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

Summary

EudraCT number	2011-004539-30
Trial protocol	AT DE IT NL
Global end of trial date	01 September 2016

Results information

Result version number	v2
This version publication date	17 November 2017
First version publication date	17 March 2017
Version creation reason	• Correction of full data set EMA results maintenance

Trial information

Trial identification

Sponsor protocol code	BAY59-7939/14373

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01684423
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 September 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 September 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective 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 explained to all subjects and/or their legally authorized representative. Participating subjects and/or their legally authorized representative 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	19 February 2013
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	Austria: 6
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Switzerland: 4
Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Netherlands: 3
Worldwide total number of subjects	64
EEA total number of subjects	34

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)	0
Children (2-11 years)	40
Adolescents (12-17 years)	24
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at multiple centers in 10 countries worldwide between 19 February 2013 (first subject first visit) and 01 September 2016 (last subject last visit).

Pre-assignment

Screening details:

A total of 68 subjects were screened, of these 4 subjects failed screening. The remaining 64 subjects were randomized, of whom 63 subjects were treated.

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 (BAY59-7939) tablet, OD, Age: 12 - <18 years

Arm description:

Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days.

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

Dosage and administration details:

Subjects aged from 12 - <18 years were administered with age and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to less than 50 kilogram (kg) received a dose (equivalent to 20 milligram [mg] in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of greater than or equal to 50 kg received a dose of 20 mg.

Arm title	Comparator, Age: 12 - <18 years

Arm description:

Subjects aged from 12 - <18 years 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 12 - <18 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).

Arm title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years

Arm description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days.

Arm type	Experimental

Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY59-7939
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to less than 50 kg received a dose (equivalent to 20 mg in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of greater than or equal to 50 kg received a dose of 20 mg.

Arm title	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years

Arm description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily.

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 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily. Subjects with a body weight of 9 to less than 50 kg received a total daily dose (equivalent to 20 mg in adults) ranging from 6.4 to 15 mg and subjects with a body weight of greater than or equal to 50 kg received a total daily dose of 20 mg.

Arm title	Comparator, Age: 6 - <12 years

Arm description:

Subjects aged from 6 - <12 years 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 6 - <12 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 INR-adjusted (vitamin K antagonist).

Number of subjects in period 1[1]	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years
Started	11	13	13
Completed	11	13	12
Not completed	0	0	1
Withdrawal by subject	-	-	1

Number of subjects in period 1[1]	Rivaroxaban (BAY59-7939) suspension, BID,	Comparator, Age: 6 - <12 years

	Age: 6 - <12 years	
Started	19	7
Completed	19	7
Not completed	0	0
Withdrawal by subject	-	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Not all enrolled subjects received treatment. Only treated subjects were included in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years
Reporting group description:	
Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days.	
Reporting group title	Comparator, Age: 12 - <18 years
Reporting group description:	
Subjects aged from 12 - <18 years received comparator as per standard of care.	
Reporting group title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years
Reporting group description:	
Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days.	
Reporting group title	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years
Reporting group description:	
Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily.	
Reporting group title	Comparator, Age: 6 - <12 years
Reporting group description:	
Subjects aged from 6 - <12 years received comparator as per standard of care.	

Reporting group values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years
Number of subjects	11	13	13
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	15.5	14.8	8.5
standard deviation	± 1.2	± 1	± 2.1
Gender categorical			
Units: Subjects			
Female	8	7	5
Male	3	6	8

Reporting group values	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	Comparator, Age: 6 - <12 years	Total
Number of subjects	19	7	63
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	8.3	9	
standard deviation	± 1.9	± 2	-

Gender categorical Units: Subjects			
Female	6	3	29
Male	13	4	34

End points

End points reporting groups

Reporting group title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years
Reporting group description:	
Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days.	
Reporting group title	Comparator, Age: 12 - <18 years
Reporting group description:	
Subjects aged from 12 - <18 years received comparator as per standard of care.	
Reporting group title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years
Reporting group description:	
Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days.	
Reporting group title	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years
Reporting group description:	
Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily.	
Reporting group title	Comparator, Age: 6 - <12 years
Reporting group description:	
Subjects aged from 6 - <12 years received comparator as per standard of care.	
Subject analysis set title	Safety analysis set (SAS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
SAS (N= 63) included all subjects who received at least one dose of study medication.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS (N= 64) included all subjects who completed screening.	
Subject analysis set title	Pharmacokinetic analysis set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PKS (N= 42) 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= 42) included all subjects with at least one blood sample for clotting parameters in accordance with the pharmacodynamic sampling strategy.	

