



Clinical trial results:

A Prospective, Open-label, Active-controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of Rivaroxaban for Thromboprophylaxis in Pediatric Subjects 2 to 8 Years of Age after the Fontan Procedure

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-002610-76 |
| Trial protocol | BE FR ES NL |
| Global end of trial date | 16 July 2020 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v2 (current) |
| This version publication date | 28 June 2021 |
| First version publication date | 31 January 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | CR108075 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02846532 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Janssen Research & Development, LLC |
| Sponsor organisation address | 920 Route 202, Raritan, United States, |
| Public contact | Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry group, Janssen Research & Development, LLC, ClinicalTrialsEU@its.jnj.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 | 24 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 July 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 July 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to characterize the single- and multiple-dose pharmacokinetic (PK) and PK/pharmacodynamic (PD) profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 years of age with single ventricle physiology who had completed the Fontan procedure within 4 months prior to enrollment (Part A); and to evaluate the safety and efficacy of rivaroxaban, administered twice daily (exposure matched to rivaroxaban 10 milligram [mg] once daily in adults) compared to acetylsalicylic acid (ASA), given once daily (approximately 5 milligram per kilogram [mg/kg]) for thromboprophylaxis in the same population as in Part A (Part B).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements. Safety evaluations included bleeding events, adverse events, adverse events of special interest (AESIs), clinical laboratory tests (hematology, serum chemistry etc.), other safety observations were performed throughout the study for all subjects.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 17 November 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Argentina: 6 |
| Country: Number of subjects enrolled | Belgium: 9 |
| Country: Number of subjects enrolled | Brazil: 17 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Japan: 9 |
| Country: Number of subjects enrolled | Mexico: 8 |
| Country: Number of subjects enrolled | Malaysia: 10 |
| Country: Number of subjects enrolled | Netherlands: 1 |
| Country: Number of subjects enrolled | United States: 40 |
| Worldwide total number of subjects | 112 |
| EEA total number of subjects | 16 |

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) | 112 |
| 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: -

Pre-assignment

Screening details:

A total of 112 subjects were enrolled in the study, out of which 12 were enrolled in Part A and 100 in Part B and 107 completed the study.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Rivaroxaban (Part A) |

Arm description:

Subjects were enrolled to receive rivaroxaban as 0.1 percent (%) (1 milligram per milliliter [mg/ml]) oral suspension as per subjects age and body weight adjusted dosing (target exposure to match that of rivaroxaban 10 mg given once daily in adults) with the regular twice daily regimen (morning and evening dosing), initially up to 12 Days. The single and multiple-dose rivaroxaban pharmacokinetics (PK), pharmacodynamics (PD), and initial safety and tolerability data available from each subject was assessed prior to continue 12 months of rivaroxaban therapy of Part A.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rivaroxaban |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Rivaroxaban was administered twice daily as a 0.1 percent (%) (1 milligram per milliliter [mg/ml]) oral suspension (age- and body weight-adjusted dosing).

| | |
|------------------|----------------------|
| Arm title | Rivaroxaban (Part B) |
|------------------|----------------------|

Arm description:

Subjects who were randomized to receive rivaroxaban as 0.1 % (1 mg/ml) oral suspension as per subjects age and body weight adjusted dosing (target exposure to match that of rivaroxaban 10 mg given once daily in adults) with the regular twice daily regimen (morning and evening dosing). The single and multiple-dose rivaroxaban PK, PD, safety and tolerability data available from each subject was assessed during 12 months of rivaroxaban therapy of Part B.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rivaroxaban |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

Rivaroxaban was administered twice daily as a 0.1% (1 mg/ml) oral suspension (age- and body weight-adjusted dosing).

| | |
|------------------|------------------|
| Arm title | Aspirin (Part B) |
|------------------|------------------|

Arm description:

Subjects who were randomized to receive Aspirin 5 milligram per kilogram (ml/kg) once daily up to 12 months.

| | |
|--|----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Aspirin |
| Investigational medicinal product code | |
| Other name | Acetylsalicylic acid (ASA) |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Aspirin was administered approximately as 5 milligram per kilogram (mg/kg) once daily dose up to 12 months.

| Number of subjects in period 1 | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) |
|---------------------------------------|----------------------|----------------------|------------------|
| Started | 12 | 66 | 34 |
| Completed | 11 | 63 | 33 |
| Not completed | 1 | 3 | 1 |
| Other | 1 | 2 | - |
| Lost to follow-up | - | 1 | 1 |

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | Rivaroxaban (Part A) |
| Reporting group description: | |
| Subjects were enrolled to receive rivaroxaban as 0.1 percent (%) (1 milligram per milliliter [mg/ml]) oral suspension as per subjects age and body weight adjusted dosing (target exposure to match that of rivaroxaban 10 mg given once daily in adults) with the regular twice daily regimen (morning and evening dosing), initially up to 12 Days. The single and multiple-dose rivaroxaban pharmacokinetics (PK), pharmacodynamics (PD), and initial safety and tolerability data available from each subject was assessed prior to continue 12 months of rivaroxaban therapy of Part A. | |
| Reporting group title | Rivaroxaban (Part B) |
| Reporting group description: | |
| Subjects who were randomized to receive rivaroxaban as 0.1 % (1 mg/ml) oral suspension as per subjects age and body weight adjusted dosing (target exposure to match that of rivaroxaban 10 mg given once daily in adults) with the regular twice daily regimen (morning and evening dosing). The single and multiple-dose rivaroxaban PK, PD, safety and tolerability data available from each subject was assessed during 12 months of rivaroxaban therapy of Part B. | |
| Reporting group title | Aspirin (Part B) |
| Reporting group description: | |
| Subjects who were randomized to receive Aspirin 5 milligram per kilogram (ml/kg) once daily up to 12 months. | |

| Reporting group values | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) |
|---|----------------------|----------------------|------------------|
| Number of subjects | 12 | 66 | 34 |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 12 | 66 | 34 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65 to 84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Title for AgeContinuous Units: years | | | |
| arithmetic mean | 2.5 | 4.1 | 4.2 |
| standard deviation | ± 0.67 | ± 1.74 | ± 1.8 |
| Title for Gender Units: subjects | | | |
| Female | 5 | 30 | 11 |
| Male | 7 | 36 | 23 |

| Reporting group values | Total | | |
|---|-------|--|--|
| Number of subjects | 112 | | |
| Title for AgeCategorical Units: subjects | | | |
| Children (2-11 years) | 112 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65 to 84 years | 0 | | |
| 85 years and over | 0 | | |

| | | | |
|--|----|--|--|
| Title for AgeContinuous Units: years arithmetic mean standard deviation | - | | |
| Title for Gender Units: subjects | | | |
| Female | 46 | | |
| Male | 66 | | |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | Rivaroxaban (Part A) |
| Reporting group description: Subjects were enrolled to receive rivaroxaban as 0.1 percent (%) (1 milligram per milliliter [mg/ml]) oral suspension as per subjects age and body weight adjusted dosing (target exposure to match that of rivaroxaban 10 mg given once daily in adults) with the regular twice daily regimen (morning and evening dosing), initially up to 12 Days. The single and multiple-dose rivaroxaban pharmacokinetics (PK), pharmacodynamics (PD), and initial safety and tolerability data available from each subject was assessed prior to continue 12 months of rivaroxaban therapy of Part A. | |
| Reporting group title | Rivaroxaban (Part B) |
| Reporting group description: Subjects who were randomized to receive rivaroxaban as 0.1 % (1 mg/ml) oral suspension as per subjects age and body weight adjusted dosing (target exposure to match that of rivaroxaban 10 mg given once daily in adults) with the regular twice daily regimen (morning and evening dosing). The single and multiple-dose rivaroxaban PK, PD, safety and tolerability data available from each subject was assessed during 12 months of rivaroxaban therapy of Part B. | |
| Reporting group title | Aspirin (Part B) |
| Reporting group description: Subjects who were randomized to receive Aspirin 5 milligram per kilogram (ml/kg) once daily up to 12 months. | |

Primary: Percentage of Subjects with any Thrombotic Event (Venous or Arterial and Symptomatic or Asymptomatic)

| | |
|--|--|
| End point title | Percentage of Subjects with any Thrombotic Event (Venous or Arterial and Symptomatic or Asymptomatic) ^[1] |
| End point description: Thrombotic event was defined as the appearance of a new thrombotic burden within the cardiovascular system on either routine surveillance or clinically indicated imaging, or the occurrence of a clinical event known to be strongly associated with thrombus (such as cardioembolic stroke, pulmonary embolism). The event included ischemic stroke, pulmonary embolism, venous thrombosis, arterial/intracardiac thrombosis, and other thrombosis. Full Analysis Set included all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent. | |
| End point type | Primary |
| End point timeframe: Up to 12 months | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

| End point values | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) | |
|----------------------------------|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 12 | 64 | 34 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Ischemic stroke | 0 | 0 | 2.9 | |
| Pulmonary embolism | 0 | 1.6 | 0 | |
| Venous thrombosis | 8.3 | 0 | 5.9 | |
| Arterial/intracardiac thrombosis | 0 | 0 | 0 | |
| Other thrombosis | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Primary: Plasma Concentration of Rivaroxaban

| | |
|-----------------|---|
| End point title | Plasma Concentration of Rivaroxaban ^{[2][3]} |
|-----------------|---|

End point description:

The plasma rivaroxaban concentrations for Parts A and B were evaluated. PK Analysis Set: All subjects who received at least 1 dose of study drug and had quantifiable rivaroxaban plasma concentrations were included in the descriptive PK analysis. Here '99999' indicates that the data was not analyzed for specified timepoints of the Part B. Here, 'n' (number of subjects analyzed) signifies the number of subjects evaluable at a specified timepoint.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Part A: up to 4 hours postdose (Day 1), Pre-dose, up to 8 hours postdose (Day 4), Pre-dose, up to 4 hours postdose (Month 3); Part B: up to 4 hours postdose (Day 1), Pre-dose, up to 4 hours postdose (Month 3)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

[3] - 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: The statistics were not planned for any of the baseline periods.

| End point values | Rivaroxaban (Part A) | Rivaroxaban (Part B) | | |
|---|----------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 | 64 | | |
| Units: microgram per liter (ug/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1: 0.5 - 1.5 hours postdose (n=12,60) | 46.69 (± 39.4) | 92.86 (± 72.6) | | |
| Day 1: 1.5 - 4 hours postdose (n=12,61) | 86.62 (± 43.1) | 103.61 (± 62.6) | | |
| Day 4: Up to 3 hours pre-dose (n=12,0) | 36.58 (± 37.4) | 99999 (± 99999) | | |
| Day 4: 0.5 - 1.5 hours postdose (n=12,0) | 107.58 (± 54.2) | 99999 (± 99999) | | |
| Day 4: 1.5 - 4 hours postdose (n=12,0) | 147.18 (± 116) | 99999 (± 99999) | | |
| Day 4: 6 - 8 hours postdose (n=12,0) | 66.81 (± 64.6) | 99999 (± 99999) | | |
| Month 3: Up to 3 hours pre-dose (n=10,52) | 38.23 (± 25.7) | 29.41 (± 25.5) | | |
| Month 3: 0.5 - 1.5 hours postdose (n=10,55) | 86.25 (± 32.0) | 94.12 (± 82.2) | | |
| Month 3: 2.5 - 4 hours postdose (n=10,57) | 96.67 (± 58.4) | 102.99 (± 56.0) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Bleeding Events

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Bleeding Events |
|-----------------|---|

End point description:

Bleeding events were categorized into major, clinically relevant non-major bleeding (CRNM), and trivial bleeding events. Major bleeding: overt bleeding and associated with a fall in hemoglobin of 2 gram per deciliter (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; or occurring in a critical site: intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal; or contributing to death. CRNM bleeding: overt bleeding not meeting the criteria for major bleeding but associated with: Medical intervention, or Unscheduled contact with a physician, cessation of study treatment, or Discomfort for the subject such as pain, or Impairment of activities of daily life. Trivial bleeding: any other overt bleeding event that does not meet criteria for CRNM bleeding. Safety analysis set.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 12 months

| End point values | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) | |
|--|----------------------|----------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 12 | 64 | 34 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | | | | |
| Major Bleeding | 0 | 1.6 | 0 | |
| Clinically relevant non-major bleeding | 8.3 | 6.3 | 8.8 | |
| Trivial bleeding | 25.0 | 32.8 | 35.3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-emergent Adverse Event (TEAE)

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Treatment-emergent Adverse Event (TEAE) |
|-----------------|---|

End point description:

TEAEs were defined as those adverse events (AEs) that occurred from the first day of study drug to the last day of study drug + 2 days inclusive. An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that

medicinal (investigational or non-investigational) product. Safety Analysis Set: all subjects in Part A who receive at least 1 dose of study agent and all subjects in Part B who are randomized and receive at least 1 dose of study agent.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to 12 months | |

| End point values | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) | |
|-------------------------------|-------------------------|-------------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 12 | 64 | 34 | |
| Units: percentage of subjects | | | | |
| number (not applicable) | 91.7 | 85.9 | 85.3 | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 14 months

Adverse event reporting additional description:

The safety population consisted of all subjects in Part A who received at least 1 dose of study drug and all subjects in Part B who were randomized and received at least 1 dose of study drug.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.0 |
|--------------------|------|

Reporting groups

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|-----------------------|----------------------|
| Reporting group title | Rivaroxaban (Part A) |
|-----------------------|----------------------|

Reporting group description:

Subjects were randomized to receive rivaroxaban as 0.1 percent (%) (1 milligram per milliliter [mg/ml]) oral suspension as per subjects age and body weight adjusted dosing (which is equivalent dose to 10 mg once daily in adults) with the regular twice daily regimen (morning and evening dosing), initially up to 12 Days. The single and multiple-dose rivaroxaban pharmacokinetics (PK), pharmacodynamics (PD), and initial safety and tolerability data available from each subject was assessed prior to continue 12 months of rivaroxaban therapy of Part A.

| | |
|-----------------------|----------------------|
| Reporting group title | Rivaroxaban (Part B) |
|-----------------------|----------------------|

Reporting group description:

Subjects were randomized to receive rivaroxaban as 0.1 % (1 mg/ml) oral suspension as per subjects age and body weight adjusted dosing (which is equivalent dose to 10 mg once daily in adults) with the regular twice daily regimen (morning and evening dosing). The single and multiple-dose rivaroxaban PK, PD, safety and tolerability data available from each subject was assessed during 12 months of rivaroxaban therapy of Part B.

| | |
|-----------------------|------------------|
| Reporting group title | Aspirin (Part B) |
|-----------------------|------------------|

Reporting group description:

Subjects were randomized to receive Aspirin 5 milligram per kilogram (mg/kg) once daily up to 12 months.

| Serious adverse events | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) |
|---|----------------------|----------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 12 (50.00%) | 18 / 64 (28.13%) | 8 / 34 (23.53%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Investigation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Weight Decreased | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Stoma Site Pain | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Shock Haemorrhagic | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Supraventricular Tachycardia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Partial Seizures with Secondary Generalisation | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Swelling Face | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Periorbital Oedema | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chylothorax | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural Effusion | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 9 / 64 (14.06%) | 2 / 34 (5.88%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 10 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Bronchitis | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis Viral | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 64 (1.56%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stoma Site Cellulitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vaccination Site Abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral Upper Respiratory Tract Infection | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound Abscess | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Rivaroxaban (Part A) | Rivaroxaban (Part B) | Aspirin (Part B) |
|---|----------------------|----------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 12 (91.67%) | 55 / 64 (85.94%) | 29 / 34 (85.29%) |
| Injury, poisoning and procedural complications | | | |
| Arthropod Bite | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 64 (3.13%) | 1 / 34 (2.94%) |
| occurrences (all) | 1 | 2 | 1 |
| Fall | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 64 (3.13%) | 5 / 34 (14.71%) |
| occurrences (all) | 0 | 2 | 8 |
| Injury | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament Sprain | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin Abrasion | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 64 (6.25%) | 1 / 34 (2.94%) |
| occurrences (all) | 0 | 14 | 1 |
| Skin Laceration | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 0 | 2 |
| Traumatic Haemorrhage | | | |

| | | | |
|--|----------------------|------------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 64 (0.00%) 0 | 2 / 34 (5.88%) 2 |
| Wound Haemorrhage subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 1 / 64 (1.56%) 1 | 0 / 34 (0.00%) 0 |
| Vascular disorders Haematoma subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 2 / 64 (3.13%) 2 | 1 / 34 (2.94%) 1 |
| Blood and lymphatic system disorders Increased Tendency to Bruise subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 16 / 64 (25.00%) 35 | 7 / 34 (20.59%) 15 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 0 / 12 (0.00%) 0 | 0 / 64 (0.00%) 0 | 2 / 34 (5.88%) 2 |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 12 (16.67%) 2 | 3 / 64 (4.69%) 5 | 2 / 34 (5.88%) 2 |
| Gingival Bleeding subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 2 / 64 (3.13%) 2 | 0 / 34 (0.00%) 0 |
| Tooth Loss subjects affected / exposed occurrences (all) | 1 / 12 (8.33%) 1 | 0 / 64 (0.00%) 0 | 0 / 34 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 12 (25.00%) 5 | 10 / 64 (15.63%) 20 | 3 / 34 (8.82%) 3 |

| | | | |
|---|-----------------|------------------|-----------------|
| Respiratory, thoracic and mediastinal disorders | | | |
| Catarrh | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences (all) | 5 | 1 | 0 |
| Chylothorax | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 12 / 64 (18.75%) | 4 / 34 (11.76%) |
| occurrences (all) | 0 | 15 | 4 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 6 / 64 (9.38%) | 3 / 34 (8.82%) |
| occurrences (all) | 0 | 21 | 4 |
| Pleural Effusion | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 4 / 64 (6.25%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 6 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 64 (4.69%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 4 | 2 |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis Diaper | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 6 / 64 (9.38%) | 5 / 34 (14.71%) |
| occurrences (all) | 0 | 44 | 25 |
| Rash | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 4 / 64 (6.25%) | 2 / 34 (5.88%) |
| occurrences (all) | 2 | 6 | 2 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 1 | 4 |
| Renal and urinary disorders | | | |
| Acute Kidney Injury | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|-----------------|------------------|-----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Musculoskeletal Stiffness | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in Extremity | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 64 (6.25%) | 0 / 34 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 3 / 64 (4.69%) | 0 / 34 (0.00%) |
| occurrences (all) | 3 | 3 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear Infection | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 3 / 64 (4.69%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 3 | 3 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 5 / 64 (7.81%) | 0 / 34 (0.00%) |
| occurrences (all) | 0 | 7 | 0 |
| Gastroenteritis Viral | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 3 / 64 (4.69%) | 1 / 34 (2.94%) |
| occurrences (all) | 1 | 3 | 2 |
| Influenza | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 64 (6.25%) | 1 / 34 (2.94%) |
| occurrences (all) | 0 | 4 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 14 / 64 (21.88%) | 6 / 34 (17.65%) |
| occurrences (all) | 1 | 27 | 19 |
| Otitis Media | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 4 / 64 (6.25%) | 3 / 34 (8.82%) |
| occurrences (all) | 0 | 7 | 4 |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 5 / 64 (7.81%) | 1 / 34 (2.94%) |
| occurrences (all) | 0 | 7 | 1 |
| Pharyngitis Streptococcal | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 1 | 0 | 1 |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 2 / 64 (3.13%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 2 | 3 |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 2 / 64 (3.13%) | 2 / 34 (5.88%) |
| occurrences (all) | 1 | 4 | 3 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 1 / 64 (1.56%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 1 | 2 |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 12 (0.00%) | 5 / 64 (7.81%) | 2 / 34 (5.88%) |
| occurrences (all) | 0 | 9 | 2 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 9 / 64 (14.06%) | 5 / 34 (14.71%) |
| occurrences (all) | 4 | 17 | 6 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 1 / 64 (1.56%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Viral Infection | | | |
| subjects affected / exposed | 2 / 12 (16.67%) | 2 / 64 (3.13%) | 1 / 34 (2.94%) |
| occurrences (all) | 6 | 3 | 2 |
| Viral Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 3 / 12 (25.00%) | 0 / 64 (0.00%) | 1 / 34 (2.94%) |
| occurrences (all) | 3 | 0 | 6 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hyponatraemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 12 (8.33%) | 0 / 64 (0.00%) | 0 / 34 (0.00%) |
| occurrences (all) | 1 | 0 | 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

None reported