



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 equivalent) |

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 equivalent) |
|------------------|-------------------------------------------------------|

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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | 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 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 (BAY59-7939) 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 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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | 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 standard deviation | 63.5 ± 44.9 | 61.2 ± 49.9 | 3.5 ± 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 standard deviation | 21.34 ± 12.63 | 20.53 ± 15.17 | 7.30 ± 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 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 (BAY59-7939) 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 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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | 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 (C_{max}) of Rivaroxaban in Plasma after Single Dose Administration

| | |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Maximum Observed Drug Concentration (C _{max}) 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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | 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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | | |
|---------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------|--|--|
| 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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | | |
|---------------------------------------------|------------------------------------------------------------------|-------------------------------------------------------------------|--|--|
| 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 equivalent) | Group B: Rivaroxaban Phase II Dose (20 mg equivalent) | 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 occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 23 (0.00%) 0 | 0 / 2 (0.00%) 0 |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| Stoma site haemorrhage subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 2 | 0 / 2 (0.00%) 0 |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| General disorders and administration site conditions Injection site bruising subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| Vessel puncture site bruise subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| Vessel puncture site pruritus subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 23 (4.35%) 1 | 0 / 2 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 2 / 23 (8.70%) 2 | 0 / 2 (0.00%) 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: