



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 standard deviation | 38.3 ± 11.2 | 38.5 ± 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 occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 2 / 29 (6.90%) 2 | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Immune system disorders Allergy to arthropod bite subjects affected / exposed occurrences (all) | 0 / 30 (0.00%) 0 | 1 / 29 (3.45%) 1 | |
| Infections and infestations Otitis media subjects affected / exposed occurrences (all) | 1 / 30 (3.33%) 1 | 0 / 29 (0.00%) 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: