Clinical trial results:
A Phase III Randomized, Open Label, Multi-center Study of the Safety and Efficacy of Apixaban for Venous Thromboembolism Prevention versus No Systemic Anticoagulant Prophylaxis during Induction Chemotherapy in Children with Newly Diagnosed Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (T or B cell) Treated with Asparaginase

Summary

EudraCT number	2014-000328-47
Trial protocol	Outside EU/EEA BE PL CZ
Global end of trial date	07 July 2021

Results information

Result version number	v1 (current)
This version publication date	23 January 2022
First version publication date	23 January 2022

Trial information

Trial identification

Sponsor protocol code	CV185-155

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02369653
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	08 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 July 2021
Global end of trial reached?	Yes
Global end of trial date	07 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on the composite endpoint of adjudicated non-fatal deep vein thromboses (DVT, including symptomatic and asymptomatic), pulmonary embolism (PE), and cerebral venous sinus thrombosis (CVST); and VTE-related-death. To assess the effect of prophylactic oral or enteric apixaban versus no systemic anticoagulant during ~28 days of induction chemotherapy including asparaginase on adjudicated major bleeding events.

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	22 October 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: 12
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czechia: 1
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Russian Federation: 26
Country: Number of subjects enrolled	United States: 386
Worldwide total number of subjects	512
EEA total number of subjects	32

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)	8
Children (2-11 years)	398
Adolescents (12-17 years)	106
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:

512 participants were randomized and received study treatment.

Period 1

Period 1 title	Overall Study (overall 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 will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range during approximately 28 days of induction chemotherapy including asparaginase. Weight range - Dose >/=35 kg - 2.5 mg twice daily <35 to 25 kg - 2 mg twice daily <25 to 18 kg - 1.5 mg twice daily <18 to 10.5 kg - 1 mg twice daily <10.5 to 6 kg - 0.5 mg twice daily

Arm type	Experimental
Investigational medicinal product name	BMS-562247
Investigational medicinal product code	
Other name	apixaban
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg

Investigational medicinal product name	BMS-562247
Investigational medicinal product code	
Other name	apixaban
Pharmaceutical forms	Oral solution
Routes of administration	Nasogastric use , Gastric use, Oral use

Dosage and administration details:

0.4 mg/mL

Investigational medicinal product name	BMS-562247
Investigational medicinal product code	
Other name	apixaban
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg

Investigational medicinal product name	Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for infusion
Routes of administration	Other use

Dosage and administration details:

3 - 4 drug, systemic induction chemotherapy regimen consisting of a corticosteroid, vincristine, and single or multiple dose asparaginase (with or without daunorubicin)

Arm title	Standard of Care

Arm description:

No systemic anticoagulant prophylaxis during induction chemotherapy

Arm type	Experimental
Investigational medicinal product name	Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, Solution for infusion
Routes of administration	Other use

Dosage and administration details:

3 - 4 drug, systemic induction chemotherapy regimen consisting of a corticosteroid, vincristine, and single or multiple dose asparaginase (with or without daunorubicin)

Number of subjects in period 1	Apixaban	Standard of Care
Started	256	256
Completed	242	249
Not completed	14	7
Adverse event, serious fatal	1	2
Participant withdrew consent	13	3
Lost to follow-up	-	1
Administrative reason by sponsor	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Apixaban
Reporting group description:	
Participants will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range during approximately 28 days of induction chemotherapy including asparaginase. Weight range - Dose >/=35 kg - 2.5 mg twice daily <35 to 25 kg - 2 mg twice daily <25 to 18 kg - 1.5 mg twice daily <18 to 10.5 kg - 1 mg twice daily <10.5 to 6 kg - 0.5 mg twice daily	
Reporting group title	Standard of Care
Reporting group description:	
No systemic anticoagulant prophylaxis during induction chemotherapy	

Reporting group values	Apixaban	Standard of Care	Total
Number of subjects	256	256	512
Age categorical Units: Participants			
Infants and toddlers (28 days-23 months)	1	7	8
Children (2-11 years)	206	192	398
Adolescents (12-17 years)	49	57	106
Age Continuous Units: years			
arithmetic mean	7.2	7.1	
standard deviation	± 4.34	± 4.39	-
Sex: Female, Male Units: Participants			
Female	115	107	222
Male	141	149	290
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	25	27	52
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	12	12	24
White	194	194	388
More than one race	0	0	0
Unknown or Not Reported	23	22	45
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	59	63	122
Not Hispanic or Latino	196	192	388
Unknown or Not Reported	1	1	2

End points

End points reporting groups

Reporting group title	Apixaban
Reporting group description:	
Participants will be administered apixaban twice daily by mouth or via a NGT or GT according to weight range during approximately 28 days of induction chemotherapy including asparaginase. Weight range - Dose >/=35 kg - 2.5 mg twice daily <35 to 25 kg - 2 mg twice daily <25 to 18 kg - 1.5 mg twice daily <18 to 10.5 kg - 1 mg twice daily <10.5 to 6 kg - 0.5 mg twice daily	
Reporting group title	Standard of Care
Reporting group description:	
No systemic anticoagulant prophylaxis during induction chemotherapy	
Subject analysis set title	Participants ≥ 35 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants will be administered 2.5 mg apixaban twice daily by mouth or via a NGT or GT during approximately 28 days of induction chemotherapy including asparaginase.	
Subject analysis set title	Participants 25 to < 35 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants will be administered 2 mg apixaban twice daily by mouth or via a NGT or GT during approximately 28 days of induction chemotherapy including asparaginase.	
Subject analysis set title	Participants 18 to < 25 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants will be administered 1.5 mg apixaban twice daily by mouth or via a NGT or GT during approximately 28 days of induction chemotherapy including asparaginase.	
Subject analysis set title	Participants 10.5 to < 18 kg
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants will be administered 1 mg apixaban twice daily by mouth or via a NGT or GT during approximately 28 days of induction chemotherapy including asparaginase.	

Primary: Composite of Non-Fatal DVT, PE, and CVST, and VTE-Related-Death

End point title	Composite of Non-Fatal DVT, PE, and CVST, and VTE-Related-Death
End point description:	
The number of non-fatal deep vein thromboses (DVT) (including asymptomatic and symptomatic), pulmonary embolism (PE), cerebral venous sinus thrombosis (CVST); and venous thromboembolism (VTE) related-death objectively confirmed by a blinded, independent adjudication committee. Symptomatic events are included during the intended treatment period. Asymptomatic events are included from scans up to Day 40.	
End point type	Primary
End point timeframe:	
From first dose up to approximately 40 days after first dose	

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	31	45		

Statistical analyses

Statistical analysis title	Statistical Analysis of Primary Efficacy Endpoint
Comparison groups	Standard of Care v Apixaban
Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0403
Method	Cochran-Mantel-Haenszel

Primary: 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 major bleeding adjudicated by a blinded, independent adjudication committee. Adjudicated major bleeding is defined as bleeding that satisfies one or more of the following criteria: 1) fatal bleeding 2) clinically overt bleeding associated with a decrease in hemoglobin of at least 20g/L (ie, 2g/dL) in a 24-hour period 3) bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS; and/or 4) bleeding that requires surgical intervention in an operating suite, including interventional radiology.

End point type	Primary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	2	2		

Statistical analyses

Statistical analysis title	Statistical Analysis of Primary Safety Endpoint
Comparison groups	Apixaban v Standard of Care

Number of subjects included in analysis	512
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Cochran-Mantel-Haenszel

Secondary: The Number of Participants with Non-fatal Asymptomatic Deep Vein Thromboses (DVT)

End point title	The Number of Participants with Non-fatal Asymptomatic Deep Vein Thromboses (DVT)

End point description:

The number of participants with non-fatal asymptomatic deep vein thromboses (DVT) adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 40 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	27	38		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Non-fatal Symptomatic Deep Vein Thromboses (DVT)

End point title	The Number of Participants with Non-fatal Symptomatic Deep Vein Thromboses (DVT)

End point description:

The number of participants with non-fatal symptomatic deep vein thromboses (DVT) adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	4	6		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Non-fatal Pulmonary Embolism (PE)

End point title	The Number of Participants with Non-fatal Pulmonary Embolism (PE)

End point description:

The number of participants with non-fatal pulmonary embolism (PE) adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Cerebral Venous Sinus Thrombosis (CVST)

End point title	The Number of Participants with Cerebral Venous Sinus Thrombosis (CVST)

End point description:

The number of participants with cerebral venous sinus thrombosis (CVST) adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Venous Thromboembolism (VTE)-related-death

End point title	The Number of Participants with Venous Thromboembolism (VTE)-related-death

End point description:

The number of participants with venous thromboembolism (VTE)-related-death adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Major and Clinically Relevant Non-Major Bleeding (CRNMB)

End point title	The Number of Participants with Major and Clinically Relevant Non-Major Bleeding (CRNMB)

End point description:

The number of participants with major and clinically relevant non-major bleeding (CRNMB) adjudicated by a blinded, independent adjudication committee CRNM bleeding is defined as bleeding that satisfies one or both of the following: 1) overt bleeding for which blood product is administered and not directly attributable to the subject’s underlying medical condition and 2) 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 up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	13	5		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participant Deaths

End point title	The Number of Participant Deaths

End point description:

The number of participant deaths adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose date until the end of the treatment period + 30 days (Up to approximately 59 days)

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	1	3		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with an Arterial Thromboembolic Event

End point title	The Number of Participants with an Arterial Thromboembolic Event

End point description:

The number of participants with an arterial thromboembolic event including paradoxical embolism and stroke adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with a CVAD-Related Infection

End point title	The Number of Participants with a CVAD-Related Infection

End point description:

The number of participants with a central venous access device (CVAD)-related infection adjudicated by a blinded, independent adjudication committee

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	1	6		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Catheter Replacements Needed During the Study

End point title	The Number of Catheter Replacements Needed During the Study

End point description:

The number of catheter replacements needed during the study

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of CVAD Patency Restoration Events After Thrombolytic Therapy Use

End point title	The Number of CVAD Patency Restoration Events After Thrombolytic Therapy Use

End point description:

The number of central venous access device (CVAD) patency restoration events after thrombolytic therapy use

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number Participants Experiencing Superficial Vein Thrombosis Events

End point title	The Number Participants Experiencing Superficial Vein Thrombosis Events

End point description:

The number participants experiencing superficial vein thrombosis events. Clots that occur in a superficial vein ie, cephalic vein, basilic vein (upper extremity) or saphenous vein (lower extremity) confirmed by radiographic imaging.

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Clinically Relevant Non-Major Bleeding Events (CRNMB)

End point title	The Number of Participants with Clinically Relevant Non-Major Bleeding Events (CRNMB)

End point description:

The number of participants with clinically relevant non-major bleeding events (CRNMB) adjudicated by a blinded, independent adjudication committee.

CRNM bleeding is defined as bleeding that satisfies one or both of the following:
1) overt bleeding for which blood product is administered and not directly attributable to the subject's underlying medical condition and
2) 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 up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	11	3		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Participants with Minor Bleeding Events

End point title	The Number of Participants with Minor Bleeding Events

End point description:

The number of participants with minor bleeding events adjudicated by a blinded, independent adjudication committee. Minor bleeding defined as any overt or macroscopic evidence of bleeding that does not fulfill the criteria for either major bleeding or CRNMB

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Participants	37	20		

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Platelet Transfusions Needed During the Study

End point title	The Number of Platelet Transfusions Needed During the Study

End point description:

The number of platelet transfusions needed during the study. The events are not adjudicated. A subject could have more than one platelet transfusion.

End point type	Secondary

End point timeframe:

From first dose up to approximately 34 days after first dose

End point values	Apixaban	Standard of Care		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	256	256		
Units: Platelet Transfusions	266	248		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax)

End point title	Maximum Observed Concentration (Cmax)

End point description:

The maximum observed concentration (Cmax) was measured to assess the pharmacokinetics of oral or enteric apixaban in pediatric subjects receiving induction chemotherapy.

End point type	Secondary

End point timeframe:

pre-dose, 1-4 hours post dose

End point values	Participants ≥ 35 kg	Participants 25 to < 35 kg	Participants 18 to < 25 kg	Participants 10.5 to < 18 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	30	50	73
Units: ng/mL				
geometric mean (geometric coefficient of variation)	56.5 (± 36.5)	63.6 (± 38.6)	61.4 (± 43.9)	54.2 (± 46.8)

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Observed Concentration (Cmin)

End point title	Trough Observed Concentration (Cmin)

End point description:

The trough observed concentration (Cmin) was measured to assess the pharmacokinetics of oral or enteric apixaban in pediatric subjects receiving induction chemotherapy.

End point type	Secondary

End point timeframe:

pre-dose, 1-4 hours post dose

End point values	Participants ≥ 35 kg	Participants 25 to < 35 kg	Participants 18 to < 25 kg	Participants 10.5 to < 18 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	30	50	73
Units: ng/mL				
geometric mean (geometric coefficient of variation)	18.8 (± 57.8)	18.1 (± 97.4)	12 (± 142)	12.9 (± 113)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve [AUC(TAU)]

End point title	Area Under the Concentration-Time Curve [AUC(TAU)]

End point description:

The area under the concentration-time curve [AUC(TAU)] was measured to assess the pharmacokinetics of oral or enteric apixaban in pediatric subjects receiving induction chemotherapy.

End point type	Secondary

End point timeframe:

pre-dose, 1-4 hours post dose

End point values	Participants ≥ 35 kg	Participants 25 to < 35 kg	Participants 18 to < 25 kg	Participants 10.5 to < 18 kg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	30	50	73
Units: ng•h/mL				
geometric mean (geometric coefficient of variation)	470 (± 35.3)	510 (± 42.7)	453 (± 44.8)	416 (± 48.5)

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-FXa Activity

End point title	Anti-FXa Activity[1]

End point description:

Anti-FXa Activity was measured to characterize the relationship between apixaban plasma concentration and anti-FXa activity in pediatric subjects receiving induction chemotherapy

End point type	Secondary

End point timeframe:

pre-dose and 2.5 hours after dosing on day 7. Day 8 and day 15.

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Anti-FXa Activity endpoint is measured for only participants randomized to apixaban.

End point values	Apixaban			
Subject group type	Reporting group			
Number of subjects analysed	210			
Units: Anti-FXa activity (ng/mL)				
arithmetic mean (standard deviation)	70.1 (± 31.1)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

SAE's collected between first dose and 30 days after last dose of study therapy. NSAE's collected between first dose and 2 days after last dose of study therapy. All Cause Mortality collected from first dose up to DBL date: Sep-13-2021.

Adverse event reporting additional description:

256 is the number of subjects who randomized to each of Apixaban or SOC arm respectively. Only 250 subjects received apixaban dose. So the additional 6 subjects who randomized to apixaban but received no dose were classified into SOC.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Standard of care

Reporting group description:

Subjects with ALL or Lymphoblastic Lymphoma (T or B cell) received Standard of care with no administration of systemic prophylactic anticoagulant for approximately 28 days.

Reporting group title	Apixaban

Reporting group description:

Subjects aged 1-18 years with Acute Lymphoblastic Leukemia (ALL) or Lymphoblastic Lymphoma (T or B cell) with body weight greater than or equal to (>=) 35 kilogram (kg) were administered 2.5 milligram (mg) Apixaban, less than 35 to 25 kg were administered 2 mg Apixaban, less than 25 to 18 kg were administered 1.5 mg Apixaban, less than 18 to 10.5 kg were administered 1 mg Apixaban, less than 10.5 to 6 kg were administered 0.5 mg Apixaban orally twice daily including Asparaginase for approximately 28 days

Serious adverse events	Standard of care	Apixaban	
Total subjects affected by serious adverse events			
subjects affected / exposed	83 / 262 (31.68%)	91 / 250 (36.40%)	
number of deaths (all causes)	4	1	
number of deaths resulting from adverse events			
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	6 / 262 (2.29%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 6	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	3 / 262 (1.15%)	9 / 250 (3.60%)	
occurrences causally related to treatment / all	0 / 3	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 262 (0.00%)	3 / 250 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	2 / 262 (0.76%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subclavian vein thrombosis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	1 / 262 (0.38%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
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			
Device related thrombosis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 262 (0.00%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			

subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 262 (2.67%)	7 / 250 (2.80%)	
occurrences causally related to treatment / all	0 / 7	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	2 / 262 (0.76%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
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			
Testicular cyst			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heavy menstrual bleeding			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			

subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 262 (0.00%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 262 (0.38%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
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 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatic enzyme increased			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Human rhinovirus test positive			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test abnormal			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Epidural haemorrhage			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis chemical			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Post lumbar puncture syndrome			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access complication			
subjects affected / exposed	2 / 262 (0.76%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 1	1 / 1	
Intracardiac thrombus			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tachycardia			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumopericardium			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral venous sinus thrombosis			
subjects affected / exposed	3 / 262 (1.15%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Encephalopathy			
subjects affected / exposed	2 / 262 (0.76%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Guillain-Barre syndrome			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (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	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukoencephalopathy			
subjects affected / exposed	0 / 262 (0.00%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy peripheral			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Posterior reversible encephalopathy syndrome			
subjects affected / exposed	2 / 262 (0.76%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 262 (0.76%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			

subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peripheral motor neuropathy			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (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			
Anaemia			
subjects affected / exposed	3 / 262 (1.15%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coagulopathy			
subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
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	16 / 262 (6.11%)	15 / 250 (6.00%)	
occurrences causally related to treatment / all	0 / 17	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	3 / 262 (1.15%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Ocular hypertension			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 262 (1.15%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	5 / 262 (1.91%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	5 / 262 (1.91%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	3 / 262 (1.15%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	3 / 262 (1.15%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumatosis intestinalis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumoperitoneum			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperbilirubinaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
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 / 262 (0.00%)	1 / 250 (0.40%)	
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 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 262 (0.00%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inappropriate antidiuretic hormone			

secretion			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone pain			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (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			
Appendicitis			
subjects affected / exposed	2 / 262 (0.76%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cytomegalovirus infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	2 / 262 (0.76%)	3 / 250 (1.20%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia bacteraemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fungal sepsis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus bacteraemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infective thrombosis			

subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 262 (0.00%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 262 (1.15%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	5 / 262 (1.91%)	6 / 250 (2.40%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			

subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatococcal infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
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 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 262 (0.38%)	0 / 250 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 262 (0.00%)	2 / 250 (0.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	4 / 262 (1.53%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			

subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	2 / 262 (0.76%)	4 / 250 (1.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperlipidaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 262 (0.00%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 262 (0.38%)	1 / 250 (0.40%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Standard of care	Apixaban	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	211 / 262 (80.53%)	221 / 250 (88.40%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	39 / 262 (14.89%)	46 / 250 (18.40%)	
occurrences (all)	49	68	
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 262 (6.87%)	28 / 250 (11.20%)	
occurrences (all)	21	35	
Blood bilirubin increased			

subjects affected / exposed	16 / 262 (6.11%)	17 / 250 (6.80%)	
occurrences (all)	21	34	
Neutrophil count decreased			
subjects affected / exposed	26 / 262 (9.92%)	19 / 250 (7.60%)	
occurrences (all)	48	38	
Platelet count decreased			
subjects affected / exposed	55 / 262 (20.99%)	53 / 250 (21.20%)	
occurrences (all)	122	133	
White blood cell count decreased			
subjects affected / exposed	28 / 262 (10.69%)	20 / 250 (8.00%)	
occurrences (all)	65	38	
Vascular disorders			
Hypertension			
subjects affected / exposed	26 / 262 (9.92%)	21 / 250 (8.40%)	
occurrences (all)	36	29	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	13 / 262 (4.96%)	15 / 250 (6.00%)	
occurrences (all)	16	16	
Nervous system disorders			
Headache			
subjects affected / exposed	20 / 262 (7.63%)	15 / 250 (6.00%)	
occurrences (all)	21	17	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	88 / 262 (33.59%)	81 / 250 (32.40%)	
occurrences (all)	173	154	
Febrile neutropenia			
subjects affected / exposed	7 / 262 (2.67%)	13 / 250 (5.20%)	
occurrences (all)	7	14	
Neutropenia			
subjects affected / exposed	15 / 262 (5.73%)	17 / 250 (6.80%)	
occurrences (all)	34	42	
Thrombocytopenia			
subjects affected / exposed	25 / 262 (9.54%)	25 / 250 (10.00%)	
occurrences (all)	84	67	
General disorders and administration			

site conditions			
Fatigue			
subjects affected / exposed	20 / 262 (7.63%)	14 / 250 (5.60%)	
occurrences (all)	20	14	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	12 / 262 (4.58%)	17 / 250 (6.80%)	
occurrences (all)	12	17	
Abdominal pain			
subjects affected / exposed	48 / 262 (18.32%)	34 / 250 (13.60%)	
occurrences (all)	55	40	
Constipation			
subjects affected / exposed	50 / 262 (19.08%)	54 / 250 (21.60%)	
occurrences (all)	52	58	
Diarrhoea			
subjects affected / exposed	16 / 262 (6.11%)	24 / 250 (9.60%)	
occurrences (all)	18	26	
Nausea			
subjects affected / exposed	20 / 262 (7.63%)	13 / 250 (5.20%)	
occurrences (all)	24	14	
Vomiting			
subjects affected / exposed	17 / 262 (6.49%)	17 / 250 (6.80%)	
occurrences (all)	20	19	
Stomatitis			
subjects affected / exposed	15 / 262 (5.73%)	12 / 250 (4.80%)	
occurrences (all)	20	13	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	12 / 262 (4.58%)	16 / 250 (6.40%)	
occurrences (all)	12	17	
Epistaxis			
subjects affected / exposed	14 / 262 (5.34%)	22 / 250 (8.80%)	
occurrences (all)	16	32	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	19 / 262 (7.25%)	28 / 250 (11.20%)	
occurrences (all)	19	34	
Pain in extremity			
subjects affected / exposed	25 / 262 (9.54%)	27 / 250 (10.80%)	
occurrences (all)	27	30	
Pain in jaw			
subjects affected / exposed	15 / 262 (5.73%)	14 / 250 (5.60%)	
occurrences (all)	16	14	
Arthralgia			
subjects affected / exposed	14 / 262 (5.34%)	12 / 250 (4.80%)	
occurrences (all)	15	12	
Muscular weakness			
subjects affected / exposed	14 / 262 (5.34%)	9 / 250 (3.60%)	
occurrences (all)	14	9	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	30 / 262 (11.45%)	19 / 250 (7.60%)	
occurrences (all)	54	29	
Hypoalbuminaemia			
subjects affected / exposed	34 / 262 (12.98%)	29 / 250 (11.60%)	
occurrences (all)	41	44	
Hyponatraemia			
subjects affected / exposed	30 / 262 (11.45%)	35 / 250 (14.00%)	
occurrences (all)	39	54	
Hypocalcaemia			
subjects affected / exposed	21 / 262 (8.02%)	11 / 250 (4.40%)	
occurrences (all)	30	16	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 August 2015	Dose adjustment, expanded age of eligible subjects, and exclusion Criteria updates
14 December 2016	Added to Secondary endpoints apixaban pharmacokinetics and anti-FXa activity. Exclusion criteria updates. Indicated that SAEs need to be collected up to 30 days after the last dose of study medication
08 December 2017	Changed apixaban dosing scheme from a mg/kg dosing to a fixed-dose, body weight-tiered regimen. Introduced the 0.5 mg tablet with dosing instructions. Changed design of study to indicate that all forms of asparaginase could be used. Changed enrollment to include children >/= 1 and < 18 years of age and >/=6 kg of weight.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported