Clinical trial results:
30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis

Summary

EudraCT number	2014-000566-22
Trial protocol	IE IT ES AT NL BE GB FR HU FI
Global end of trial date	05 April 2017

Results information

Result version number	v1
This version publication date	30 August 2018
First version publication date	06 September 2017

Trial information

Trial identification

Sponsor protocol code	BAY59-7939/14374

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02309411
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000430-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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the incidence of major bleeding and clinically relevant non-major bleeding.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 January 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Brazil: 3
Country: Number of subjects enrolled	Canada: 1
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Japan: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	United States: 8
Worldwide total number of subjects	46
EEA total number of subjects	23

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)	15
Children (2-11 years)	31
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 27 study centers in 14 countries: Australia, Austria, Brazil, Canada, Hungary, Israel, Italy, Japan, Netherlands, Russia, Spain, Switzerland, United Kingdom, and United States between 15 January 2015 (first subject first visit) and 05 April 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 51 subjects were screened, of these 5 subjects were screen failures; 4 subjects withdrew from study and 1 subject failed screening. Total of 46 subjects were assigned to treatment. One child (age: 2-6 years) was assigned to anticoagulant comparator, but received rivaroxaban and displayed in rivaroxaban group (age: 2-6 years) for analyses.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Rivaroxaban, suspension, BID, Age: 2-6 years

Arm description:

Subjects aged from 2 to 6 years were administered with age- and body weight-adjusted dose of rivaroxaban (BAY59-7939) oral suspension twice daily (BID) under fed conditions for 30 days.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY59-7939
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects aged from 2 to 6 years were administered with age- and body weight-adjusted dose of rivaroxaban (BAY59-7939) oral suspension BID under fed conditions for 30 days.

Arm title	Rivaroxaban suspension, BID, Age: 6 months-2 years

Arm description:

Subjects aged from 6 months to 2 years were administered with age- and body weight-adjusted dose of rivaroxaban oral suspension BID under fed conditions for 30 days.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY59-7939
Other name	
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Subjects aged from 6 months to 2 years were administered with age- and body weight-adjusted dose of rivaroxaban oral suspension BID under fed conditions for 30 days.

Arm title	Anticoagulants, Comparator, Age: 2-6 years

Arm description:

Subjects aged from 2 to 6 years were received comparator as per standard of care.

Arm type	Active comparator
Investigational medicinal product name	Comparator
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection, Tablet
Routes of administration	Oral use, Parenteral use

Dosage and administration details:

Subjects aged from 2 to 6 years received comparator as per standard of care. The dosage given was to be adjusted based on the individual body weight (low molecular weight heparin, fondaparinux) or international normalized ratio (INR) adjusted (vitamin K antagonist).

Number of subjects in period 1	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years	Anticoagulants, Comparator, Age: 2-6 years
Started	25	15	6
Completed	23	14	6
Not completed	2	1	0
Physician decision	1	-	-
Consent withdrawn by subject	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban, suspension, BID, Age: 2-6 years
Reporting group description:	
Subjects aged from 2 to 6 years were administered with age- and body weight-adjusted dose of rivaroxaban (BAY59-7939) oral suspension twice daily (BID) under fed conditions for 30 days.	
Reporting group title	Rivaroxaban suspension, BID, Age: 6 months-2 years
Reporting group description:	
Subjects aged from 6 months to 2 years were administered with age- and body weight-adjusted dose of rivaroxaban oral suspension BID under fed conditions for 30 days.	

Reporting group title	Anticoagulants, Comparator, Age: 2-6 years
Reporting group description:	
Subjects aged from 2 to 6 years were received comparator as per standard of care.	

Reporting group values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years	Anticoagulants, Comparator, Age: 2-6 years
Number of subjects	25	15	6
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 3.77 ± 1.03	 1.26 ± 0.45	 3.67 ± 0.82
Gender categorical Units: Subjects			
Female	12	9	3
Male	13	6	3

Reporting group values	Total		
Number of subjects	46		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	 -		
Gender categorical Units: Subjects			
Female	24		
Male	22		

End points

End points reporting groups

Reporting group title	Rivaroxaban, suspension, BID, Age: 2-6 years

Reporting group description:

Subjects aged from 2 to 6 years were administered with age- and body weight-adjusted dose of rivaroxaban (BAY59-7939) oral suspension twice daily (BID) under fed conditions for 30 days.

Reporting group title	Rivaroxaban suspension, BID, Age: 6 months-2 years

Reporting group description:

Subjects aged from 6 months to 2 years were administered with age- and body weight-adjusted dose of rivaroxaban oral suspension BID under fed conditions for 30 days.

Reporting group title	Anticoagulants, Comparator, Age: 2-6 years

Reporting group description:

Subjects aged from 2 to 6 years were received comparator as per standard of care.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

SAF (N= 46) included all subjects who received at least one dose of the study medication.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS (N=46) included all enrolled children (before Amendment 4, all children were randomized by interactive voice/web response system [IxRS], after Amendment 4 all children were assigned to rivaroxaban by IxRS). Screening failures were excluded.

Subject analysis set title	Pharmacokinetics Analysis Set (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PKS (N= 40) included all subjects with at least one pharmacokinetic sample in accordance with the pharmacokinetic sampling strategy.

Subject analysis set title	Pharmacodynamic Analysis Set (PDS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

PDS (N= 39) included all subjects with at least one blood sample for clotting tests in accordance with the pharmacodynamic sampling strategy was included.

Primary: Number of Subjects With Major Bleeding and Clinically Relevant Non-Major Bleeding Events

End point title	Number of Subjects With Major Bleeding and Clinically Relevant Non-Major Bleeding Events[1]

End point description:

Major bleeding is defined as overt bleeding and:
•associated with a fall in hemoglobin of 2 gram/decilitre (g/dL) or more, or
•leading to a transfusion of the equivalent of 2 or more units of packed red blood cells or whole blood in adults, or
•occurring in a critical site, for example (e.g.) intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or
•contributing to death.

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding, but associated with:
•medical intervention, or
•unscheduled contact (visit or telephone call) with a physician, or
•cessation (temporary) of study treatment, or
•discomfort for the child such as pain or
•impairment of activities of daily life (such as loss of school days or hospitalization).

End point type	Primary

End point timeframe:

During or within 2 days after stop of study treatment

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years	Anticoagulants, Comparator, Age: 2-6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[2]	15[3]	6[4]	
Units: subjects				
Major bleeding events	0	0	0	
Clinically relevant non-major bleeding events	0	0	1	

Notes:

[2] - SAF

[3] - SAF

[4] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Symptomatic Recurrent Venous Thromboembolism

End point title	Number of Subjects With Symptomatic Recurrent Venous Thromboembolism

End point description:

Venous thromboembolism is the formation of a blood clot (thrombus) inside a blood vessel, obstructing the flow of blood through the circulatory system. The occurrence of recurrent venous thromboembolism was summarized by age group. Symptomatic recurrence, which is the composite of deep Vein Thrombosis (DVT), non-fatal Pulmonary Embolism (PE), and fatal PE of venous thrombosis, had to be documented using appropriate (repeat) imaging test.

End point type	Secondary

End point timeframe:

From start of the study treatment up to 30-days post study treatment period (approximately 60 days)

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years	Anticoagulants, Comparator, Age: 2-6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[5]	15[6]	6[7]	
Units: subjects	0	0	0	

Notes:

[5] - FAS

[6] - FAS

[7] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Asymptomatic Deterioration in Thrombotic Burden on Repeat Imaging

End point title	Number of Subjects With Asymptomatic Deterioration in Thrombotic Burden on Repeat Imaging

End point description:

The occurrence of asymptomatic deterioration in thrombotic burden was summarized by age group. At the end of the 30-day treatment period, a repeat imaging of the thrombus was performed. The images of the index event and repeat imaging were adjudicated by the central independent adjudication committee (CIAC). The thrombotic burden at the time of the index event was compared to the thrombotic burden at the time of repeat imaging. The outcome of the adjudication was classified as normalized, improved, no relevant change, deteriorated, or not evaluable. Due to missing repeated imaging, thrombotic burden assessments were not done in some subjects.

End point type	Secondary

End point timeframe:

At the end of the 30-day treatment period

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years	Anticoagulants, Comparator, Age: 2-6 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	25[8]	15[9]	6[10]	
Units: subjects				
Normalized	6	4	1	
Improved	15	4	3	
No relevant change	1	3	1	
Deteriorated	0	0	0	
Not evaluable	0	0	0	
Not available	0	0	0	
Missing	3	4	1	

Notes:

[8] - FAS

[9] - FAS

[10] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Prothrombin Time at Specified Time Points

End point title	Change From Baseline in Prothrombin Time at Specified Time

	Points[11]

End point description:

Prothrombin time is a global clotting test used for the assessment of the extrinsic pathway of the blood coagulation cascade. Day 30 (10-16 hours post-dose) was considered as a baseline.

End point type	Secondary

End point timeframe:

Day 1 (2.5-4 hours post-dose); Day 15 (2-8 hours post-dose)

Notes:

[11] - 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: Pharmacodynamic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[12]	14[13]		
Units: Seconds				
arithmetic mean (standard deviation)				
Day 1: 2.5-4 hours post-dose	2.777 (± 4.845)	2.514 (± 3.53)		
Day 15: 2-8 hours post-dose	2.586 (± 2.387)	4.764 (± 4.738)		

Notes:

[12] - PDS with evaluable subjects for this end point.

[13] - PDS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Activated Partial Thromboplastin Time at Specified Time Points

End point title	Change From Baseline in Activated Partial Thromboplastin Time at Specified Time Points[14]

End point description:

The Activated partial thromboplastin time (aPTT) is a screening test for the intrinsic pathway. Day 30 (10-16 hours post-dose) was considered as a baseline.

End point type	Secondary

End point timeframe:

Day 1 (2.5-4 hours post-dose); Day 15 (2-8 hours post-dose)

Notes:

[14] - 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: Pharmacodynamic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[15]	14[16]		
Units: Seconds				
arithmetic mean (standard deviation)				
Day 1: 2.5-4 hours post-dose	6.455 (± 17.036)	-3.479 (± 40.443)		
Day 15: 2-8 hours post-dose	2.814 (± 6.375)	21 (± 66.761)		

Notes:

[15] - PDS with evaluable subjects for this end point.

[16] - PDS with evaluable subjects for this end point.

Statistical analyses

No statistical analyses for this end point

Secondary: Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Specified Time Points

End point title	Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Specified Time Points[17]

End point description:

Concentration of rivaroxaban in plasma was measured at Day 1, 15 and 30 at specified time points. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group. Geometric mean and percentage geometric coefficient of variation (%CV) were reported.

End point type	Secondary

End point timeframe:

Day 1 (30-90 minutes, 2.5-4 hours post-dose); Day 15 (2-8 hours post-dose) and Day 30 (10-16 hours post-dose)

Notes:

[17] - 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: Pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[18]	15[19]		
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
Day 1: 30-90 minutes post-dose (n=24,15)	72.8494 (± 153.76)	68.0072 (± 160.77)		
Day 1: 2.5-4 hours post-dose (n=24,14)	108.6053 (± 58.18)	76.5371 (± 112.91)		
Day 15: 2-8 hours post-dose (n=24,14)	112.3578 (± 46.37)	61.3817 (± 451.46)		
Day 30: 10-16 hours post-dose (n=23,14)	19.8714 (± 189.49)	5.9545 (± 354.51)		

Notes:

[18] - PKS

[19] - PKS

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Anti-factor Xa Values at Specified Time Points

End point title	Anti-factor Xa Values at Specified Time Points[20]

End point description:

The individual anti-Factor Xa activity was determined ex-vivo using a photometric method. The anti-factor Xa assay is designed to measure plasma heparin, low molecular weight heparin and other anticoagulants. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Other pre-specified

End point timeframe:

Day 1 (2.5-4 hours post-dose); Day 15 (2-8 hours post-dose) and Day 30 (10-16 hours post-dose)

Notes:

[20] - 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: Pharmacodynamic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban, suspension, BID, Age: 2-6 years	Rivaroxaban suspension, BID, Age: 6 months-2 years		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25[21]	14[22]		
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 1: 2.5-4 hours post-dose (n=22,14)	128.457 (± 69.615)	87.831 (± 84.178)		
Day 15: 2-8 hours post-dose (n=22,13)	103.105 (± 58.343)	131.369 (± 96.489)		
Day 30: 10-16 hours post-dose (n=22,14)	19.069 (± 17.463)	16.952 (± 19.725)		

Notes:

[21] - PDS

[22] - PDS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration until 30 day post study treatment (approximately 60 days)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	Rivaroxaban BID (suspension) (2 - 6 years group)
Reporting group description:	
Subjects aged from 2 to 6 years were administered with age- and body weight-adjusted dose of rivaroxaban oral suspension BID under fed conditions for 30 days.	
Reporting group title	Rivaroxaban BID (suspension) (6 months - 2 years group)
Reporting group description:	
Subjects aged from 6 months to 2 years were administered with age- and body weight-adjusted dose of rivaroxaban oral suspension BID under fed conditions for 30 days.	
Reporting group title	Anticoagulants, comparator (2 - 6 years group)
Reporting group description:	
Subjects aged from 2 to 6 years were received comparator as per standard of care.	

Serious adverse events	Rivaroxaban BID (suspension) (2 - 6 years group)	Rivaroxaban BID (suspension) (6 months - 2 years group)	Anticoagulants, comparator (2 - 6 years group)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	2 / 15 (13.33%)	1 / 6 (16.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Optic atrophy			

subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Rivaroxaban BID (suspension) (2 - 6 years group)	Rivaroxaban BID (suspension) (6 months - 2 years group)	Anticoagulants, comparator (2 - 6 years group)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 25 (56.00%)	11 / 15 (73.33%)	3 / 6 (50.00%)
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Catheter placement			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Feeling cold			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Mucosal inflammation			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	3 / 25 (12.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	3	2	0
Immune system disorders			

Hypersensitivity			
subjects affected / exposed	1 / 25 (4.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Productive cough			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Pulmonary congestion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pulmonary granuloma			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rhinorrhoea			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Bronchomalacia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Tracheomalacia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood fibrinogen decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Bronchoscopy			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutrophil count decreased			

subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
White blood cell count decreased			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Accident			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Scratch			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Subcutaneous haematoma			
subjects affected / exposed	1 / 25 (4.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	2	2	0
Wound haemorrhage			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Lip injury			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	4	0	0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Polyneuropathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	2 / 25 (8.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	2	1	0
Febrile neutropenia			
subjects affected / exposed	1 / 25 (4.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	1	1	1
Monocytosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Neutropenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	1 / 6 (16.67%)
occurrences (all)	0	1	1
Thrombocytopenia			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Thrombocytosis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Cytopenia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Ocular hyperaemia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Eye pruritus			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Abdominal pain upper			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Constipation			

subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Diarrhoea			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Haematochezia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Anal erosion			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 25 (0.00%)	2 / 15 (13.33%)	0 / 6 (0.00%)
occurrences (all)	0	2	0
Erythema			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Myopathy			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Neck pain			

subjects affected / exposed	2 / 25 (8.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Ear infection			
subjects affected / exposed	2 / 25 (8.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Gastroenteritis			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Lower respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	2 / 25 (8.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Pharyngitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Scarlet fever			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tonsillitis			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tooth abscess			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Tracheobronchitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 25 (4.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	1	1	0
Viral rash			
subjects affected / exposed	1 / 25 (4.00%)	0 / 15 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0

Viral tonsillitis			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 25 (12.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	3	0	1
Respiratory tract infection viral			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Staphylococcal skin infection			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	0 / 25 (0.00%)	1 / 15 (6.67%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hypertriglyceridaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hypoalbuminaemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	0 / 25 (0.00%)	0 / 15 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 September 2014	This amendment was issued for the following modifications: •Erroneous dosing information was corrected •The suspension information was adjusted and summary of oral suspension preparation was provided.
14 April 2015	This amendment covered the following changes: •The comparator arm was removed. The sample size was considered too small to support meaningful comparison of rivaroxaban versus standard of care with regard to safety and efficacy. Furthermore, due to the comparator arm removal, the total subject number was reduced. •Inclusion criterion was changed to enable enrollment of children who are on long-term anticoagulant treatment. Additionally, instructions on how to safely handle the switch from heparin, fondaparinux, and Vitamin K antagonist (VKA) to rivaroxaban and vice versa were made available in the protocol. •The platelet count threshold for exclusion of children was adjusted from less than (<) 100 X 10^9 per liter (/L) to < 50 X 10^9/L. •Minor clarifications for consistency.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In this study, sample size calculation was based on feasibility assessment due to low incidence of venous thrombosis in children and on pharmacokinetic moderate inter-individual variability of rivaroxaban.

Notes: