Clinical trial results:
Single-dose study testing a rivaroxaban granules for oral suspension formulation in children from 2 months to 12 years with previous thrombosis

Summary

EudraCT number	2015-000962-76
Trial protocol	AT BE IE ES FI HU SE FR IT
Global end of trial date	22 May 2018

Results information

Result version number	v1 (current)
This version publication date	02 December 2018
First version publication date	02 December 2018

Trial information

Trial identification

Sponsor protocol code	17992

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02497716
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)	No
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	22 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to characterize the pharmacokinetic (PK) profile of rivaroxaban (BAY59-7939, Xarelto) administered as granules for oral suspension.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with 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 the 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	04 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 6
Country: Number of subjects enrolled	Hungary: 1
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	United States: 5
Worldwide total number of subjects	47
EEA total number of subjects	28

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	18
Children (2-11 years)	29
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 globally between 04 November 2015 (first subject first visit) and 22 May 2018 (last subject last visit).

Pre-assignment

Screening details:

Overall, 56 subjects were screened. Of them, 9 subjects were screening failures and 47 subjects were enrolled and 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	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)

Arm description:

Subjects were administered with body weight-adjusted single low dose from the previous phase I study 12892 (2009-0173130-30) of rivaroxaban (BAY59-7939) as a granules for an oral suspension under fed conditions.

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

Dosage and administration details:

Subjects were administered with body weight-adjusted single low dose from the previous phase I study 12892 (2009-0173130-30) of rivaroxaban as a granules for an oral suspension under fed conditions.

Arm title	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)

Arm description:

Subjects were administered with body weight adjusted single oral dose from the previous phase II studies 14373 (2011-004539-30) and 14374 (2014-000566-22) of rivaroxaban as a granules for an oral suspension under fed conditions.

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

Dosage and administration details:

Subjects were administered with body weight-adjusted single oral dose from the previous phase II studies 14373 (2011-004539-30) and 14374 (2014-000566-22) of rivaroxaban as a granules for an oral suspension under fed conditions.

Arm title	Group C: Rivaroxaban (0.4 mg/kg Body Weight)

Arm description:

Subjects were administered with body weight-adjusted rivaroxaban granules for oral suspension at a single oral dose of 0.4 milligram/kilogram (mg/kg) body weight for subjects weighing 3 to less than (<) 12 kilogram (kg).

Arm type	Experimental

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

Dosage and administration details:

Subjects were administered with body weight-adjusted rivaroxaban granules for oral suspension at a single oral dose of 0.4 mg/kg body weight for subjects weighing 3 to < 12 kg.

Number of subjects in period 1	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Started	22	23	2
Completed	22	23	2

Baseline characteristics

Reporting groups	
Reporting group title	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)
Reporting group description:	
Subjects were administered with body weight-adjusted single low dose from the previous phase I study 12892 (2009-0173130-30) of rivaroxaban (BAY59-7939) as a granules for an oral suspension under fed conditions.	
Reporting group title	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)
Reporting group description:	
Subjects were administered with body weight adjusted single oral dose from the previous phase II studies 14373 (2011-004539-30) and 14374 (2014-000566-22) of rivaroxaban as a granules for an oral suspension under fed conditions.	
Reporting group title	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Reporting group description:	
Subjects were administered with body weight-adjusted rivaroxaban granules for oral suspension at a single oral dose of 0.4 milligram/kilogram (mg/kg) body weight for subjects weighing 3 to less than (<) 12 kilogram (kg).	

Reporting group values	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Number of subjects	22	23	2
Age Categorical			
Units: Subjects			
Age Continuous			
Units: months			
arithmetic mean	63.5	61.2	3.5
standard deviation	± 44.9	± 49.9	± 0.7
Gender Categorical			
Units: Subjects			
Female	9	8	1
Male	13	15	1
Weight			
The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n=44, Group A = 20, Group B = 22, Group C = 2).			
Units: kilograms (kg)			
arithmetic mean	21.34	20.53	7.30
standard deviation	± 12.63	± 15.17	± 0.85

Reporting group values	Total		
Number of subjects	47		
Age Categorical			
Units: Subjects			
Age Continuous			
Units: months			
arithmetic mean			
standard deviation	-		

Gender Categorical Units: Subjects			
Female	18		
Male	29		
Weight			
The number of subjects analysed signifies subjects who were evaluable for this parameter, for each arm respectively, (n=44, Group A = 20, Group B = 22, Group C = 2).			
Units: kilograms (kg) arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)
Reporting group description:	
Subjects were administered with body weight-adjusted single low dose from the previous phase I study 12892 (2009-0173130-30) of rivaroxaban (BAY59-7939) as a granules for an oral suspension under fed conditions.	
Reporting group title	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)
Reporting group description:	
Subjects were administered with body weight adjusted single oral dose from the previous phase II studies 14373 (2011-004539-30) and 14374 (2014-000566-22) of rivaroxaban as a granules for an oral suspension under fed conditions.	
Reporting group title	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Reporting group description:	
Subjects were administered with body weight-adjusted rivaroxaban granules for oral suspension at a single oral dose of 0.4 milligram/kilogram (mg/kg) body weight for subjects weighing 3 to less than (<) 12 kilogram (kg).	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all subjects who received at least one dose of study medication (N=47).	
Subject analysis set title	Pharmacokinetic analysis set (PKS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PKS included all subjects who received at least one dose of study medication and with a valid PK profile for rivaroxaban (N=45).	
Subject analysis set title	Pharmacodynamic analysis set (PDS)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PDS included all subjects with at least 1 blood sample for clotting parameters in accordance with the PD sampling strategy (N=45).	

Primary: Area Under the Concentration- Versus Time Curve from Zero to Infinity (AUC) of Rivaroxaban in Plasma after Single Dose Administration

End point title	Area Under the Concentration- Versus Time Curve from Zero to Infinity (AUC) of Rivaroxaban in Plasma after Single Dose Administration[1]
End point description:	
Area under the concentration- versus time curve from zero to infinity of rivaroxaban in plasma after single dose administration was measured. Geometric Mean and percentage of geometric coefficient of variation were reported.	
End point type	Primary
End point timeframe:	
6 months to <2 years: pre dose to 5 hours of post dose on Day 1; 2 to <6 years: pre dose to 24 hours of post dose on Day 2; 6 to <12 years: pre dose to 24 hours of post dose on Day 2	

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: Only descriptive statistics were done, no inferential statistics performed.

End point values	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[2]	21[3]	2[4]	
Units: microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)	724.982 (± 1.558)	1006.956 (± 1.490)	531.281 (± 1.237)	

Notes:

[2] - PKS

[3] - PKS

[4] - PKS

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Observed Drug Concentration (Cmax) of Rivaroxaban in Plasma after Single Dose Administration

End point title	Maximum Observed Drug Concentration (Cmax) of Rivaroxaban in Plasma after Single Dose Administration[5]

End point description:

Maximum observed drug concentration of rivaroxaban in plasma after single dose administration was measured. Geometric Mean and percentage of geometric coefficient of variation were reported.

End point type	Primary

End point timeframe:

6 months to <2 years: pre dose to 5 hours of post dose on Day 1; 2 to <6 years: pre dose to 24 hours of post dose on Day 2; 6 to <12 years: pre dose to 24 hours of post dose on Day 2

Notes:

[5] - 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: Only descriptive statistics were done, no inferential statistics performed.

End point values	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[6]	21[7]	2[8]	
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)	97.188 (± 24.10)	133.026 (± 22.66)	145.273 (± 22.80)	

Notes:

[6] - PKS

[7] - PKS

[8] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin Time (PT) at Specific Time Points

End point title	Prothrombin Time (PT) at Specific Time Points[9]

End point description:

Prothrombin time (PT) is a global clotting test used for the assessment of the extrinsic pathway of the blood coagulation cascade. Median and full range were reported.

End point type	Secondary

End point timeframe:

6 months to <2 years: pre dose to 5 hours of post dose on Day 1; 2 to <6 years: pre dose to 24 hours of post dose on Day 2; 6 to <12 years: pre dose to 24 hours of post dose on Day 2

Notes:

[9] - 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: PD samples were not collected for Group C

End point values	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[10]	21[11]		
Units: Second (sec)				
median (full range (min-max))				
0 Minutes (n=22,21)	13.400 (12.60 to 15.40)	13.000 (11.80 to 15.80)		
30 - 90 minutes post dose (n=9,6)	16.400 (14.00 to 23.50)	18.200 (13.40 to 21.70)		
90 minutes - 5 hours post dose (n=13,15)	15.300 (12.50 to 31.10)	16.700 (13.90 to 23.30)		
2 - 5 hours post dose (n=9,6)	17.300 (14.00 to 25.50)	16.850 (13.80 to 20.80)		
8 - 12 hours post dose (n=16,12)	15.000 (13.40 to 19.40)	14.400 (12.50 to 21.20)		
20 - 24 hours post dose (n=20,21)	14.000 (12.40 to 15.30)	13.600 (12.30 to 17.40)		

Notes:

[10] - PDS with evaluable number of subjects.

[11] - PDS with evaluable number of subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Activated Partial Thromboplastin Time (aPTT) at Specific Time Points

End point title	Activated Partial Thromboplastin Time (aPTT) at Specific Time Points[12]

End point description:

The Activated partial thromboplastin time (aPTT) is a screening test for the intrinsic pathway. Median and full range were reported.

End point type	Secondary

End point timeframe:

6 months to <2 years: pre dose to 5 hours of post dose on Day 1; 2 to <6 years: pre dose to 24 hours of post dose on Day 2; 6 to <12 years: pre dose to 24 hours of post dose on Day 2

Notes:

[12] - 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: PD samples were not collected for Group C.

End point values	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22[13]	21[14]		
Units: sec				
median (full range (min-max))				
0 Minutes (n=22,21)	31.300 (27.00 to 42.10)	29.700 (18.80 to 39.80)		
30 - 90 minutes post dose (n=9,6)	36.300 (32.60 to 48.20)	39.000 (30.00 to 49.20)		
90 minutes - 5 hours post dose (n=13,15)	36.500 (27.50 to 79.40)	39.100 (31.80 to 44.50)		
2 - 5 hours post dose (n=9,6)	37.400 (34.20 to 51.60)	36.900 (32.80 to 47.90)		
8 - 12 hours post dose (n=16,12)	35.250 (31.40 to 42.50)	34.750 (27.30 to 49.00)		
20 - 24 hours post dose (n=20,21)	32.150 (29.10 to 180.00)	31.100 (20.30 to 47.40)		

Notes:

[13] - PDS with evaluable number of subjects.

[14] - PDS with evaluable number of subjects.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Composite of Major Bleeding and Clinically Relevant Non-Major Bleeding

End point title	Number of Subjects with Composite of Major Bleeding and Clinically Relevant Non-Major Bleeding

End point description:

Major bleeding was defined as over bleeding and associated with a fall in hemoglobin of 2 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 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 with a physician, or discomfort for the child such as pain.

End point type	Secondary

End point timeframe:

From start of treatment up to follow up (11 days)

End point values	Group A: Rivaroxaban Phase I Dose (10 mg equvalent)	Group B: Rivaroxaban Phase II Dose (20 mg equvalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	22[15]	23[16]	2[17]	
Units: Subject	0	0	0	

Notes:
[15] - FAS with evaluable number of subjects.
[16] - FAS with evaluable number of subjects.
[17] - FAS with evaluable number of subjects.

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 up to 11 days after end of treatment	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Group A: Rivaroxaban Phase I Dose (10 mg equivalent)
Reporting group description:	
Subjects were administered with body weight-adjusted single low dose from the previous phase I study 12892 (2009-0173130-30) of rivaroxaban as a granules for an oral suspension under fed conditions.	
Reporting group title	Group B: Rivaroxaban Phase II Dose (20 mg equivalent)
Reporting group description:	
Subjects were administered with body weight-adjusted single oral dose from the previous phase II studies 14373 (2011-004539-30) and 14374 (2014-000566-22) of rivaroxaban as a granules for an oral suspension under fed conditions.	
Reporting group title	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Reporting group description:	
Subjects were administered with body weight-adjusted rivaroxaban granules for oral suspension at a single oral dose of 0.4 mg/kg body weight for subjects weighing 3 to < 12 kg.	

Serious adverse events	Group A: Rivaroxaban Phase I Dose (10 mg equivalent)	Group B: Rivaroxaban Phase II Dose (20 mg equivalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 22 (0.00%)	0 / 23 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

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

Non-serious adverse events	Group A: Rivaroxaban Phase I Dose (10 mg equivalent)	Group B: Rivaroxaban Phase II Dose (20 mg equivalent)	Group C: Rivaroxaban (0.4 mg/kg Body Weight)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	7 / 23 (30.43%)	0 / 2 (0.00%)
Investigations			
Activated partial thromboplastin time prolonged			

subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	0 / 2 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Stoma site haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Injection site bruising			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site bruise			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vessel puncture site pruritus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	0 / 2 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	0 / 2 (0.00%)
occurrences (all)	0	2	0
Skin and subcutaneous tissue disorders			
Rash			

subjects affected / exposed occurrences (all)	1 / 22 (4.55%) 1	0 / 23 (0.00%) 0	0 / 2 (0.00%) 0
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	1 / 23 (4.35%) 1	0 / 2 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 March 2016	The following modifications were done in this amendment. 1.Addition of a dose group. 2.Naming of the two dose groups. 3.Replacement of the Cockcroft Gault formula by the Schwartz formula. 4.Adjustment of number of subjects. 5.Clarification for local lab PT reporting. 6.Addition of data from relative bioavailability study in adults. 7.Adjustment of PK/PD evaluations to reflect that 2 doses will be tested. 8.Update of study procedures. 9.Addition of premature termination information.
20 March 2017	The following modifications were done in this amendment: 1.Rename of dosage formulation from dry powder to granules for oral suspension. 2.Extension of age group. 3.Addition of new dose group (group C). 4.Removal of central lab PD samples/ additional PK samples in children of Group C. 5.Extension of hospital stay from 5 to 8 hours on Day 1. 6.Additional PK parameter drug concentration in plasma 8 hours after administration (C_8h) was added.

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 decimals is equals to zero.

Notes: