirmed by PK sub analysis, participants received 0.2mg BID for 7 days and 0.1mg BID thereafter.

Serious adverse events	Participants treated with Standard of Care	Participants receiving Apixaban	
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 73 (23.29%)	40 / 152 (26.32%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Embryonal rhabdomyosarcoma			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Post thrombotic syndrome			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superficial vein thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 73 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 73 (1.37%)	4 / 152 (2.63%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			

subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 73 (1.37%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Transplant rejection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
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			
Heavy menstrual bleeding			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
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			
Respiratory failure			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumomediastinum			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute chest syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperventilation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
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 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Munchausen's syndrome			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Selective eating disorder			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 73 (0.00%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood urea increased			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical observation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Gun shot wound			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lower limb fracture			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt thrombosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suture rupture			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Complex regional pain syndrome			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hypoxic-ischaemic encephalopathy subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral venous sinus thrombosis subjects affected / exposed	0 / 73 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic outlet syndrome subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cold type haemolytic anaemia subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			

subjects affected / exposed	2 / 73 (2.74%)	3 / 152 (1.97%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelosuppression			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	0 / 73 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye movement disorder			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus paralytic			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 73 (0.00%)	2 / 152 (1.32%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polyuria			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Connective tissue disorder			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytarabine syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related bacteraemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mycoplasma infection			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection bacterial			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic shock syndrome			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
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 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyomyositis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			

subjects affected / exposed	0 / 73 (0.00%)	1 / 152 (0.66%)	
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	0 / 73 (0.00%)	1 / 152 (0.66%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 152 (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	Participants treated with Standard of Care	Participants receiving Apixaban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	59 / 73 (80.82%)	132 / 152 (86.84%)	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	10 / 73 (13.70%)	14 / 152 (9.21%)	
occurrences (all)	10	14	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 73 (13.70%)	27 / 152 (17.76%)	
occurrences (all)	13	43	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 73 (5.48%)	5 / 152 (3.29%)	
occurrences (all)	24	17	
Leukopenia			
subjects affected / exposed	4 / 73 (5.48%)	3 / 152 (1.97%)	
occurrences (all)	23	7	
Anaemia			

subjects affected / exposed occurrences (all)	8 / 73 (10.96%) 42	5 / 152 (3.29%) 14	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	4 / 73 (5.48%)	5 / 152 (3.29%)	
occurrences (all)	4	6	
Injection site bruising			
subjects affected / exposed	12 / 73 (16.44%)	1 / 152 (0.66%)	
occurrences (all)	13	1	
Injection site haemorrhage			
subjects affected / exposed	4 / 73 (5.48%)	0 / 152 (0.00%)	
occurrences (all)	4	0	
Non-cardiac chest pain			
subjects affected / exposed	5 / 73 (6.85%)	12 / 152 (7.89%)	
occurrences (all)	6	16	
Pyrexia			
subjects affected / exposed	7 / 73 (9.59%)	11 / 152 (7.24%)	
occurrences (all)	9	20	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 73 (6.85%)	11 / 152 (7.24%)	
occurrences (all)	7	15	
Abdominal discomfort			
subjects affected / exposed	4 / 73 (5.48%)	0 / 152 (0.00%)	
occurrences (all)	5	0	
Vomiting			
subjects affected / exposed	4 / 73 (5.48%)	22 / 152 (14.47%)	
occurrences (all)	4	31	
Nausea			
subjects affected / exposed	5 / 73 (6.85%)	12 / 152 (7.89%)	
occurrences (all)	6	15	
Diarrhoea			
subjects affected / exposed	6 / 73 (8.22%)	15 / 152 (9.87%)	
occurrences (all)	6	19	
Constipation			

subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 73 (4.11%) 3 4 / 73 (5.48%) 4	10 / 152 (6.58%) 12 8 / 152 (5.26%) 9	
Reproductive system and breast disorders Heavy menstrual bleeding subjects affected / exposed occurrences (all)	3 / 73 (4.11%) 5	16 / 152 (10.53%) 20	
Respiratory, thoracic and mediastinal disorders Nasal congestion subjects affected / exposed occurrences (all) Epistaxis subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all)	2 / 73 (2.74%) 2 14 / 73 (19.18%) 15 6 / 73 (8.22%) 7 1 / 73 (1.37%) 1 6 / 73 (8.22%) 6	10 / 152 (6.58%) 13 27 / 152 (17.76%) 51 9 / 152 (5.92%) 9 12 / 152 (7.89%) 16 9 / 152 (5.92%) 10	
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	2 / 73 (2.74%) 2 3 / 73 (4.11%) 3 6 / 73 (8.22%) 6	8 / 152 (5.26%) 11 11 / 152 (7.24%) 24 15 / 152 (9.87%) 25	

Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all)	2 / 73 (2.74%) 2	11 / 152 (7.24%) 11	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	4 / 73 (5.48%) 5	3 / 152 (1.97%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 July 2015	The protocol amendments include several key updates. Firstly, the eligibility criteria were refined to specify that participants must be children aged 12 to <18 years at the time of consent, with a note that an approved amended protocol will be implemented before enrolling each subsequent age group. In Section 2.2, the examples of Index VTE status were corrected from "progression, regression, or resolution" to "unchanged, regression, or resolution." Section 7.1 was updated to include targeted physical examinations for evidence of bleeding at Day 14, Day 42, and Day 84 (End of Treatment, EOT) visits, as well as when clinically indicated. Additionally, visits on Days 28 and 63 were added, which can be conducted either by telephone or on-site. Lastly, the statement regarding radiologic images was revised to include "Day 84 (EOT)" and "if not medically necessary," now reading: "Radiologic images that require sedation or radiation at the Day 42 or Day 84 (EOT) visits are not required and may be omitted, if not medically necessary." These updates ensure clarity and compliance with the amended guidelines.
01 March 2017	The protocol amendments include several significant updates. Appendix 2 was added to provide the dose selection rationale for Amendment 3, detailing eliquis (apixaban) dose recommendations for subjects aged 2 to 18 years, both those who are ≥ 35 kg and those who are <35 kg. Section 12, which covers the background and rationale for dose selection, was updated to include the revised eliquis (apixaban) doses for Age Groups 1 and 2 in Table 1. The follow-up period was changed from "30 $\pm$ 5 days post End of Treatment" to "35 $\pm$ 5 days post End of Treatment" to comply with current Pfizer and BMS SOPs. Inclusion criterion 1 was updated to allow for the enrollment of children aged 2 to 18 years at the time of consent, covering both age groups 1 and 2. Inclusion criterion 6 was corrected to ensure consistency across the protocol, requiring contraception use for at least 33 days (5 half-lives plus 30 days) after the last dose of the assigned treatment for women of childbearing potential. Additional instructions were added for subjects on eliquis (apixaban) treatment who required the medication beyond Day 84. Section 9.1 on Sample Size Determination was updated to specify that the study team, in conjunction with regulators, will evaluate exposure duration, imaging results, and other trial aspects to determine if the data from the subjects are sufficient to address the study objectives. Throughout the trial, the sponsor will monitor the number of subjects who do not complete 12 weeks of eliquis (apixaban) treatment and will determine if additional subjects need to be recruited to supplement the safety database. These updates ensure the protocol remains clear, consistent, and compliant with current guidelines.
30 October 2017	Appendix 3 was added to provide the dose selection rationale for Amendment 4, detailing dose recommendations for subjects aged ≥ 3 months and weighing ≥ 6 kg. The Schedule of Activities in Section 6.4 was updated to include a 6-week or 12-week Extension Phase for subjects continuing on eliquis (apixaban). A footnote "p" was added to clarify that sites should continue the mg/kg dosing regimen for subjects randomized and dosed using the eliquis (apixaban) oral solution when Protocol Amendment 3 was effective, as depicted in Table 1. Section 12, covering the background and rationale for dose selection, was updated to reflect both the mg/kg dosing under Protocol Amendment 3 for subjects already dosed and the fixed-dose body weight-tiered regimen for subjects randomized or switched to the 0.5 mg tablet under Protocol Amendment 4. Inclusion criterion 1 was updated to allow the enrollment of children aged 3 months to 18 years with a minimum weight of 6 kg at the time of consent. Inclusion criterion 6 was updated per the Portugal Competent Authority's request to include abstinence from heterosexual intercourse as acceptable contraception for women of childbearing potential. Neonates were defined throughout the protocol as ≥ 34 weeks gestational or ≥ 37 weeks post-conceptual but not more than 27 days of age.

31 August 2018	The protocol amendments include adding language in Section 5 to specify that only Vitamin K Antagonist formulations are to be administered to pediatric subjects in Germany, per local regulations. Section 7.2 and Table 4 were added to provide an overview and summary of the maximum potential blood volume collected in pediatric subjects during the study, based on a regulatory request.
06 September 2019	The protocol amendments include several key updates. Appendix 4 was added to provide the dose selection rationale for Amendment 6, detailing dose recommendations for age group 3 subjects aged ≥ 28 days to 2 years and weighing ≥ 4 kg. The Schedule of Activities was updated to allow SOC administration up to 14 days prior to randomization and to permit local labs to replace central labs to minimize blood volume collected in younger subjects. Section 12 was updated with PK data to inform updated dosing. Section 3 added the definition of the index event and specified that midpoint imaging for subjects aged 2 years is only required at the investigator's discretion, but an EOT image should be collected. Inclusion criterion 1 was updated to allow enrollment of children aged 28 days to 18 years with a minimum weight of 4 kg. Inclusion criterion 3 was updated to include children aged 2 years with the intent to treat for 6 to 12 weeks. Exclusion criterion 1 was updated to extend the unacceptable length of time for anticoagulation treatment for the index VTE prior to randomization from 7 to 14 days. Additional inclusion and exclusion criteria were added for safety and program consistency, including criteria for oral, nasogastric, or gastric feeding tolerance, exclusion of subjects using aggressive lifesaving therapies, and exclusion of subjects with certain medical conditions. Section 5 was updated to include a 0.1 mg eliquis (apixaban) formulation and limit SOC to heparin (UFH or LMWH) for subjects aged 2 years. Section 7.6 was added to include details on the adjudication of safety and efficacy endpoints. Section 8.5 was added to define medication errors for eliquis (apixaban). Section 9.1 updated the sample size determination from 150 to 250 with rationale. These updates ensure the protocol remains clear, consistent, and compliant with current guidelines.
12 February 2020	Appendix 5 was added to provide the dose selection rationale for Age Group 4 (≤ 27 days of age) in Amendment 7, including dose recommendations for neonates. Section 12.4 updated Table 2 to include starting doses for neonates in both PK and post-PK cohorts and explained dosing adjustments when a subject reaches 28 days or older. Section 2.2 clarified that endpoints would include "other thrombotic events" as a component of the primary endpoint, given the prevalence of catheter-related thrombosis in neonates. This change was reflected throughout the protocol for consistency, and other thrombotic events were also added as a secondary endpoint. The description of PE was updated to include both symptomatic and asymptomatic cases. Inclusion criterion 1 was updated to define neonates and clarify that neonates could be enrolled if they achieved a minimum weight of 2.6 kg, with relevant updates made elsewhere in the protocol. Inclusion criterion 2 was updated to include central venous catheter-related thrombosis as an example of index VTE. Exclusion criterion 1 was updated to describe pretreatment SOC requirements for both PK and post-PK cohorts. Exclusion criterion 12 was updated to include allergies to other ingredients in the eliquis (apixaban) formulation or hypersensitivity to any components of the comparators. Section 6.2.4 added language for physical examination, allowing the investigator to contact the study sponsor to discuss a possible change in dosing regimen if there is a 20% change in weight for subjects aged 2 years or older. Section 6.4 clarified that the Extension Phase is only applicable to subjects in age groups 1 through 3.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 March 2020	Recruitment in the trial was temporarily paused for 3 weeks at all sites due to the impact of COVID-19 pandemic.	04 May 2020

Notes:

Limitations and caveats

None reported