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

End point title	Number of Subjects With Major and Clinically Relevant Non-Major Bleeding Events[1]
End point description:	
Central independent adjudication committee (CIAC) classified bleeding as follows: 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, 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:

From start of study drug administration until end of the 30-day treatment period

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 (BAY59-7939) tablet, OD, Age: 12 - <18 years	Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[2]	13[3]	13[4]	19[5]
Units: subjects				
Major bleeding events	0	0	0	0
Clinically relevant non-major bleeding events	3	0	0	1

Notes:

[2] - FAS

[3] - FAS

[4] - FAS

[5] - FAS

End point values	Comparator, Age: 6 - <12 years			
Subject group type	Reporting group			
Number of subjects analysed	7[6]			
Units: subjects				
Major bleeding events	0			
Clinically relevant non-major bleeding events	0			

Notes:

[6] - FAS

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:

The occurrence of recurrent venous thromboembolism was summarized by age group. Symptomatic recurrence of venous thrombosis was documented by the appropriate imaging test.

End point type	Secondary

End point timeframe:

From start of study drug administration until end of the 30-day treatment period

End point values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[7]	13[8]	13[9]	19[10]
Units: subjects	0	0	0	0

Notes:

[7] - FAS

[8] - FAS

[9] - FAS

[10] - FAS

End point values	Comparator, Age: 6 - <12 years			
Subject group type	Reporting group			
Number of subjects analysed	7[11]			
Units: subjects	0			

Notes:

[11] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Asymptomatic Deterioration in Thrombotic Burden

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

End point description:

The occurrence of asymptomatic deterioration in thrombotic burden was summarized by age group. Asymptomatic deterioration in thrombotic burden was documented by the appropriate imaging test and the results were classified as normalized, improved, no relevant change, deteriorated, not evaluable or not available.

End point type	Secondary

End point timeframe:

Repeat imaging at the end of the 30 day treatment period

End point values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11[12]	13[13]	13[14]	19[15]
Units: subjects				
Normalized	3	2	2	4
Improved	4	0	8	9
No relevant change	0	0	1	2
Deteriorated	0	0	0	0
Not evaluable	0	2	0	0
Not available	4	9	2	4

Notes:

[12] - FAS

[13] - FAS

[14] - FAS

[15] - FAS

End point values	Comparator, Age: 6 - <12 years			
Subject group type	Reporting group			
Number of subjects analysed	7[16]			
Units: subjects				
Normalized	1			
Improved	4			
No relevant change	0			
Deteriorated	0			
Not evaluable	1			
Not available	1			

Notes:

[16] - 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[17]

End point description:

Prothrombin time is a global clotting test used for the assessment of the extrinsic pathway of the blood coagulation cascade. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group and '99999' signifies no subjects were evaluated for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 24 hours post-dose on Day 31

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: Pharmacodynamic and pharmacokinetic parameters were evaluated only for subjects who

received active study medication.

End point values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[18]	12[19]	19[20]	
Units: seconds				
arithmetic mean (standard deviation)				
Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)	8.964 (± 3.822)	9.083 (± 2.513)	3.147 (± 2.099)	
Day 15: 6 to 8 hours post-dose (n= 11, 12,19)	4.218 (± 2.977)	2.817 (± 1.628)	1.984 (± 1.341)	
Day 31: 10 to 16 hours post-dose (n= 0, 0, 18)	99999 (± 99999)	99999 (± 99999)	0.156 (± 1.155)	
Day 31: 20 to 24 hours post-dose (n= 11, 11, 0)	-0.082 (± 1.02)	-0.327 (± 1.332)	99999 (± 99999)	

Notes:

[18] - PDS with number of subjects evaluable for this specific end point

[19] - PDS with number of subjects evaluable for this specific end point

[20] - PDS with number of subjects evaluable for this specific 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[21]

End point description:

The Activated partial thromboplastin time (aPTT) is a screening test for the intrinsic pathway. In the below table, ‘n’ signifies those subjects who were evaluable for this measure at given time points for each group and '99999' signifies no subjects were evaluated for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 24 hours post-dose on Day 31

Notes:

[21] - 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 and pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[22]	12[23]	19[24]	
Units: seconds				
arithmetic mean (standard deviation)				

Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)	10.982 (± 4.47)	12.818 (± 5.21)	2.995 (± 5.616)	
Day 15: 6 to 8 hours post-dose (n= 11, 12,19)	6.136 (± 2.641)	5.9 (± 4.942)	1.858 (± 4.774)	
Day 31: 10 to 16 hours post-dose (n= 0, 0, 18)	99999 (± 99999)	99999 (± 99999)	-0.483 (± 6.488)	
Day 31: 20 to 24 hours post-dose (n= 11, 11, 0)	1.345 (± 3.19)	1.24 (± 4.992)	99999 (± 99999)	

Notes:

[22] - PDS with number of subjects evaluable for this specific end point

[23] - PDS with number of subjects evaluable for this specific end point

[24] - PDS with number of subjects evaluable for this specific end point

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-factor Xa Values at Specified Time Points

End point title	Anti-factor Xa Values at Specified Time Points[25]

End point description:

The individual anti-Factor Xa activity was determined ex-vivo using a photometric method. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group and '99999' signifies no subjects were evaluated for the given time points for respective reporting groups.

End point type	Secondary

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 24 hours post-dose on Day 31

Notes:

[25] - 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 and pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[26]	12[27]	19[28]	
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 15: pre-dose	16.081 (± 6.136)	8.136 (± 3.069)	31.553 (± 25.416)	
Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)	185.481 (± 53.326)	252.853 (± 71.072)	99.415 (± 54.415)	
Day 15: 6 to 8 hours post-dose (n= 11, 12,19)	105.223 (± 54.339)	68.67 (± 32.845)	77.929 (± 50.074)	
Day 31: 10 to 16 hours post-dose (n= 0, 0, 18)	99999 (± 99999)	99999 (± 99999)	30.927 (± 18.037)	
Day 31: 20 to 24 hours post-dose (n= 9, 10, 0)	16.038 (± 7.653)	8.409 (± 3.664)	99999 (± 99999)	

Notes:

[26] - PDS with number of subjects evaluable for this specific end point

[27] - PDS with number of subjects evaluable for this specific end point

[28] - PDS with number of subjects evaluable for this specific 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[29]

End point description:

Geometric and percentage geometric coefficient of variation (%CV) were reported. In the below table, 'n' signifies those subjects who were evaluable for this measure at given time points for each group.

End point type	Secondary

End point timeframe:

0 hours (pre-dose) to 8 hours post-dose on Day 15 and 20-24 hours (OD dosing) and 10-16 hours (BID dosing), respectively, post-dose on Day 31

Notes:

[29] - 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 and pharmacokinetic parameters were evaluated only for subjects who received active study medication.

End point values	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11[30]	12[31]	19[32]	
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
Day 15: pre-dose	20.4822 (± 40.6726)	7.4367 (± 152.9768)	41.6025 (± 183.6873)	
Day 15: 2 to 4 hours post-dose (n= 11, 12, 19)	219.6933 (± 35.7518)	240.6319 (± 18.3387)	119.2201 (± 52.9889)	
Day 15: 6 to 8 hours post-dose (n= 11, 12,19)	124.6723 (± 49.1882)	96.8051 (± 41.8155)	100.5992 (± 52.6497)	
Day 31: 10 to 16 hours post-dose (n= 0, 0, 19)	99999 (± 99999)	99999 (± 99999)	43.5223 (± 81.7283)	
Day 31: 20 to 24 hours post-dose (n= 11, 11, 0)	21.3252 (± 43.1274)	9.4654 (± 167.7545)	99999 (± 99999)	

Notes:

[30] - PKS with number of subjects evaluable for this specific end point

[31] - PKS with number of subjects evaluable for this specific end point

[32] - PKS with number of subjects evaluable for this specific end point

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 untill 30 day post study treatment (approximately 60 days).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years

Reporting group description:

Subjects aged from 12 - <18 years were administered with age- and body weight-adjusted oral dose ofrivaroxaban (BAY59-7939) immediate-release (IR) tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to 50 kilogram (kg) received a dose (equivalent to 20 milligram [mg] in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of 50 to 100 kg received a dose of 20 mg.

Reporting group title	Anticoagulant Comparator, Age: 12 - <18 years

Reporting group description:

Subjects aged from 12 - <18 years received anticoagulant comparator as per standard regimen. The dosage given was adjusted based on the individual age and body weight.

Reporting group title	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years

Reporting group description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) IR tablet once daily under fed conditions for 30 days. Subjects with a body weight of 14 to 50 kg received a dose (equivalent to 20 mg in adults) ranging from 5 to 15 mg, and subjects with a body weight (comparable to adults) of 50 to 100 kg received a dose of 20 mg.

Reporting group title	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years

Reporting group description:

Subjects aged from 6 - <12 years were administered with age- and body weight-adjusted oral dose of rivaroxaban (BAY59-7939) suspension under fed conditions twice daily. Subjects with a body weight of 9 to 50 kg received a total daily dose (equivalent to 20 mg in adults) ranging from 6.4 to 15 mg and subjects with a body weight of 50 to 100 kg received a total daily dose of 20 mg.

Reporting group title	Anticoagulant Comparator, Age: 6 - <12 years

Reporting group description:

Subjects aged from 6 - <12 years received anticoagulant comparator as per standard regimen. The dosage given was adjusted based on the individual age and body weight.

Serious adverse events	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Anticoagulant Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Influenza B virus test positive			

subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (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
Endocrine disorders			
Hypothalamo-pituitary disorder			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	Anticoagulant Comparator, Age: 6 - <12 years	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 19 (10.53%)	0 / 7 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Influenza B virus test positive			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (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			
Multiple sclerosis relapse			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypothalamo-pituitary disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Rivaroxaban (BAY59-7939) tablet, OD, Age: 12 - <18 years	Anticoagulant Comparator, Age: 12 - <18 years	Rivaroxaban (BAY59-7939) tablet, OD, Age: 6 - <12 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 11 (81.82%)	8 / 13 (61.54%)	6 / 13 (46.15%)
Vascular disorders			
Post thrombotic syndrome			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hot flush			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Chest pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Peripheral swelling			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Localised oedema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vessel puncture site haematoma			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Vessel puncture site swelling			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	4 / 11 (36.36%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	8	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Dyspnoea			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Epistaxis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	2	0	2
Nasal congestion			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Oropharyngeal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Investigations			
Haemoglobin decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Platelet count decreased			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Contusion			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	2	2	0
Skin abrasion			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 11 (18.18%)	0 / 13 (0.00%)	2 / 13 (15.38%)
occurrences (all)	2	0	2
Vocal cord paralysis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Increased tendency to bruise			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	2
Neutropenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1

Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	2 / 13 (15.38%)
occurrences (all)	0	0	3
Abdominal pain upper			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Dyspepsia			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Gingival bleeding			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	2	0
Nausea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tooth loss			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	1	1	0
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Hyperhidrosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Rash			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	0	0	1
Swelling face			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Flank pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	1 / 11 (9.09%)	1 / 13 (7.69%)	1 / 13 (7.69%)
occurrences (all)	1	1	1
Pain in jaw			

subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	1 / 13 (7.69%)
occurrences (all)	1	0	1
Rhinitis			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Tooth abscess			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Upper respiratory tract infection			
subjects affected / exposed	1 / 11 (9.09%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	1	0	0
Urinary tract infection			
subjects affected / exposed	0 / 11 (0.00%)	0 / 13 (0.00%)	0 / 13 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 11 (0.00%)	1 / 13 (7.69%)	0 / 13 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Rivaroxaban (BAY59-7939) suspension, BID, Age: 6 - <12 years	Anticoagulant Comparator, Age: 6 - <12 years	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 19 (63.16%)	2 / 7 (28.57%)	
Vascular disorders			
Post thrombotic syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Hot flush			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			

Chest discomfort			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Chest pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	2 / 19 (10.53%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Pyrexia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Peripheral swelling			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Localised oedema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site haematoma			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Vessel puncture site swelling			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dyspnoea			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Epistaxis			

subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Nasal congestion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Investigations			
Haemoglobin decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 19 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Skin abrasion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 19 (15.79%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Vocal cord paralysis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	

Multiple sclerosis relapse			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Increased tendency to bruise			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Neutropenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Eye disorders			
Eye pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 19 (5.26%)	1 / 7 (14.29%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 7 (14.29%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	

Gingival bleeding			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tooth loss			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	2 / 19 (10.53%)	1 / 7 (14.29%)	
occurrences (all)	2	1	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Dermatitis allergic			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Erythema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	3	0	
Swelling face			

subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Flank pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 19 (5.26%)	0 / 7 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 19 (0.00%)	0 / 7 (0.00%)	
occurrences (all)	0	0	
Urinary tract infection			

subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 7 (0.00%) 0	
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	0 / 19 (0.00%) 0	0 / 7 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2013	The following modifications were done in this amendment: •Addition of thrombotic burden assessment as a secondary objective. The secondary outcomes text was modified to reflect the addition of the asymptomatic deterioration in the thrombotic burden. •Study indication was broadened to include right atrial thrombosis and catheter-related thrombosis. Also the inclusion criterion was broadened to include children with catheter-related thrombosis who had been treated with standard of care anticoagulant for at least 6 weeks. •Lab tests for bilirubin and alanine aminotransferase (ALT) were added in the inclusion and exclusion criteria. •Visit window at Day 15 was extended from +/-3 days to +/- 5 days. The text explaining when the repeat imaging needs to be done was also included. •Addition of height collection and lab tests during the days Day -60 to Day -10 and at Day 1 (10 days prior to randomization) •Clarification that the blood test as well as repeat imaging (when clinically feasible) was to be collected also at Day 31. •Deletion of description of the type of thrombosis to be considered as outcomes •Addition of the pharmacokinetic/pharmacodynamic sampling instructions for the case rivaroxaban dose was temporarily interrupted •Adverse events of special interest were clarified to reflect the newly added exclusion criterion •Added that subjects with concomitant therapy with other anticoagulants or fibrinolytic during the study treatment were to be prematurely discontinued from study treatment •Clarifications for the: dose confirmation, catheter related thrombosis, results of the EINSTEIN adult studies, definition of vascular events, and for the content of the study booklet were done
16 September 2014	In this amendment a more detailed description for the rivaroxaban oral suspension was added with clear separation from the tablet group.
14 April 2015	The following modifications were done in this amendment: •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. Also, due to the comparator arm removal the total subject number was reduced. •There was a change in the Inclusion criterion 1 to enable enrollment of children who are on long-term anticoagulant treatment. In addition to this, instructions on how to safely handle the switch from heparin, fondaparinux, and vitamin K antagonist to rivaroxaban and vice versa were made available in the protocol. •The platelet count threshold for exclusion of children was adjusted from < 100 * 10^9/liter to < 50 * 10^9/liter

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.

Occurrence of "±” in relation with geometric CV is auto-generated. Decimal places were automatically truncated if last decimal equals zero.

Notes: