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	v1
This version publication date	31 January 2021
First version publication date	31 January 2021

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	0.9	
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

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

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

None reported