



Clinical trial results:

7-day study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children from birth to less than 6 months with arterial or venous thrombosis

Summary

EudraCT number	2014-002385-74
Trial protocol	ES AT DE NL PL FR FI IT
Global end of trial date	18 December 2017

Results information

Result version number	v2 (current)
This version publication date	17 February 2019
First version publication date	27 June 2018
Version creation reason	• Correction of full data set Control of data.

Trial information

Trial identification

Sponsor protocol code	BAY59-7939/17618
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02564718
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)	EMA-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	18 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 December 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 characterize the pharmacokinetic (PK)/pharmacodynamic (PD) profile of a 7-day treatment with oral rivaroxaban (BAY59-7939).

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 Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and 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 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	Turkey: 1
Worldwide total number of subjects	10
EEA total number of subjects	8

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)	10
Children (2-11 years)	0
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 9 study centers in 7 countries between 19 November 2015 (first subject first visit) and 18 December 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 11 subjects were screened, of these 1 subject was not included in the study due to withdrawal by parent. A total of 10 subjects were assigned to treatment.

Period 1

Period 1 title	Overall Study (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) suspension bid

Arm description:

Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 3.2 milligram (mg) oral dose of rivaroxaban oral suspension twice daily (bid) for 7 days.

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

Dosage and administration details:

Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 3.2 mg oral dose of rivaroxaban oral suspension bid under fed conditions for 7 days.

Arm title	Rivaroxaban (BAY59-7939) suspension tid
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Arm description:

Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 2.9 mg oral dose of rivaroxaban oral suspension thrice daily (tid) for 7 days.

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

Dosage and administration details:

Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 2.9 mg oral dose of rivaroxaban oral suspension tid under fed conditions for 7 days.

Number of subjects in period 1	Rivaroxaban (BAY59-7939) suspension bid	Rivaroxaban (BAY59-7939) suspension tid
Started	5	5
Completed	5	4
Not completed	0	1
Withdrew from treatment	-	1

Baseline characteristics

Reporting groups

Reporting group title	Rivaroxaban (BAY59-7939) suspension bid
Reporting group description: Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 3.2 milligram (mg) oral dose of rivaroxaban oral suspension twice daily (bid) for 7 days.	
Reporting group title	Rivaroxaban (BAY59-7939) suspension tid
Reporting group description: Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 2.9 mg oral dose of rivaroxaban oral suspension thrice daily (tid) for 7 days.	

Reporting group values	Rivaroxaban (BAY59-7939) suspension bid	Rivaroxaban (BAY59-7939) suspension tid	Total
Number of subjects	5	5	10
Age categorical Units: Subjects			

Age Continuous Units: months arithmetic mean standard deviation	1.81 ± 2.24	1.12 ± 0.60	-
Sex: Female, Male Units: Subjects			
Female	1	4	5
Male	4	1	5
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	3	5	8
More than one race	0	0	0
Unknown or Not Reported	1	0	1
Prothrombin Time Units: seconds (sec) arithmetic mean standard deviation	13.3 ± 0.378	13.9 ± 1.31	-
Activated Partial Thromboplastin Time (aPTT) Units: seconds (sec) arithmetic mean standard deviation	34.0 ± 4.05	34.9 ± 2.62	-
Weight Units: kilograms (kg) arithmetic mean standard deviation	4.33 ± 2.19	3.70 ± 0.85	-

End points

End points reporting groups

Reporting group title	Rivaroxaban (BAY59-7939) suspension bid
Reporting group description: Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 3.2 milligram (mg) oral dose of rivaroxaban oral suspension twice daily (bid) for 7 days.	
Reporting group title	Rivaroxaban (BAY59-7939) suspension tid
Reporting group description: Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 2.9 mg oral dose of rivaroxaban oral suspension thrice daily (tid) for 7 days.	
Subject analysis set title	PK analysis set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: PKS included all subjects with at least one PK sample in accordance with the PK sampling strategy.	
Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: SAF included all subjects who received at least one dose of rivaroxaban.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: FAS included all subjects from whom informed consent was obtained and who contributed any data thereafter.	
Subject analysis set title	PD analysis set (PDS)
Subject analysis set type	Sub-group analysis
Subject analysis set description: PDS included all subjects with at least one blood sample for clotting parameters in accordance with the PD sampling strategy.	

Primary: Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Day 1

End point title	Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Day 1 ^[1]
End point description: Concentration of pharmacokinetic parameters of rivaroxaban in plasma was evaluated. 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	Primary
End point timeframe: 30 minutes to 1.5 hours post-dose, 2 to 4 hours post-dose (bid dosing) and 30 minutes to 3 hours post-dose, 7 to 8 hours post-dose on Day 1 (tid dosing)	

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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[2]	5 ^[3]		
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
30 minutes to 1.5 hours post-dose (n= 5,0)	85.2001 (± 37.72)	99999 (± 99999)		
30 minutes to 3 hours post-dose (n= 0,5)	99999 (± 99999)	42.6837 (± 39.35)		
2 to 4 hours post-dose (n= 4,0)	73.7641 (± 64.38)	99999 (± 99999)		
7 to 8 hours post-dose (n= 0,5)	99999 (± 99999)	12.1027 (± 130.13)		

Notes:

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

[3] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Day 3

End point title	Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Day 3 ^[4]
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End point description:

Concentration of pharmacokinetic parameters of rivaroxaban in plasma was evaluated. 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	Primary
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End point timeframe:

2 to 8 hours post-dose on Day 3 (bid dosing) and 30 minutes to 3 hours post-dose; 7 to 8 hours post-dose on Day 3 (tid dosing)

Notes:

[4] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[5]	4 ^[6]		
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)				
30 minutes to 3 hours post-dose (n= 0,4)	99999 (± 99999)	32.2879 (± 267.05)		
2 to 8 hours post-dose (n= 5,0)	102.3285 (± 40.36)	99999 (± 99999)		
7 to 8 hours post-dose (n= 0,5)	99999 (± 99999)	9.1716 (± 160.52)		

Notes:

[5] - PKS

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

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Day 8

End point title	Concentration of Rivaroxaban in Plasma as a Measure of Pharmacokinetics at Day 8 ^[7]
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End point description:

Concentration of pharmacokinetic parameters of rivaroxaban in plasma was evaluated.

End point type	Primary
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End point timeframe:

10 to 16 hours post-dose on Day 8 (bid dosing)

Notes:

[7] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[8]	0 ^[9]		
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)	2.5696 ($\pm$ 70.82)	()		

Notes:

[8] - PKS

[9] - No subjects were evaluated for the given time point for this reporting group

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Prothrombin Time at Day 1

End point title	Change From Baseline in Prothrombin Time at Day 1 ^[10]
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End point description:

Prothrombin time is a global clotting test used for the assessment of the extrinsic pathway of the blood coagulation cascade.

End point type	Primary
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End point timeframe:

10-16 hours post-dose on Day 8 (baseline), 2-4 hours after the first dose on Day 1 (bid dosing) and 7-8 hours after the first dose on Day 1 (tid dosing)

Notes:

[10] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3 ^[11]	4 ^[12]		
Units: seconds (sec)				
arithmetic mean (standard deviation)	11.6 (± 17.3)	0.025 (± 0.714)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Prothrombin Time at Day 3

End point title	Change From Baseline in Prothrombin Time at Day 3 ^[13]
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End point description:

Prothrombin time is a global clotting test used for the assessment of the extrinsic pathway of the blood coagulation cascade.

End point type	Primary
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End point timeframe:

10-16 hours post-dose on Day 8 (baseline), 2-8 hours post-dose on Day 3 (bid dosing) and 0.5-3 hours post-dose on Day 3 (tid dosing)

Notes:

[13] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[14]	3 ^[15]		
Units: seconds (sec)				
arithmetic mean (standard deviation)	3.74 (± 2.84)	1.13 (± 2.10)		

Notes:

[14] - PDS

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

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Activated Partial Thromboplastin Time (aPTT) at Day 1

End point title	Change From Baseline in Activated Partial Thromboplastin Time (aPTT) at Day 1 ^[16]
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End point description:

The Activated partial thromboplastin time (aPTT) is a screening test for the intrinsic pathway and is sensitive for deficiencies of factors I, II, V, VIII, IX, X, XI and XII.

End point type	Primary
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End point timeframe:

2-4 hours after the first dose on Day 1 (bid dosing) and 7-8 hours after the first dose on Day 1 (tid dosing)

Notes:

[16] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3 ^[17]	4 ^[18]		
Units: seconds (sec)				
arithmetic mean (standard deviation)	13.6 (± 12.4)	2.33 (± 5.53)		

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Activated Partial Thromboplastin Time (aPTT) at Day 3

End point title	Change From Baseline in Activated Partial Thromboplastin Time (aPTT) at Day 3 ^[19]
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End point description:

The Activated partial thromboplastin time (aPTT) is a screening test for the intrinsic pathway and is sensitive for deficiencies of factors I, II, V, VIII, IX, X, XI and XII.

End point type	Primary
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End point timeframe:

2-8 hours post-dose on Day 3 (bid dosing) and 0.5-3 hours post-dose on Day 3 (tid dosing)

Notes:

[19] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[20]	3 ^[21]		
Units: seconds (sec)				
arithmetic mean (standard deviation)	7.02 (± 5.08)	3.47 (± 7.59)		

Notes:

[20] - PDS

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

Statistical analyses

No statistical analyses for this end point

Primary: Anti-factor Xa Activity (anti-Xa) Values at Day 1

End point title	Anti-factor Xa Activity (anti-Xa) Values at Day 1 ^[22]
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End point description:

The individual anti-Factor Xa activity was determined ex-vivo using a photometric method.

End point type	Primary
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End point timeframe:

2-4 hours after the first dose on Day 1 (bid dosing) and 7-8 hours after the first dose on Day 1 (tid dosing)

Notes:

[22] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4 ^[23]	5 ^[24]		
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)	63.3 (± 60.8)	18.0 (± 8.37)		

Notes:

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

[24] - PDS

Statistical analyses

No statistical analyses for this end point

Primary: Anti-factor Xa Activity (anti-Xa) Values at Day 3

End point title	Anti-factor Xa Activity (anti-Xa) Values at Day 3 ^[25]
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End point description:

The individual anti-Factor Xa activity was determined ex-vivo using a photometric method.

End point type	Primary
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End point timeframe:

2-8 hours post-dose on Day 3 (bid dosing) and 0.5-3 hours post-dose on Day 3 (tid dosing)

Notes:

[25] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[26]	3 ^[27]		
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)	67.3 (± 48.7)	59.8 (± 46.8)		

Notes:

[26] - PDS

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

Statistical analyses

No statistical analyses for this end point

Primary: Anti-factor Xa Activity (anti-Xa) Values at Day 8

End point title	Anti-factor Xa Activity (anti-Xa) Values at Day 8 ^[28]
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End point description:

The individual anti-Factor Xa activity was determined ex-vivo using a photometric method.

End point type	Primary
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End point timeframe:

10-16 hours post-dose on Day 8 (both bid and tid dosing)

Notes:

[28] - 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) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[29]	4 ^[30]		
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)	7.25 (± 0.00)	9.92 (± 5.35)		

Notes:

[29] - PDS

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

Statistical analyses

No statistical analyses for this end point

Secondary: 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
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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/deciliter (g/dL) or more,
- 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, example: 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

End point type	Secondary
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End point timeframe:

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

End point values	Rivaroxaban (BAY59-7939) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[31]	5 ^[32]		
Units: count of subjects				
Major bleeding events	0	0		

Clinically relevant non-major bleeding events	0	0		
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Notes:

[31] - SAF

[32] - SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Symptomatic Recurrent Venous Thromboembolism and Asymptomatic Deterioration in Thrombotic Burden on Repeat Imaging

End point title	Number of Subjects With Symptomatic Recurrent Venous Thromboembolism and Asymptomatic Deterioration in Thrombotic Burden on Repeat Imaging
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End point description:

Symptomatic recurrence of thromboembolism and asymptomatic deterioration was documented using the appropriate imaging test and confirmed by CIAC which was unaware of treatment assignment. Asymptomatic deterioration in thrombotic burden on repeat imaging, as assessed by the CIAC. Adjudication results were the basis for the final analyses.

End point type	Secondary
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End point timeframe:

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

End point values	Rivaroxaban (BAY59-7939) suspension bid	Rivaroxaban (BAY59-7939) suspension tid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5 ^[33]	5 ^[34]		
Units: count of subjects				
Symptomatic recurrent venous thromboembolism	0	0		
Asymptomatic deterioration in thrombotic burden	0	0		

Notes:

[33] - FAS

[34] - FAS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of study treatment up to 30 days after the last administration of study drug

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Rivaroxaban (BAY59-7939) suspension bid
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Reporting group description:

Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 3.2 mg oral dose of rivaroxaban oral suspension bid for 7 days.

Reporting group title	Rivaroxaban (BAY59-7939) suspension tid
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Reporting group description:

Subjects aged less than 6 months were administered with age- and body weight-adjusted 0.5 to 2.9 mg oral dose of rivaroxaban oral suspension tid for 7 days.

Serious adverse events	Rivaroxaban (BAY59-7939) suspension bid	Rivaroxaban (BAY59-7939) suspension tid	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Atrial thrombosis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 5 (20.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Rivaroxaban (BAY59-7939) suspension bid	Rivaroxaban (BAY59-7939) suspension tid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
Gastrointestinal disorders			
Vomiting			

subjects affected / exposed	1 / 5 (20.00%)	0 / 5 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2015	The following modifications were done in this amendment: • A minimum body weight of 2600 grams was added to inclusion criteria to ensure that the total volume of blood collected in the course of the study did not exceed the total volume allowed by respective guidelines • Blood pressure measurement was added at screening • The International normalized ratio (INR) measurement was added at Day 1 in the study flow charts and the visit description at screening. Rivaroxaban could be started only if the INR was below 2.5. Therefore, the INR had to be collected before rivaroxaban was started. • A body weight-adjusted dosing table for rivaroxaban oral suspension was added. • The text of Day 1 was changed in order to enroll subjects without prior central independent adjudication committee (CIAC) confirmation if they met the inclusion criteria and did not meet any of the exclusion criteria.
10 May 2016	The following modifications were done in this amendment: • The study population was extended by removing the requirement of having a "catheter-related" arterial or venous thrombosis. • Inclusion criterion was changed. The minimum time of initial heparinization before start of rivaroxaban treatment was reduced from at least 2 weeks to at least 5 days. • In exclusion criterion, the word uncontrolled was added. Subject with a antihypertensive therapy leading to normal blood pressure values (ie. less than 95th percentile) were allowed to be enrolled in the study. • In exclusion criterion, it was clarified that subject should not have an indication for continued antiplatelet or Non-steroid anti-inflammatory drug (NSAID) therapy. However, incidental use is allowed. • The rivaroxaban formulation was changed from "ready-to-use" suspension to "granules for oral suspension". • The process for assessment of the index event by the CIAC was clarified. The CIAC assessed the index event; however, inclusion of subject into the study did not depend on the outcome of the assessment. • At Day 3 drug accountability and compliance were not be assessed. It was decided to measure the volume only after completion of treatment. • Timing of rivaroxaban administration in relation to feeding was defined. Rivaroxaban should be administered immediately before or (early) during feeding.
15 November 2016	The following modifications were done in this amendment: • The dosing regimen was modified from twice daily schedule to three times daily administration of the same individual dose previously used with the twice daily schedule. • Provision of additional imaging tests for adjudication was added. Investigators were asked to also submit diagnostic tests other than ultrasound for evaluation of repeat imaging by the CIAC, if available.

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: