Clinical trial results:
Single-dose, open-label, randomized, 2-way crossover bioequivalence study of 20 mg granules for oral suspension rivaroxaban versus 20 mg tablets rivaroxaban under fed condition in healthy subjects

Summary

EudraCT number	2017-000609-18
Trial protocol	DE
Global end of trial date	27 October 2017

Results information

Result version number	v1 (current)
This version publication date	06 September 2018
First version publication date	06 September 2018

Trial information

Trial identification

Sponsor protocol code	BAY59-7939/19366

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 October 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to establish bioequivalence with respect to area under concentration versus time curve from zero to infinity after single dose administration (AUC), AUC from time zero to the last data point (AUC[0-tlast]) and maximum observed drug concentration (Cmax) of 20 milligrams (mg) granules for oral suspension versus 20 mg tablets rivaroxaban (BAY59-7939, Xarelto) when administered as single oral dose under fed conditions.

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 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 July 2017
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	Germany: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	30
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at one study center in Germany, between 04 July 2017 (first subject first visit) and 04 September 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 68 subjects were enrolled, of these 38 subjects were screen failures: 2 subjects withdrew consent, 6 subjects were qualified but not needed and 30 subjects failed screening. A total of 30 subjects were randomized and received at least one dose of rivaroxaban.

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	Treatment A-B

Arm description:

Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A) during treatment period 1; followed by a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B) during treatment period 2. A wash-out period of at least 7 days was maintained between the treatments.

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

Dosage and administration details:

Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A).

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 received a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B).

Arm title	Treatment B-A

Arm description:

Subjects received a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B) during treatment period 1; followed by a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A) during treatment period 2. A wash-out period of at least 7 days was maintained between the treatments.

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 received a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B).

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

Dosage and administration details:

Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A).

Number of subjects in period 1	Treatment A-B	Treatment B-A
Started	15	15
Completed	14	14
Not completed	1	1
Withdrawal by subject	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment A-B
Reporting group description:	
Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A) during treatment period 1; followed by a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B) during treatment period 2. A wash-out period of at least 7 days was maintained between the treatments.	
Reporting group title	Treatment B-A
Reporting group description:	
Subjects received a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B) during treatment period 1; followed by a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A) during treatment period 2. A wash-out period of at least 7 days was maintained between the treatments.	

Reporting group values	Treatment A-B	Treatment B-A	Total
Number of subjects	15	15	30
Age Categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	38.3	38.5	
standard deviation	± 11.2	± 12.0	-
Gender Categorical			
Units: Subjects			
Male	15	15	30

End points

End points reporting groups

Reporting group title	Treatment A-B

Reporting group description:

Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A) during treatment period 1; followed by a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B) during treatment period 2. A wash-out period of at least 7 days was maintained between the treatments.

Reporting group title	Treatment B-A

Reporting group description:

Subjects received a single oral dose of 20 mg rivaroxaban oral suspension in the fed state on Day 1 (Treatment B) during treatment period 1; followed by a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 (Treatment A) during treatment period 2. A wash-out period of at least 7 days was maintained between the treatments.

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 the study medication (N=30).

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

Subject analysis set description:

PKS included all subjects who completed all treatment periods, and for whom valid sets of pharmacokinetic samples were taken (N=28).

Subject analysis set title	20 mg Rivaroxaban tablet (Treatment A)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 during either of the treatment periods (N=29).

Subject analysis set title	20 mg Rivaroxaban oral suspension (Treatment B)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received a single oral dose of 20 mg rivaroxaban granules for oral suspension in the fed state on Day 1 during either of the treatment periods (N=30).

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

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 geometric coefficient of variation were reported.

End point type	Primary

End point timeframe:

pre dose (0 hour) up to 72 hours post dose

End point values	20 mg Rivaroxaban tablet (Treatment A)	20 mg Rivaroxaban oral suspension (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[1]	28[2]		
Units: microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)	2600 (± 28.7)	2560 (± 30.5)		

Notes:

[1] - PKS

[2] - PKS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Logarithms of AUC were analyzed using analysis of variance (ANOVA) including sequence, subject (sequence), period, and treatment effects. Based on these analyses point estimates (Least squares [LS] mean) and 90% confidence intervals (CIs) for the treatment ratio: 20 mg granules for oral suspension/tablet were calculated by re- transformation of the logarithmic results given by the ANOVA. Database auto-calculates total number of subjects erroneously, analyzed number of subjects was 28.

Comparison groups	20 mg Rivaroxaban oral suspension (Treatment B) v 20 mg Rivaroxaban tablet (Treatment A)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean
Point estimate	0.9843
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.9433
upper limit	1.0271

Primary: Area Under the Concentration Versus Time Curve From Time Zero to the Last Data Point Greater Than (>) Lower Limit Of Quantification (LLOQ) (AUC[0-tlast]) of Rivaroxaban in Plasma After Single Dose Administration

End point title	Area Under the Concentration Versus Time Curve From Time Zero to the Last Data Point Greater Than (>) Lower Limit Of Quantification (LLOQ) (AUC[0-tlast]) of Rivaroxaban in Plasma After Single Dose Administration

End point description:

Area under the concentration versus time curve from time zero to the last data point greater than (>) lower limit of quantification of rivaroxaban in plasma after single dose administration was measured. Geometric mean and percentage geometric coefficient of variation were reported.

End point type	Primary

End point timeframe:

pre dose (0 hour) up to 72 hours post dose

End point values	20 mg Rivaroxaban tablet (Treatment A)	20 mg Rivaroxaban oral suspension (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[3]	28[4]		
Units: microgram*hour per liter (mcg*h/L)				
geometric mean (geometric coefficient of variation)	2570 (± 28.6)	2540 (± 30.6)		

Notes:

[3] - PKS

[4] - PKS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Logarithms of AUC(0-tlast) were analyzed using ANOVA including sequence, subject (sequence), period, and treatment effects. Based on these analyses point estimates (LS mean) and 90 % CIs for the treatment ratio: 20 mg granules for oral suspension/tablet were calculated by re- transformation of the logarithmic results given by the ANOVA. Database auto-calculates total number of subjects erroneously, analyzed number of subjects was 28.

Comparison groups	20 mg Rivaroxaban oral suspension (Treatment B) v 20 mg Rivaroxaban tablet (Treatment A)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean
Point estimate	0.9869
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.946
upper limit	1.0295

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

End point description:

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

End point type	Primary

End point timeframe:

pre dose (0 hour) up to 72 hours post dose

End point values	20 mg Rivaroxaban tablet (Treatment A)	20 mg Rivaroxaban oral suspension (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	28[5]	28[6]		
Units: microgram per liter (mcg/L)				
geometric mean (geometric coefficient of variation)	343 (± 27.1)	302 (± 24.0)		

Notes:

[5] - PKS

[6] - PKS

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Logarithms of Cmax were analyzed using ANOVA including sequence, subject (sequence), period, and treatment effects. Based on these analyses point estimates (LS mean) and 90% CIs for the treatment ratio: 20 mg granules for oral suspension/tablet were calculated by re- transformation of the logarithmic results given by the ANOVA. Database auto-calculates total number of subjects erroneously, analyzed number of subjects was 28.

Comparison groups	20 mg Rivaroxaban oral suspension (Treatment B) v 20 mg Rivaroxaban tablet (Treatment A)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	LS mean
Point estimate	0.8822
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.8146
upper limit	0.9554

Secondary: Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects With Treatment-emergent Adverse Events (TEAEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. AEs that started or worsened after first administration of study medication up to 14 days after end of treatment with study medication were considered to be treatment emergent (TE).

End point type	Secondary

End point timeframe:

from start of study drug administration up to 14 days after last study drug administration

End point values	20 mg Rivaroxaban tablet (Treatment A)	20 mg Rivaroxaban oral suspension (Treatment B)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29[7]	30[8]		
Units: count of subjects	5	2		

Notes:

[7] - SAF with evaluable number of subjects for this specific end point

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: from start of study drug administration until 14 days after the last study drug administration	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	20 mg Rivaroxaban oral suspension
Reporting group description: Subjects received a single oral dose of 20 mg rivaroxaban granules for oral suspension in the fed state on Day 1 during either of the treatment periods.	
Reporting group title	20 mg Rivaroxaban tablet
Reporting group description: Subjects received a single oral dose of 20 mg rivaroxaban tablet in the fed state on Day 1 during either of the treatment periods.	

Serious adverse events	20 mg Rivaroxaban oral suspension	20 mg Rivaroxaban tablet	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 29 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	20 mg Rivaroxaban oral suspension	20 mg Rivaroxaban tablet	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	5 / 29 (17.24%)	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Vascular access site haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			

Dizziness			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 30 (3.33%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Immune system disorders			
Allergy to arthropod bite			
subjects affected / exposed	0 / 30 (0.00%)	1 / 29 (3.45%)	
occurrences (all)	0	1	
Infections and infestations			
Otitis media			
subjects affected / exposed	1 / 30 (3.33%)	0 / 29 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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: