Clinical trial results:
Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism

Summary

EudraCT number	2014-000565-47
Trial protocol	ES AT IT NL BE DE GB PL IE FR FI HU SE SK PT
Global end of trial date	30 January 2019

Results information

Result version number	v1 (current)
This version publication date	14 August 2019
First version publication date	14 August 2019

Trial information

Trial identification

Sponsor protocol code	14372

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02234843
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, Therapeutic Area Head, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Therapeutic Area Head, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000430-PIP01-08
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 January 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 January 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary efficacy objective is: To assess the incidence of symptomatic recurrent venous thromboembolism The principal safety objective is: To assess the incidence of overt major and clinically relevant non-major bleeding.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects and/or parent(s)/ legal guardian(s) as appropriate. Participating adult 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. For children all relevant study information was summarized in an integrated child information sheet, an informed consent and an informed assent form provided. Consent was asked from the parent(s)/ legal guardian(s) and, if appropriate as determined by local regulation, age and individual child capability, was asked from the child, according to country-specific regulations. The parent(s)/legal guardian(s) and the child, if applicable, would have sample time and opportunity to ask questions and would be informed about the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for their decision. A child could only enter the study if the parent(s)/legal guardian(s) voluntarily agree to sign and date the informed consent and the child provided informed consent or assent, as appropriate and determined by local regulation, age and individual child capability, and had done so. 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	12 November 2014
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: 3
Country: Number of subjects enrolled	Australia: 10
Country: Number of subjects enrolled	Austria: 12
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Brazil: 5
Country: Number of subjects enrolled	Canada: 25
Country: Number of subjects enrolled	China: 9
Country: Number of subjects enrolled	Finland: 1
Country: Number of subjects enrolled	France: 26

Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Ireland: 2
Country: Number of subjects enrolled	Israel: 15
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Japan: 6
Country: Number of subjects enrolled	Mexico: 5
Country: Number of subjects enrolled	Netherlands: 31
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	Russian Federation: 46
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Turkey: 8
Country: Number of subjects enrolled	United Kingdom: 51
Country: Number of subjects enrolled	United States: 154
Worldwide total number of subjects	500
EEA total number of subjects	201

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	12
Infants and toddlers (28 days-23 months)	42
Children (2-11 years)	170
Adolescents (12-17 years)	276
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at 109 study centers in 28 countries: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Finland, France, Germany, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Mexico, Netherlands, Portugal, Russia, Singapore, Slovakia, Spain, Sweden, Switzerland, Turkey, UK, and USA between 13 Nov 2014 and 30 Jan 2019.

Pre-assignment

Screening details:

A total of 520 children were screened for this study. Twenty children did not pass the screen of inclusion/exclusion criteria. A total of 500 children were randomized 2:1 to study treatment.

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, aged 12-<18

Arm description:

Children aged 12-<18 years randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY 59-7939
Other name	Xarelto
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Children with body weight of ≥ 30 kg were treated according to a once daily (o.d.) regimen, irrespective of whether they received rivaroxaban tablets or oral suspension. For switching from heparin/fondaparinux to rivaroxaban, the pharmacological activity of unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux was taken into account. Children who switched from rivaroxaban to heparin/ fondaparinux could switch at the time of the next scheduled dose. Children who switched from rivaroxaban to vitamin K antagonist (VKA) needed to continue rivaroxaban for 48 hours after the first dose of VKA.

Arm title	Rivaroxaban, aged 6-<12

Arm description:

Children aged 6-<12 years randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY 59-7939
Other name	Xarelto
Pharmaceutical forms	Tablet, Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Children with body weight of ≥ 30 kg were treated according to a once daily (o.d.) regimen, irrespective of whether they received rivaroxaban tablets or oral suspension. Children with body weight between 12

and < 30 kg received rivaroxaban twice daily (b.i.d) with a dosing intervals of approximately 12 hours. For switching from heparin/fondaparinux to rivaroxaban, the pharmacological activity of unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux was taken into account. Children who switched from rivaroxaban to heparin/ fondaparinux could switch at the time of the next scheduled dose. Children who switched from rivaroxaban to vitamin K antagonist (VKA) needed to continue rivaroxaban for 48 hours after the first dose of VKA.

Arm title	Rivaroxaban, aged 2-<6

Arm description:

Children aged 2-<6 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY 59-7939
Other name	Xarelto
Pharmaceutical forms	Oral suspension, Tablet
Routes of administration	Oral use

Dosage and administration details:

Children with body weight between 12 and < 30 kg received rivaroxaban twice daily (b.i.d) with a dosing intervals of approximately 12 hours. Children with body weight below 12 kg received rivaroxaban three times daily (t.i.d.) with dosing interval of approximately 8 hours. For switching from heparin/fondaparinux to rivaroxaban, the pharmacological activity of unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux was taken into account. Children who switched from rivaroxaban to heparin/ fondaparinux could switch at the time of the next scheduled dose. Children who switched from rivaroxaban to vitamin K antagonist (VKA) needed to continue rivaroxaban for 48 hours after the first dose of VKA.

Arm title	Rivaroxaban, aged 0.5-<2

Arm description:

Children aged 0.5-<2 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Arm type	Experimental
Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY 59-7939
Other name	Xarelto
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

Children with body weight between 12 and < 30 kg received rivaroxaban twice daily (b.i.d) with a dosing intervals of approximately 12 hours. Children with body weight below 12 kg received rivaroxaban three times daily (t.i.d.) with dosing interval of approximately 8 hours. For switching from heparin/fondaparinux to rivaroxaban, the pharmacological activity of unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux was taken into account. Children who switched from rivaroxaban to heparin/ fondaparinux could switch at the time of the next scheduled dose. Children who switched from rivaroxaban to vitamin K antagonist (VKA) needed to continue rivaroxaban for 48 hours after the first dose of VKA.

Arm title	Rivaroxaban, aged birth-<0.5

Arm description:

Children aged birth-<0.5 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Arm type	Experimental

Investigational medicinal product name	Rivaroxaban
Investigational medicinal product code	BAY 59-7939
Other name	Xarelto
Pharmaceutical forms	Oral suspension
Routes of administration	Oral use

Dosage and administration details:

. Children with body weight below 12 kg received rivaroxaban three times daily (t.i.d.) with dosing interval of approximately 8 hours. For switching from heparin/fondaparinux to rivaroxaban, the pharmacological activity of unfractionated heparin (UFH), low molecular weight heparin (LMWH) and fondaparinux was taken into account. Children who switched from rivaroxaban to heparin/ fondaparinux could switch at the time of the next scheduled dose. Children who switched from rivaroxaban to vitamin K antagonist (VKA) needed to continue rivaroxaban for 48 hours after the first dose of VKA.

Arm title	Comparator, aged 12-<18

Arm description:

Children aged 12-<18 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Low molecular weight Heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Fondaparinux
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Vitamin K Antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per standard of care

Arm title	Comparator, aged 6-<12

Arm description:

Children aged 6-<12 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Low molecular weight Heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Fondaparinux
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Vitamin K Antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per standard of care

Arm title	Comparator, aged 2-<6

Arm description:

Children aged 2-<6 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Low molecular weight Heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Fondaparinux
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Vitamin K Antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per standard of care

Arm title	Comparator, aged 0.5-<2

Arm description:

Children aged 0.5-<2 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Low molecular weight Heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Fondaparinux
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Vitamin K Antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per standard of care

Arm title	Comparator, aged birth-<0.5

Arm description:

Children aged birth-<0.5 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Arm type	Active comparator
Investigational medicinal product name	Unfractionated Heparin (UFH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Low molecular weight Heparin (LMWH)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Fondaparinux
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

As per standard of care

Investigational medicinal product name	Vitamin K Antagonist (VKA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

As per standard of care

Number of subjects in period 1	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6
Started	184	67	47
Completed	162	61	44
Not completed	22	6	3
Physician decision	4	1	-
Recovery	1	-	-
Consent withdrawn by subject	5	1	1
Death	1	-	-
Other	-	2	-
Adverse event	5	1	1
Non-compliance with study drug	1	-	-

Efficacy outcome reached	2	-	-
Lost to follow-up	-	1	-
Patient convenience	2	-	-
Protocol deviation	1	-	1

Number of subjects in period 1	Rivaroxaban, aged 0.5-<2	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18
Started	21	16	92
Completed	16	14	79
Not completed	5	2	13
Physician decision	1	-	-
Recovery	-	-	-
Consent withdrawn by subject	-	-	7
Death	-	-	-
Other	1	-	1
Adverse event	3	2	1
Non-compliance with study drug	-	-	1
Efficacy outcome reached	-	-	2
Lost to follow-up	-	-	-
Patient convenience	-	-	1
Protocol deviation	-	-	-

Number of subjects in period 1	Comparator, aged 6-<12	Comparator, aged 2-<6	Comparator, aged 0.5-<2
Started	34	22	9
Completed	32	20	8
Not completed	2	2	1
Physician decision	-	1	-
Recovery	-	-	-
Consent withdrawn by subject	-	-	-
Death	-	-	-
Other	-	1	-
Adverse event	-	-	1
Non-compliance with study drug	1	-	-
Efficacy outcome reached	-	-	-
Lost to follow-up	1	-	-
Patient convenience	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Comparator, aged birth-<0.5
Started	8
Completed	8
Not completed	0

Physician decision	-
Recovery	-
Consent withdrawn by subject	-
Death	-
Other	-
Adverse event	-
Non-compliance with study drug	-
Efficacy outcome reached	-
Lost to follow-up	-
Patient convenience	-
Protocol deviation	-

Baseline characteristics

Reporting groups

Reporting group title	Rivaroxaban, aged 12-<18

Reporting group description:

Children aged 12-<18 years randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension.

Reporting group title	Rivaroxaban, aged 6-<12

Reporting group description:

Children aged 6-<12 years randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Rivaroxaban, aged 2-<6

Reporting group description:

Children aged 2-<6 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Rivaroxaban, aged 0.5-<2

Reporting group description:

Children aged 0.5-<2 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Rivaroxaban, aged birth-<0.5

Reporting group description:

Children aged birth-<0.5 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Comparator, aged 12-<18

Reporting group description:

Children aged 12-<18 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged 6-<12

Reporting group description:

Children aged 6-<12 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged 2-<6

Reporting group description:

Children aged 2-<6 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged 0.5-<2

Reporting group description:

Children aged 0.5-<2 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged birth-<0.5

Reporting group description:

Children aged birth-<0.5 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group values	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6
Number of subjects	184	67	47
Age Categorical Units: Subjects			
12-<18 years	184	0	0
6-<12 years	0	67	0
2-<6 years	0	0	47
0.5-<2 years	0	0	0
Birth-<0.5 years	0	0	0
Gender Categorical Units: Subjects			
Female	97	24	24
Male	87	43	23

Reporting group values	Rivaroxaban, aged 0.5-<2	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18
Number of subjects	21	16	92
Age Categorical Units: Subjects			
12-<18 years	0	0	92
6-<12 years	0	0	0
2-<6 years	0	0	0
0.5-<2 years	21	0	0
Birth-<0.5 years	0	16	0
Gender Categorical Units: Subjects			
Female	10	5	55
Male	11	11	37

Reporting group values	Comparator, aged 6-<12	Comparator, aged 2-<6	Comparator, aged 0.5-<2
Number of subjects	34	22	9
Age Categorical Units: Subjects			
12-<18 years	0	0	0
6-<12 years	34	0	0
2-<6 years	0	22	0
0.5-<2 years	0	0	9
Birth-<0.5 years	0	0	0
Gender Categorical Units: Subjects			
Female	15	9	5
Male	19	13	4

Reporting group values	Comparator, aged birth-<0.5	Total	
Number of subjects	8	500	
Age Categorical Units: Subjects			
12-<18 years	0	276	
6-<12 years	0	101	
2-<6 years	0	69	
0.5-<2 years	0	30	
Birth-<0.5 years	8	24	
Gender Categorical Units: Subjects			
Female	1	245	
Male	7	255	

End points

End points reporting groups

Reporting group title	Rivaroxaban, aged 12-<18

Reporting group description:

Children aged 12-<18 years randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension.

Reporting group title	Rivaroxaban, aged 6-<12

Reporting group description:

Children aged 6-<12 years randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Rivaroxaban, aged 2-<6

Reporting group description:

Children aged 2-<6 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Rivaroxaban, aged 0.5-<2

Reporting group description:

Children aged 0.5-<2 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Rivaroxaban, aged birth-<0.5

Reporting group description:

Children aged birth-<0.5 years randomized to rivaroxaban received oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux . Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Reporting group title	Comparator, aged 12-<18

Reporting group description:

Children aged 12-<18 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged 6-<12

Reporting group description:

Children aged 6-<12 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged 2-<6

Reporting group description:

Children aged 2-<6 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged 0.5-<2

Reporting group description:

Children aged 0.5-<2 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Reporting group title	Comparator, aged birth-<0.5

Reporting group description:

Children aged birth-<0.5 years randomized to the comparator group continued with unfractionated heparin (UFH), low molecular weight heparin (LMWH) or fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

This population included all randomized children

Subject analysis set title	Safety analysis set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

This population included all randomized children who received at least one dose of study medication

Subject analysis set title	Pharmacokinetics analysis set (PKS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Includes all children randomized to rivaroxaban with at least one PK sample.

Subject analysis set title	Pharmacodynamics analysis set (PDS)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Includes all children randomized to rivaroxaban with at least one PD sample.

Subject analysis set title	Rivaroxaban group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Children randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux. Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Subject analysis set title	Comparator group
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Children randomized to the comparator group continued with UFH/LMWH/fondaparinux or may switch to VKA therapy. VKA dosages were adjusted to maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux could be discontinued once the INR was above 2.0 on two separate occasions, 24 hours apart.

Primary: Incidence rates of all symptomatic recurrent venous thromboembolism during the main treatment period

End point title	Incidence rates of all symptomatic recurrent venous thromboembolism during the main treatment period

End point description:

The Central independent adjudication committee (CIAC) classified symptomatic recurrent venous thromboembolism (VTE). Incidence = number of events / number at risk, where: number of events = number of subjects having the event in the time window. number at risk = number of subjects in reference population

End point type	Primary

End point timeframe:

During the main study treatment period (i.e., 3 months, except for children with CVC-VTE aged <2 years for whom it was 1 month)

End point values	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	184	67	47	21
Units: Incidence				
number (confidence interval 95%)	2.2 (0.7 to 5.3)	0.0 (0.0 to 5.3)	0.0 (0.0 to 6.8)	0.0 (0.0 to 8.3)

End point values	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18	Comparator, aged 6-<12	Comparator, aged 2-<6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16	92	34	22
Units: Incidence				
number (confidence interval 95%)	0.0 (0.0 to 14.6)	3.3 (0.9 to 8.6)	2.9 (0.2 to 15.1)	4.5 (0.2 to 20.7)

End point values	Comparator, aged 0.5-<2	Comparator, aged birth-<0.5	Rivaroxaban group	Comparator group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	9	8	335	165
Units: Incidence				
number (confidence interval 95%)	0.0 (0.0 to 18.4)	0.0 (0.0 to 29.9)	1.2 (0.4 to 3.0)	3.0 (1.2 to 6.6)

Statistical analyses

Statistical analysis title	Efficacy up to the end of main treatment period
Comparison groups	Rivaroxaban group v Comparator group
Number of subjects included in analysis	500
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1509
Method	Expl. Cox Proportional Hazards Model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	1.41

Primary: Incidence rates of all symptomatic recurrent venous thromboembolism during extended treatment period

End point title	Incidence rates of all symptomatic recurrent venous thromboembolism during extended treatment period[1]

End point description:

Incidence rates for all children except those aged < 2 years with catheter-related thrombosis.
The Central independent adjudication committee (CIAC) classified symptomatic recurrent venous thromboembolism (VTE).
Incidence = number of events / number at risk, where: number of events = number of subjects having the event in the time window. number at risk = number of subjects in reference Population.
'99999' denotes data that cannot be calculated.

End point type	Primary

End point timeframe:

During extended treatment period: up to month 12.

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, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[2]	21[3]	19[4]	0[5]
Units: Incidence				
number (confidence interval 95%)				
Extension 1 (month 3 to 6)	0.0 (0.0 to 3.8)	0.0 (0.0 to 14.6)	0.0 (0.0 to 16.3)	(to)
Extension 2 (month 6 to 9)	2.6 (0.1 to 13.4)	0.0 (0.0 to 29.9)	0.0 (0.0 to 40.2)	(to)
Extension 3 (month 9 to 12)	0.0 (0.0 to 11.6)	0.0 (0.0 to 63.2)	0.0 (0.0 to 77.6)	(to)

Notes:

[2] - Extension 1 (n=93); extension 2 (n=38); extension 3 (n=26)

[3] - Extension 1 (n=21); extension 2 (n=9); extension 3 (n=3)

[4] - Extension 1 (n=19); extension 2 (n=6); extension 3 (n=2)

[5] - Extension 1 (n=0); extension 2 (n=0); extension 3 (n=0)

End point values	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18	Comparator, aged 6-<12	Comparator, aged 2-<6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[6]	46[7]	8[8]	7[9]
Units: Incidence				
number (confidence interval 95%)				
Extension 1 (month 3 to 6)	0.0 (0.0 to 77.6)	2.2 (0.1 to 10.9)	0.0 (0.0 to 14.6)	0.0 (0.0 to 37.7)
Extension 2 (month 6 to 9)	99999 (99999 to 99999)	5.3 (0.3 to 24.4)	0.0 (0.0 to 63.2)	0.0 (0.0 to 77.6)
Extension 3 (month 9 to 12)	99999 (99999 to 99999)	0.0 (0.0 to 23.0)	0.0 (0.0 to 95.2)	0.0 (0.0 to 77.6)

Notes:

[6] - Extension 1 (n=2); extension 2 (n=0); extension 3 (n=0)

[7] - Extension 1 (n=46); extension 2 (n=19); extension 3 (n=14)

[8] - Extension 1 (n=8); extension 2 (n=3); extension 3 (n=1)

[9] - Extension 1 (n=7); extension 2 (n=3); extension 3 (n=2)

End point values	Comparator, aged 0.5-<2	Comparator, aged birth-<0.5		

Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[10]	1[11]		
Units: Incidence				
number (confidence interval 95%)				
Extension 1 (month 3 to 6)	0.0 (0.0 to 95.0)	0.0 (0.0 to 95.0)		
Extension 2 (month 6 to 9)	99999 (99999 to 99999)	99999 (99999 to 99999)		
Extension 3 (month 9 to 12)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[10] - Extension 1 (n=1); extension 2 (n=0); extension 3 (n=0)

[11] - Extension 1 (n=1); extension 2 (n=0); extension 3 (n=0)

Statistical analyses

No statistical analyses for this end point

Primary: Number of subjects with the composite of all symptomatic recurrent venous thromboembolism during the 30 days post-study treatment period (i.e. >2 and ≤ 30 days after stop of study medication)

End point title	Number of subjects with the composite of all symptomatic recurrent venous thromboembolism during the 30 days post-study treatment period (i.e. >2 and ≤ 30 days after stop of study medication)[12]

End point description:

The Central independent adjudication committee (CIAC) classified symptomatic recurrent venous thromboembolism (VTE). Age group with primary efficacy outcome was reported.

End point type	Primary

End point timeframe:

More than 2 and up to 30 days after stop of study medication

Notes:

[12] - 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, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	184[13]	67[14]	47[15]	21[16]
Units: Number of subjects	0	0	0	0

Notes:

[13] - FAS

[14] - FAS

[15] - FAS

[16] - FAS

End point values	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18	Comparator, aged 6-<12	Comparator, aged 2-<6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[17]	92	34[18]	22[19]
Units: Number of subjects	0	2	0	0

Notes:

[17] - FAS

[18] - FAS

[19] - FAS

End point values	Comparator, aged 0.5-<2	Comparator, aged birth-<0.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9[20]	8[21]		
Units: Number of subjects	0	0		

Notes:

[20] - FAS

[21] - FAS

Statistical analyses

No statistical analyses for this end point

Primary: Incidence rates of the composite of treatment emergent overt major bleeding and clinically relevant non-major (CRNM) bleeding during main treatment period

End point title	Incidence rates of the composite of treatment emergent overt major bleeding and clinically relevant non-major (CRNM) bleeding during main treatment period[22]

End point description:

The Central independent adjudication committee (CIAC) classified bleeding as: Major bleeding defined as overt 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, or occurring in a critical site, e.g. intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal, or contributing to death. Clinically relevant non-major bleeding defined as overt bleeding not meeting the criteriafor major bleeding, but associated with: medical intervention, or unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or discomfort for the child such as pain or impairment of activities of daily life (such as loss of school days or hospitalization).

End point type	Primary

End point timeframe:

During the main study treatment period (i.e., 3 months, except for children with CVC-VTE aged <2 years for whom it was 1 month)

Notes:

[22] - 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, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	180[23]	67[24]	46[25]	21[26]
Units: Incidence				
number (confidence interval 95%)	1.7 (0.5 to 4.7)	3.0 (0.5 to 9.6)	6.5 (1.8 to 17.7)	4.8 (0.2 to 21.8)

Notes:

[23] - SAF

[24] - SAF

[25] - SAF

[26] - SAF

End point values	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18	Comparator, aged 6-<12	Comparator, aged 2-<6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	15[27]	89[28]	34[29]	22[30]
Units: Incidence				
number (confidence interval 95%)	6.7 (0.3 to 30.2)	2.2 (0.4 to 7.3)	0.0 (0.0 to 9.0)	0.0 (0.0 to 13.9)

Notes:

[27] - SAF

[28] - SAF

[29] - SAF

[30] - SAF

End point values	Comparator, aged 0.5-<2	Comparator, aged birth-<0.5	Rivaroxaban group	Comparator group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	9[31]	8[32]	329[33]	162[34]
Units: Incidence				
number (confidence interval 95%)	11.1 (0.6 to 44.3)	0.0 (0.0 to 34.9)	3 (1.6 to 5.5)	1.9 (0.5 to 3.3)

Notes:

[31] - SAF

[32] - SAF

[33] - SAF

[34] - SAF

Statistical analyses

No statistical analyses for this end point

Primary: Incidence rates of the composite of treatment emergent overt major bleeding and clinically relevant non-major (CRNM) bleeding during extended treatment period

End point title	Incidence rates of the composite of treatment emergent overt major bleeding and clinically relevant non-major (CRNM) bleeding during extended treatment period[35]

End point description:

Incidence rates for all children except those aged < 2 years with catheter-related thrombosis.
The CIAC classified bleeding as: Major bleeding defined as overt 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, or occurring in a critical site, e.g. intracranial, intraspinal, intraocular, pericardial, intraarticular, intramuscular with compartment syndrome, retroperitoneal, or contributing to death. Clinically relevant non-major bleeding defined as overt bleeding not meeting the criteriafor major bleeding, but associated with: medical intervention, or unscheduled contact (visit or telephone call) with a physician, or (temporary) cessation of study treatment, or discomfort for the child such as pain or impairment of activities of daily life (such as loss of school days or hospitalization).
'99999' denotes data that cannot be calculated.

End point type	Primary

End point timeframe:

During extended treatment period: up to month 12.

Notes:

[35] - 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, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	93[36]	21[37]	19[38]	12[39]
Units: Incidence				
number (confidence interval 95%)				
Extension 1 (month 3 to 6)	1.1 (0.1 to 5.3)	0.0 (0.0 to 14.6)	0.0 (0.0 to 16.3)	0.0 (0.0 to 23.6)
Extension 2 (month 6 to 9)	2.6 (0.1 to 13.4)	0.0 (0.0 to 29.9)	0.0 (0.0 to 40.2)	11.1 (0.6 to 44.3)
Extension 3 (month 9 to 12)	0.0 (0.0 to 11.6)	0.0 (0.0 to 63.2)	0.0 (0.0 to 77.6)	99999 (99999 to 99999)

Notes:

[36] - Extension 1 (n=93); extension 2 (n=38); extension 3 (n=26);

[37] - Extension 1 (n=21); extension 2 (n=9); extension 3 (n=3)

[38] - Extension 1 (n=19); extension 2 (n=6); extension 3 (n=2)

[39] - Extension 1 (n=12); extension 2 (n=9); extension 3 (n=0)

End point values	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18	Comparator, aged 6-<12	Comparator, aged 2-<6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	4[40]	46[41]	8[42]	7[43]
Units: Incidence				
number (confidence interval 95%)				
Extension 1 (month 3 to 6)	0.0 (0.0 to 52.7)	0.0 (0.0 to 6.9)	0.0 (0.0 to 34.9)	0.0 (0.0 to 37.7)
Extension 2 (month 6 to 9)	99999 (99999 to 99999)	5.3 (0.3 to 24.4)	0.0 (0.0 to 63.2)	0.0 (0.0 to 77.6)
Extension 3 (month 9 to 12)	99999 (99999 to 99999)	0.0 (0.0 to 23.0)	0.0 (0.0 to 95.0)	0.0 (0.0 to 77.6)

Notes:

[40] - Extension 1 (n=4); extension 2 (n=0); extension 3 (n=0)

[41] - Extension 1 (n=46); extension 2 (n=19); extension 3 (n=14)

[42] - Extension 1 (n=8); extension 2 (n=3); extension 3 (n=1)

[43] - Extension 1 (n=7); extension 2 (n=2); extension 3 (n=2)

End point values	Comparator, aged 0.5-<2	Comparator, aged birth-<0.5		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3[44]	5[45]		
Units: Incidence				
number (confidence interval 95%)				
Extension 1 (month 3 to 6)	0.0 (0.0 to 63.2)	0.0 (0.0 to 50.0)		
Extension 2 (month 6 to 9)	0.0 (0.0 to 77.6)	0.0 (0.0 to 63.2)		
Extension 3 (month 9 to 12)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Notes:

[44] - Extension 1 (n=3); extension 2 (n=2); extension 3 (n=0)

[45] - Extension 1 (n=5); extension 2 (n=3); extension 3 (n=0)

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence rates of the composite of all symptomatic recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging during the main treatment period

End point title	Incidence rates of the composite of all symptomatic recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden on repeat imaging during the main treatment period

End point description:

The secondary efficacy outcome defined as the composite of all symptomatic recurrent venous thromboembolism and asymptomatic deterioration on repeat imaging as assessed by central independent adjudication committee. (CIAC) Incidence = number of events / number at risk, where: number of events = number of subjects having the event in the time window. number at risk = number of subjects in reference population

End point type	Secondary

End point timeframe:

During the main study treatment period (i.e., 3 months, except for children with CVC-VTE aged <2 years for whom it was 1 month)

End point values	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	184[46]	67[47]	47[48]	21[49]
Units: Incidence				
number (confidence interval 95%)	2.2 (0.7 to 5.3)	0.0 (0.0 to 5.3)	2.1 (0.1 to 10.7)	0.0 (0.0 to 14.6)

Notes:

[46] - FAS

[47] - FAS

[48] - FAS

[49] - FAS

End point values	Rivaroxaban, aged birth-<0.5	Comparator, aged 12-<18	Comparator, aged 6-<12	Comparator, aged 2-<6
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	16[50]	92[51]	34[52]	22[53]
Units: Incidence				
number (confidence interval 95%)	0.0 (0.0 to 19.8)	4.3 (1.5 to 10.3)	2.9 (0.2 to 15.1)	4.5 (0.2 to 20.7)

Notes:

[50] - FAS

[51] - FAS

[52] - FAS

[53] - FAS

End point values	Comparator, aged 0.5-<2	Comparator, aged birth-<0.5	Rivaroxaban group	Comparator group
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	9[54]	8[55]	335[56]	165[57]
Units: Incidence				

number (confidence interval 95%)	0.0 (0.0 to 29.9)	0.0 (0.0 to 34.9)	1.5 (0.6 to 3.4)	3.6 (1.6 to 7.6)

Notes:

[54] - FAS

[55] - FAS

[56] - FAS

[57] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: AUC(0-24)ss in plasma

End point title	AUC(0-24)ss in plasma[58]

End point description:

AUC(0-24)ss: Area under the concentration vs. time curve from time 0 to 24 hours at steady state.

End point type	Secondary

End point timeframe:

over 24 hours

Notes:

[58] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Only for Rivaroxaban age groups values were provided.

End point values	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	173[59]	65[60]	44[61]	21[62]
Units: microgram*hour per liter				
geometric mean (geometric coefficient of variation)	2120 (± 26.4)	1960 (± 31.7)	2380 (± 40.7)	1840 (± 36.4)

Notes:

[59] - Number of observations N = 174. One child with two sets of PK parameters due to regimen switch. PKS

[60] - Number of observations N = 67.Two children with two sets of PK parameters due to regimen switch. PKS

[61] - PKS

[62] - Number of observations N = 22. One child with two sets of PK parameters due to regimen switch. PKS

End point values	Rivaroxaban, aged birth-<0.5			
Subject group type	Reporting group			
Number of subjects analysed	13[63]			
Units: microgram*hour per liter				
geometric mean (geometric coefficient of variation)	1590 (± 29.6)			

Notes:

[63] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax,ss in plasma

End point title	Cmax,ss in plasma[64]

End point description:

Maximum drug concentration in measured matrix at steady state during a dosage interval

End point type	Secondary

End point timeframe:

0 hours to 24 hours, 0 hours to 12 hours or 0 hours to 8 hours (one dosing interval in steady state)

Notes:

[64] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Only for Rivaroxaban age groups values were provided.

End point values	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	173[65]	65[66]	44[67]	21[68]
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	237 (± 20.6)	184 (± 36.2)	182 (± 31.2)	136 (± 29.4)

Notes:

[65] - Number of observations N = 174. One child with two sets of PK parameters due to regimen switch. PKS
[66] - Number of observations N = 67.Two children with two sets of PK parameters due to regimen switch.PKS
[67] - PKS

[68] - Number of observations N = 22. One child with two sets of PK parameters due to regimen switch. PKS

End point values	Rivaroxaban, aged birth-<0.5			
Subject group type	Reporting group			
Number of subjects analysed	13[69]			
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	119 (± 24.1)			

Notes:

[69] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough,ss in plasma

End point title	Ctrough,ss in plasma[70]

End point description:

Ctrough,ss refers to the drug concentration at the end of the dosage interval at steady state

End point type	Secondary

End point timeframe:

0 hours to 24 hours, 0 hours to 12 hours or 0 hours to 8 hours(one sampling interval in steady state)

Notes:

[70] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Only for Rivaroxaban age groups values were provided.

End point values	Rivaroxaban, aged 12-<18	Rivaroxaban, aged 6-<12	Rivaroxaban, aged 2-<6	Rivaroxaban, aged 0.5-<2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	173[71]	65[72]	44[73]	21[74]
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	20.7 (± 45.8)	21.4 (± 62.7)	31.6 (± 70.1)	22.9 (± 68.6)

Notes:

[71] - Number of observations N = 174. One child with two sets of PK parameters due to regimen switch. PKS
[72] - Number of observations N = 67.Two children with two sets of PK parameters due to regimen switch.PKS
[73] - PKS

[74] - Number of observations N = 22. One child with two sets of PK parameters due to regimen switch. PKS

End point values	Rivaroxaban, aged birth-<0.5			
Subject group type	Reporting group			
Number of subjects analysed	13[75]			
Units: microgram per liter				
geometric mean (geometric coefficient of variation)	18.5 (± 50.4)			

Notes:

[75] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 12-<18 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 12-<18 years[76]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day30, and up to 8 hours post dose on Day 60

Notes:

[76] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 12-<18			
Subject group type	Reporting group			
Number of subjects analysed	156[77]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=156	1.29 (± 0.28)			
Day 30 (2.5-4h) n=150	1.57 (± 0.36)			
Day 60 (2-8h) n=156	1.52 (± 0.29)			

Notes:

[77] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 6-<12 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 6-<12 years[78]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day30, and up to 8 hours post dose on Day 60

Notes:

[78] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 6-<12			
Subject group type	Reporting group			
Number of subjects analysed	20[79]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=18	1.46 (± 0.25)			
Day 30 (2.5-4h) n=20	1.67 (± 0.39)			
Day 60 (2-8h) n=20	1.52 (± 0.33)			

Notes:

[79] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered twice daily (suspension and tablet) in the age group 6-<12 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban

	administered twice daily (suspension and tablet) in the age group 6-<12 years[80]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day30, and up to 8 hours post dose on Day 60

Notes:

[80] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 6-<12			
Subject group type	Reporting group			
Number of subjects analysed	34[81]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=33	1.17 (± 0.23)			
Day 30 (2.5-4h) n=33	1.26 (± 0.22)			
Day 60 (2-8h) n=34	1.21 (± 0.19)			

Notes:

[81] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 2-<6 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 2-<6 years[82]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day30, and up to 8 hours post dose on Day 60

Notes:

[82] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 2-<6			
Subject group type	Reporting group			
Number of subjects analysed	34[83]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=1 Day 30 (2.5-4h) n=34 Day 60 (2-8h) n=32	0.99 (± 99999) 1.36 (± 0.28) 1.33 (± 0.26)			

Notes:

[83] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 0.5-<2 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 0.5-<2 years[84]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day30, and up to 8 hours post dose on Day 60

Notes:

[84] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 0.5-<2			
Subject group type	Reporting group			
Number of subjects analysed	2[85]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=0 Day 30 (2.5-4h) n=1 Day 60 (2-8h) n=2	99999 (± 99999) 1.41 (± 99999) 1.05 (± 0.17)			

Notes:

[85] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered

three times daily (suspension) in the age group 2-<6 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 2-<6 years[86]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day30, and up to 6 hours post dose on Day 60

Notes:

[86] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 2-<6			
Subject group type	Reporting group			
Number of subjects analysed	4[87]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=4	1.87 (± 1.09)			
Day 60 (2-6h) n=4	1.32 (± 0.12)			

Notes:

[87] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 0.5-<2 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 0.5-<2 years[88]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day30, and up to 6 hours post dose on Day 60

Notes:

[88] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 0.5-<2			
Subject group type	Reporting group			
Number of subjects analysed	9[89]			
Units: ratios				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=9 Day 60 (2-6h) n=7	1.25 (± 0.18) 2.00 (± 2.22)			

Notes:

[89] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Prothrombin time (PT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group birth-<0.5 years

End point title	Prothrombin time (PT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group birth-<0.5 years[90]

End point description:

Prothrombin time (PT) is a global clotting test assessing the extrinsic pathway of the blood coagulation cascade. The test is sensitive for deficiencies of Factors II, V, VII, and X, with sensitivity being best for Factors V, VII, and X and less pronounced for Factor II. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day30, and up to 6 hours post dose on Day 60

Notes:

[90] - 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: Descriptitive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged birth-<0.5			
Subject group type	Reporting group			
Number of subjects analysed	11[91]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=11 Day 60 (2-6h) n=4	1.35 (± 0.20) 1.45 (± 0.16)			

Notes:

[91] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 12-<18 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in

	the age group 12-<18 years[92]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, and up to 8 hours post dose on Day 60

Notes:

[92] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 12-<18			
Subject group type	Reporting group			
Number of subjects analysed	154[93]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=154	1.17 (± 0.28)			
Day 30 (2.5-4h) n=149	1.38 (± 0.50)			
Day 60 (2-8h) n=153	1.33 (± 0.38)			

Notes:

[93] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 6-<12 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered once daily (suspension and tablet) in the age group 6-<12 years[94]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, and up to 8 hours post dose on Day 60

Notes:

[94] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 6-<12			
Subject group type	Reporting group			
Number of subjects analysed	19[95]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=17	1.27 (± 0.20)			

Day 30 (2.5-4h) n=17	1.39 (± 0.26)			
Day 60 (2-8h) n=19	1.24 (± 0.20)			

Notes:

[95] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered twice daily (suspension and tablet) in the age group 6-<12 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered twice daily (suspension and tablet) in the age group 6-<12 years[96]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, and up to 8 hours post dose on Day 60

Notes:

[96] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 6-<12			
Subject group type	Reporting group			
Number of subjects analysed	31[97]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=30	1.11 (± 0.24)			
Day 30 (2.5-4h) n=30	1.15 (± 0.22)			
Day 60 (2-8h) n=31	1.18 (± 0.24)			

Notes:

[97] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 2-<6 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 2-<6 years[98]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, and up to 8 hours post dose on Day 60

Notes:

[98] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 2-<6			
Subject group type	Reporting group			
Number of subjects analysed	32[99]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=1	0.90 (± 99999)			
Day 30 (2.5-4h) n=32	1.29 (± 0.33)			
Day 60 (2-8h) n=29	1.23 (± 0.21)			

Notes:

[99] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 0.5-<2 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered twice daily (suspension) in the age group 0.5-<2 years[100]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, and up to 8 hours post dose on Day 60

Notes:

[100] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 0.5-<2			
Subject group type	Reporting group			
Number of subjects analysed	2[101]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=0	99999 (± 99999)			
Day 30 (2.5-4h) n=1	1.13 (± 99999)			
Day 60 (2-8h) n=2	1.10 (± 0.02)			

Notes:
[101] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 2-<6 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 2-<6 years[102]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day 30, and up to 6 hours post dose on Day 60

Notes:

[102] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 2-<6			
Subject group type	Reporting group			
Number of subjects analysed	4[103]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=4	1.50 (± 0.83)			
Day 60 (2-6h) n=4	1.13 (± 0.06)			

Notes:
[103] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 0.5-<2 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group 0.5-<2 years[104]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day 30, and up to 6 hours post dose on Day 60

Notes:

[104] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 0.5-<2			
Subject group type	Reporting group			
Number of subjects analysed	9[105]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=9 Day 60 (2-6h) n=6	1.20 (± 0.39) 1.10 (± 0.47)			

Notes:

[105] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group birth-<0.5 years

End point title	Activated partial thromboplastin time (aPTT) ratios to baseline: Rivaroxaban administered three times daily (suspension) in the age group birth-<0.5 years[106]

End point description:

The aPTT is a screening test for the intrinsic pathway and is sensitive for deficiencies of Factors I, II, V,VIII, IX, X, XI and XII. The initial read-out is in seconds.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day 30, and up to 6 hours post dose on Day 60

Notes:

[106] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged birth-<0.5			
Subject group type	Reporting group			
Number of subjects analysed	9[107]			
Units: ratio				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=9 Day 60 (2-6h) n=3	1.31 (± 0.15) 1.21 (± 0.16)			

Notes:

[107] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered once daily (suspension and tablet) in the age group 12-<18 years

End point title	Anti-Xa values: Rivaroxaban administered once daily (suspension and tablet) in the age group 12-<18 years[108]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, up to 8 hours post dose on Day 60, and up to 24 hours on Day 90

Notes:

[108] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 12-<18			
Subject group type	Reporting group			
Number of subjects analysed	167[109]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=141	164.46 (± 124.46)			
Day 30 (2.5-4h) n=164	254.66 (± 188.64)			
Day 60 (2-8h) n=167	255.40 (± 171.59)			
Day 90 (20-24h) n=58	62.12 (± 175.87)			

Notes:

[109] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered once daily (suspension and tablet) in the age group 6-<12 years

End point title	Anti-Xa values: Rivaroxaban administered once daily (suspension and tablet) in the age group 6-<12 years[110]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, up to 8 hours post dose on Day 60, and up to 24 hours on Day 90

Notes:

[110] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 6-<12			
Subject group type	Reporting group			
Number of subjects analysed	23[111]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=22	206.89 (± 105.01)			
Day 30 (2.5-4h) n=23	263.24 (± 156.73)			
Day 60 (2-8h) n=22	243.45 (± 124.92)			
Day 60 (20-24h) n=9	27.39 (± 14.66)			

Notes:

[111] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered twice daily (suspension and tablet) in the age group 6-<12 years

End point title	Anti-Xa values: Rivaroxaban administered twice daily (suspension and tablet) in the age group 6-<12 years[112]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, up to 8 hours post dose on Day 60, and up to 16 hours on Day 90

Notes:

[112] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 6-<12			
Subject group type	Reporting group			
Number of subjects analysed	37[113]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=37	96.82 (± 76.77)			
Day 30 (2.5-4h) n=36	139.10 (± 102.19)			
Day 60 (2-8h) n=35	126.53 (± 81.78)			
Day 90 (10-16h) n=20	47.49 (± 66.88)			

Notes:
[113] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered twice daily (suspension) in the age group 2-<6 years

End point title	Anti-Xa values: Rivaroxaban administered twice daily (suspension) in the age group 2-<6 years[114]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, up to 8 hours post dose on Day 60, and up to 16 hours on Day 90

Notes:

[114] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 2-<6			
Subject group type	Reporting group			
Number of subjects analysed	37[115]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (2.5-4h) n=37	177.78 (± 147.29)			
Day 60 (2-8h) n=36	150.03 (± 95.77)			
Day 90 (10-16h) n=18	54.40 (± 51.52)			

Notes:
[115] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered twice daily (suspension) in the age group 0.5-<2 years

End point title	Anti-Xa values: Rivaroxaban administered twice daily (suspension) in the age group 0.5-<2 years[116]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 4 hours post dose on Day 30, and up to 8 hours post dose on Day 60

Notes:

[116] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints..

End point values	Rivaroxaban, aged 0.5-<2			
Subject group type	Reporting group			
Number of subjects analysed	4[117]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-1.5h) n=1	247.54 (± 99999)			
Day 30 (2.5-4h) n=2	160.71 (± 153.84)			
Day 60 (2-8h) n=4	121.09 (± 81.94)			

Notes:

[117] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered three times daily (suspension) in the age group 2-<6 years

End point title	Anti-Xa values: Rivaroxaban administered three times daily (suspension) in the age group 2-<6 years[118]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day 30, up to 6 hours post dose on Day 60, and up to 16 hours on Day 90

Notes:

[118] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 2-<6			
Subject group type	Reporting group			
Number of subjects analysed	4[119]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=4	209.67 (± 127.86)			
Day 60 (2-6h) n=4	140.46 (± 78.82)			
Day 90 (10-16h) n=1	62.56 (± 99999)			

Notes:
[119] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered three times daily (suspension) in the age group 0.5-<2 years

End point title	Anti-Xa values: Rivaroxaban administered three times daily (suspension) in the age group 0.5-<2 years[120]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method. '99999' denotes the data that cannot be calculated.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day 30, up to 6 hours post dose on Day 60, and up to 16 hours on Day 90

Notes:

[120] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged 0.5-<2			
Subject group type	Reporting group			
Number of subjects analysed	12[121]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=12	111.35 (± 97.03)			
Day 30 (2-6h) n=11	147.24 (± 125.40)			
Day 90 (10-16h) n=3	23.40 (± 4.51)			
Follow-up n=1	71.30 (± 99999)			

Notes:
[121] - PDS

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Xa values: Rivaroxaban administered three times daily (suspension) in the age group birth-<0.5 years

End point title	Anti-Xa values: Rivaroxaban administered three times daily (suspension) in the age group birth-<0.5 years[122]

End point description:

This is a method for measuring the inhibition of Factor Xa activity determined by an ex vivo using a photometric method.

End point type	Secondary

End point timeframe:

Up to 3 hours post dose on Day 30, and up to 6 hours post dose on Day 60

Notes:

[122] - 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: Descriptive statistics were done, no inferential statistical analyses were performed. Baseline period arms were reported as separate endpoints.

End point values	Rivaroxaban, aged birth-<0.5			
Subject group type	Reporting group			
Number of subjects analysed	10[123]			
Units: microgram per liter (mcg/L)				
arithmetic mean (standard deviation)				
Day 30 (0.5-3h) n=10 Day 60 (2-6h) n=5	118.12 (± 82.08) 228.03 (± 181.08)			

Notes:

[123] - PDS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After randomization until last intake of study medication plus 2 days.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	Comparator group

Reporting group description:

Children randomized to the comparator group will continue with UFH, LMWH or fondaparinux or may switch to VKA therapy. VKA dosages will be adjustedto maintain the INR within the therapeutic range (target 2.5, range 2.0 - 3.0). UFH, LMWH or fondaparinux can be discontinued once the INR is above 2.0 on two separate occasions, 24 hours apart

Reporting group title	Rivaroxaban group

Reporting group description:

Children randomized to rivaroxaban received either tablet or oral suspension after at least 5 days administration of initial therapy with UFH/LMWH/fondaparinux. Children with body weight of ≥ 20 kg received rivaroxaban tablets or oral suspension. Children with body weight of < 20 kg received rivaroxaban as oral suspension.

Serious adverse events	Comparator group	Rivaroxaban group	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 162 (21.60%)	78 / 329 (23.71%)	
number of deaths (all causes)	0	2	
number of deaths resulting from adverse events	0	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Craniopharyngioma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myxofibrosarcoma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Haematoma			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Colostomy			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoidectomy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sclerotherapy			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumboperitoneal shunt			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecal disimpaction			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pyrexia			
subjects affected / exposed	2 / 162 (1.23%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral swelling			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic ovarian cyst			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Diaphragmatic paralysis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary vein stenosis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug clearance decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal stoma output decreased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic fracture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post lumbar puncture syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental underdose			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Incorrect route of product administration			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Muscular dystrophy			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial tachycardia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Low cardiac output syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postural orthostatic tachycardia syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysaesthesia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	3 / 162 (1.85%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial pressure increased			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuralgia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sciatic nerve neuropathy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis autoimmune			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemianaesthesia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparaesthesia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 162 (0.62%)	8 / 329 (2.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenopathy			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sickle cell anaemia with crisis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow failure			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Papilloedema			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal dilatation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 162 (0.00%)	6 / 329 (1.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia oral			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Drug-induced liver injury			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IgA nephropathy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephropathy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Urinary bladder haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal impairment			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Bronchiolitis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eczema herpeticum			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastoiditis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nasopharyngitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyoderma streptococcal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tonsillitis streptococcal			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicella			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis viral			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial sepsis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			

subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected dermal cyst			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candida infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolic acidosis			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Comparator group	Rivaroxaban group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 162 (74.69%)	275 / 329 (83.59%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Craniopharyngioma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Ewing's sarcoma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Lymphangioma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Skin papilloma			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Vascular disorders			
Arterial thrombosis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Haematoma			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Hypertension			
subjects affected / exposed	2 / 162 (1.23%)	3 / 329 (0.91%)	
occurrences (all)	2	4	
Hypotension			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Pallor			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	5	
Phlebitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Varicose vein			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Post thrombotic syndrome			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	4	
Deep vein thrombosis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Extremity necrosis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Superficial vein prominence			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
May-Thurner syndrome			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Bladder catheterisation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Intra-uterine contraceptive device insertion			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Ventricular drainage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal tube insertion			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Central venous catheterisation			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Hepatitis B immunisation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Oophorectomy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Mastoid operation			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tooth extraction			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	5	
Stem cell transplant			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Central venous catheter removal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Endotracheal intubation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Ventriculo-cardiac shunt			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Laryngeal mask airway insertion			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	5	
Chest discomfort			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	5 / 162 (3.09%)	16 / 329 (4.86%)	
occurrences (all)	6	18	
Cyst			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	6 / 162 (3.70%)	21 / 329 (6.38%)	
occurrences (all)	6	23	
Feeling abnormal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Feeling cold			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Gait disturbance			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Granuloma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hyperthermia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hypothermia			

subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Influenza like illness			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Injection site bruising			
subjects affected / exposed	8 / 162 (4.94%)	0 / 329 (0.00%)	
occurrences (all)	8	0	
Injection site extravasation			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Injection site haematoma			
subjects affected / exposed	3 / 162 (1.85%)	0 / 329 (0.00%)	
occurrences (all)	3	0	
Injection site haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Injection site induration			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	3	0	
Injection site mass			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Injection site pruritus			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Malaise			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Mucosal inflammation			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	4	
Oedema			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Oedema peripheral			

subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	4	
Pain			
subjects affected / exposed	0 / 162 (0.00%)	7 / 329 (2.13%)	
occurrences (all)	0	7	
Pyrexia			
subjects affected / exposed	14 / 162 (8.64%)	37 / 329 (11.25%)	
occurrences (all)	22	51	
Application site vesicles			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	4 / 162 (2.47%)	5 / 329 (1.52%)	
occurrences (all)	5	5	
Catheter site haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Puncture site haemorrhage			
subjects affected / exposed	5 / 162 (3.09%)	1 / 329 (0.30%)	
occurrences (all)	8	1	
Catheter site pain			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Catheter site rash			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Vessel puncture site haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Nodule			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Application site hypersensitivity			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Infusion site extravasation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Vaccination site pain			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Medical device site haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Allergy to animal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Anaphylactic reaction			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Hypogammaglobulinaemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Serum sickness			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Secondary immunodeficiency			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Allergy to arthropod sting			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Graft versus host disease in skin			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Graft versus host disease in liver			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Acute graft versus host disease in skin			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Reproductive system and breast disorders			
Breast mass			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Dysmenorrhoea			
subjects affected / exposed	2 / 162 (1.23%)	4 / 329 (1.22%)	
occurrences (all)	2	11	
Genital rash			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Menometrorrhagia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Menorrhagia			
subjects affected / exposed	5 / 162 (3.09%)	21 / 329 (6.38%)	
occurrences (all)	6	29	
Menstruation irregular			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Ovarian cyst			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Pelvic pain			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Polycystic ovaries			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Priapism			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Uterine haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Vaginal discharge			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Vaginal haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	10	
Genital tract inflammation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Perineal erythema			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	11 / 162 (6.79%)	18 / 329 (5.47%)	
occurrences (all)	11	20	
Dyspnoea			
subjects affected / exposed	1 / 162 (0.62%)	7 / 329 (2.13%)	
occurrences (all)	1	8	
Dyspnoea exertional			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Epistaxis			

subjects affected / exposed	20 / 162 (12.35%)	40 / 329 (12.16%)	
occurrences (all)	32	62	
Haemoptysis			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Hiccups			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	3 / 162 (1.85%)	6 / 329 (1.82%)	
occurrences (all)	4	7	
Nasal obstruction			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Painful respiration			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Pleural adhesion			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Pleural effusion			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Pleurisy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	3	
Pulmonary infarction			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Respiratory distress			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Rhinitis allergic				
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)		
occurrences (all)	1	1		
Rhinorrhoea				
subjects affected / exposed	2 / 162 (1.23%)	13 / 329 (3.95%)		
occurrences (all)	2	16		
Sinus congestion				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Sleep apnoea syndrome				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Sneezing				
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)		
occurrences (all)	1	2		
Tonsillar hypertrophy				
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)		
occurrences (all)	1	0		
Wheezing				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Upper respiratory tract inflammation				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Mediastinal cyst				
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)		
occurrences (all)	1	0		
Respiratory tract congestion				
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)		
occurrences (all)	1	0		
Sinus disorder				
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)		
occurrences (all)	1	0		
Oropharyngeal plaque				

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	4 / 162 (2.47%)	8 / 329 (2.43%)	
occurrences (all)	4	9	
Pulmonary pain			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Respiratory symptom			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Lower respiratory tract congestion			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Anxiety			
subjects affected / exposed	2 / 162 (1.23%)	4 / 329 (1.22%)	
occurrences (all)	2	5	
Attention deficit/hyperactivity disorder			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Depressed mood			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Depression			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Disorientation			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Emotional disorder			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Mood altered			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Nervousness			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Panic attack			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Somnambulism			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Phonophobia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Post stroke depression			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device leakage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Device occlusion			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Cholangitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Cholelithiasis			

subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Gallbladder disorder			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hepatic function abnormal			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Hypertransaminasaemia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Alanine aminotransferase abnormal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Alanine aminotransferase increased			
subjects affected / exposed	6 / 162 (3.70%)	6 / 329 (1.82%)	
occurrences (all)	10	11	
Aspartate aminotransferase abnormal			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 162 (0.62%)	6 / 329 (1.82%)	
occurrences (all)	1	10	
Aspiration bone marrow			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Bilirubin conjugated increased			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	4	
Biopsy liver			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Blood bicarbonate decreased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Blood bilirubin increased			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	4	
Blood bilirubin unconjugated increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Blood glucose decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Blood thyroid stimulating hormone increased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
C-reactive protein increased			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Cardiac murmur			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Coagulation factor VIII level increased			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Fibrin D dimer increased			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Full blood count abnormal			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Haemoglobin decreased			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
International normalised ratio abnormal			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Lumbar puncture			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	3	
Lymphocyte count increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Neutrophil count decreased			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	4	
Neutrophil count increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Nuclear magnetic resonance imaging			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Oxygen saturation decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Platelet count decreased			
subjects affected / exposed	2 / 162 (1.23%)	9 / 329 (2.74%)	
occurrences (all)	2	20	
Prothrombin time prolonged			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Weight increased			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
White blood cell count decreased			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Blood phosphorus decreased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Platelet count increased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Lymphocyte percentage decreased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Lipoprotein (a) increased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Bacterial test positive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Blood alkaline phosphatase decreased			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Anticoagulation drug level above therapeutic			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Anticoagulation drug level below therapeutic			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Angiogram			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Epstein-Barr virus test positive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Clostridium test positive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Staphylococcus test positive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Chlamydia test positive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Influenza B virus test positive			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Influenza A virus test positive			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Human rhinovirus test positive			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Liver function test increased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural			

complications				
Accidental overdose				
subjects affected / exposed	0 / 162 (0.00%)	7 / 329 (2.13%)		
occurrences (all)	0	7		
Alcohol poisoning				
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)		
occurrences (all)	1	0		
Arthropod bite				
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)		
occurrences (all)	1	2		
Concussion				
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)		
occurrences (all)	1	1		
Fall				
subjects affected / exposed	2 / 162 (1.23%)	5 / 329 (1.52%)		
occurrences (all)	2	6		
Foot fracture				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Greenstick fracture				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Hand fracture				
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)		
occurrences (all)	0	2		
Head injury				
subjects affected / exposed	3 / 162 (1.85%)	2 / 329 (0.61%)		
occurrences (all)	3	4		
Joint dislocation				
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)		
occurrences (all)	0	1		
Ligament sprain				
subjects affected / exposed	3 / 162 (1.85%)	1 / 329 (0.30%)		
occurrences (all)	3	1		
Overdose				

subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Road traffic accident			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Subcutaneous haematoma			
subjects affected / exposed	5 / 162 (3.09%)	14 / 329 (4.26%)	
occurrences (all)	5	21	
Tibia fracture			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Transfusion reaction			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	3	
Wound secretion			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Mouth injury			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Exposure to communicable disease			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Muscle strain			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	9 / 162 (5.56%)	15 / 329 (4.56%)	
occurrences (all)	10	19	
Incision site haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	4	
Wound haemorrhage			
subjects affected / exposed	2 / 162 (1.23%)	13 / 329 (3.95%)	
occurrences (all)	3	14	
Thermal burn			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Postoperative thoracic procedure complication			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Underdose			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Post procedural complication			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Stoma site rash			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Incision site haematoma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	2 / 162 (1.23%)	4 / 329 (1.22%)	
occurrences (all)	2	4	
Skin abrasion			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	4	
Anaphylactic transfusion reaction			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Eye contusion			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Stoma site haemorrhage subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Stoma site erythema subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Accidental underdose subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	7 / 329 (2.13%) 8	
Vascular access site haemorrhage subjects affected / exposed occurrences (all)	1 / 162 (0.62%) 1	0 / 329 (0.00%) 0	
Cerebral radiation injury subjects affected / exposed occurrences (all)	1 / 162 (0.62%) 1	0 / 329 (0.00%) 0	
Nasal injury subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Product prescribing error subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Congenital, familial and genetic disorders Hydrocele subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Immunodeficiency congenital subjects affected / exposed occurrences (all)	1 / 162 (0.62%) 1	0 / 329 (0.00%) 0	
Protein S deficiency subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Cardiac disorders Atrial tachycardia subjects affected / exposed occurrences (all)	0 / 162 (0.00%) 0	1 / 329 (0.30%) 1	
Bradycardia			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Palpitations			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Sinus tachycardia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tachycardia			
subjects affected / exposed	0 / 162 (0.00%)	6 / 329 (1.82%)	
occurrences (all)	0	6	
Nervous system disorders			
Clumsiness			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	4 / 162 (2.47%)	11 / 329 (3.34%)	
occurrences (all)	4	11	
Dizziness exertional			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Head discomfort			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	24 / 162 (14.81%)	56 / 329 (17.02%)	
occurrences (all)	28	75	
Hyperaesthesia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hypersomnia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Hypotonia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Intracranial pressure increased			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Memory impairment			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Migraine			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Muscle contractions involuntary			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Neuropathy peripheral			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	2 / 162 (1.23%)	5 / 329 (1.52%)	
occurrences (all)	2	5	
Presyncope			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Psychomotor hyperactivity			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Seizure			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Syncope			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Tension headache			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	

Tremor			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Balance disorder			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
VIth nerve disorder			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Toxic neuropathy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Choroid fissure cyst			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 162 (3.09%)	11 / 329 (3.34%)	
occurrences (all)	5	20	
Coagulopathy			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Febrile neutropenia			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Haemolysis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Increased tendency to bruise			
subjects affected / exposed	3 / 162 (1.85%)	1 / 329 (0.30%)	
occurrences (all)	3	1	
Iron deficiency anaemia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Leukocytosis			

subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	3	
Leukopenia			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	8	
Lymphadenitis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Lymphadenopathy			
subjects affected / exposed	2 / 162 (1.23%)	2 / 329 (0.61%)	
occurrences (all)	2	2	
Lymphopenia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	5	
Neutropenia			
subjects affected / exposed	4 / 162 (2.47%)	6 / 329 (1.82%)	
occurrences (all)	4	7	
Pancytopenia			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Thrombocytopenia			
subjects affected / exposed	2 / 162 (1.23%)	10 / 329 (3.04%)	
occurrences (all)	2	15	
Thrombocytosis			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	2	2	
Autoimmune neutropenia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Haemorrhagic diathesis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Bone marrow failure			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Cytopenia			

subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Ear and labyrinth disorders			
Conductive deafness			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Deafness			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Ear haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Ear pain			
subjects affected / exposed	1 / 162 (0.62%)	6 / 329 (1.82%)	
occurrences (all)	1	7	
Deafness unilateral			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Ear discomfort			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Ear pruritus			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Eye disorders			
Amblyopia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Astigmatism			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Cataract			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Diplopia			

subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Eye inflammation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Eye irritation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Eye swelling			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Eyelid ptosis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Glaucoma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Heterophoria			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Myopia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Ocular hyperaemia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Ocular hypertension			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Optic disc haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Papilloedema			

subjects affected / exposed	3 / 162 (1.85%)	4 / 329 (1.22%)	
occurrences (all)	3	5	
Photophobia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Retinal haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Strabismus			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Vision blurred			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Visual impairment			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Conjunctival hyperaemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Eye pruritus			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	9 / 162 (5.56%)	17 / 329 (5.17%)	
occurrences (all)	11	27	
Abdominal pain upper			
subjects affected / exposed	4 / 162 (2.47%)	11 / 329 (3.34%)	
occurrences (all)	4	12	

Anal fissure			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	4	
Anal fistula			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Aphthous ulcer			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Breath odour			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	10 / 162 (6.17%)	8 / 329 (2.43%)	
occurrences (all)	10	11	
Dental caries			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	11 / 162 (6.79%)	25 / 329 (7.60%)	
occurrences (all)	12	30	
Diarrhoea haemorrhagic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Dry mouth			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Dyspepsia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Faeces discoloured			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	

Food poisoning			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Gastric haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Gastritis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Gastrointestinal disorder			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Gingival bleeding			
subjects affected / exposed	1 / 162 (0.62%)	13 / 329 (3.95%)	
occurrences (all)	1	13	
Gingival pain			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Glossitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Haematemesis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Haematochezia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Mouth haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	6 / 329 (1.82%)	
occurrences (all)	0	6	
Mouth ulceration			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	

Nausea			
subjects affected / exposed	6 / 162 (3.70%)	22 / 329 (6.69%)	
occurrences (all)	7	25	
Oral pain			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Rectal haemorrhage			
subjects affected / exposed	3 / 162 (1.85%)	7 / 329 (2.13%)	
occurrences (all)	3	8	
Stomatitis			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	7	
Tongue blistering			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tongue coated			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tongue geographic			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tongue ulceration			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 162 (1.23%)	3 / 329 (0.91%)	
occurrences (all)	2	4	
Vomiting			
subjects affected / exposed	13 / 162 (8.02%)	36 / 329 (10.94%)	
occurrences (all)	17	42	
Anal haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Anal inflammation			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Large intestinal haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Perianal erythema			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Faecaloma			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Abdominal hernia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Appendix disorder			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Gastrointestinal inflammation			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Tooth socket haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Anorectal discomfort			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Anal incontinence			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Alopecia			
subjects affected / exposed	5 / 162 (3.09%)	8 / 329 (2.43%)	
occurrences (all)	5	8	
Alopecia areata			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Blister			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Blood blister			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Dermatitis atopic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Dermatitis contact			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Dermatitis diaper			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Drug eruption			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Dry skin			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	4	
Ecchymosis			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Eczema			
subjects affected / exposed	2 / 162 (1.23%)	2 / 329 (0.61%)	
occurrences (all)	2	2	
Erythema			
subjects affected / exposed	1 / 162 (0.62%)	6 / 329 (1.82%)	
occurrences (all)	1	8	
Erythema multiforme			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hirsutism			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Livedo reticularis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Night sweats			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Petechiae			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Pruritus			
subjects affected / exposed	2 / 162 (1.23%)	8 / 329 (2.43%)	
occurrences (all)	2	8	
Rash			
subjects affected / exposed	4 / 162 (2.47%)	17 / 329 (5.17%)	
occurrences (all)	4	19	
Rash erythematous			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Rash follicular			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Rash maculo-papular			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Rash papular			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Rash pruritic			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Skin discolouration			

subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Skin exfoliation			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Skin striae			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Skin ulcer			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Stasis dermatitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Umbilical haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Urticaria			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Skin swelling			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Skin haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	4	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Haematuria			
subjects affected / exposed	1 / 162 (0.62%)	5 / 329 (1.52%)	
occurrences (all)	1	8	

Hypercalciuria			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Nephrolithiasis			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Pollakiuria			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Renal atrophy			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Urinary bladder haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	5	
Urethral haemorrhage			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Urine odour abnormal			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Acute kidney injury			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	3	2	
Endocrine disorders			
Cushingoid			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 162 (2.47%)	12 / 329 (3.65%)	
occurrences (all)	4	13	
Back pain			
subjects affected / exposed	3 / 162 (1.85%)	11 / 329 (3.34%)	
occurrences (all)	3	11	
Bone pain			

subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Costochondritis			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	3	
Flank pain			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Groin pain			
subjects affected / exposed	0 / 162 (0.00%)	5 / 329 (1.52%)	
occurrences (all)	0	5	
Joint swelling			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Musculoskeletal pain			
subjects affected / exposed	2 / 162 (1.23%)	0 / 329 (0.00%)	
occurrences (all)	2	0	
Myalgia			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	5	
Neck pain			
subjects affected / exposed	1 / 162 (0.62%)	6 / 329 (1.82%)	
occurrences (all)	1	6	
Pain in extremity			
subjects affected / exposed	9 / 162 (5.56%)	23 / 329 (6.99%)	
occurrences (all)	12	25	
Pain in jaw			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Tendonitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Muscle tightness			

subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	4	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Musculoskeletal discomfort			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Infections and infestations			
Angular cheilitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Bacteriuria			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Bronchiolitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Bronchitis			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	4	
Cellulitis			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Conjunctivitis			
subjects affected / exposed	2 / 162 (1.23%)	3 / 329 (0.91%)	
occurrences (all)	2	4	
Ear infection			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Eye infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Eyelid infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	2 / 162 (1.23%)	2 / 329 (0.61%)	
occurrences (all)	2	2	
Gastroenteritis			
subjects affected / exposed	0 / 162 (0.00%)	7 / 329 (2.13%)	
occurrences (all)	0	7	
Gastroenteritis viral			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	4	
Gastrointestinal infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Giardiasis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hand-foot-and-mouth disease			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Herpes zoster			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hordeolum			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Impetigo			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Influenza			
subjects affected / exposed	3 / 162 (1.85%)	6 / 329 (1.82%)	
occurrences (all)	4	6	
Injection site infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Localised infection			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	4	
Mastoiditis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	10 / 162 (6.17%)	29 / 329 (8.81%)	
occurrences (all)	13	36	
Oral candidiasis			
subjects affected / exposed	1 / 162 (0.62%)	5 / 329 (1.52%)	
occurrences (all)	1	5	
Osteomyelitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Otitis media			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Otitis media acute			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Otitis media chronic			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Paronychia			
subjects affected / exposed	1 / 162 (0.62%)	3 / 329 (0.91%)	
occurrences (all)	1	3	
Periodontitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	

Pharyngitis			
subjects affected / exposed	4 / 162 (2.47%)	2 / 329 (0.61%)	
occurrences (all)	4	2	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	3	2	
Pneumonia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Pneumonia mycoplasmal			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Postoperative wound infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	4 / 162 (2.47%)	11 / 329 (3.34%)	
occurrences (all)	4	12	
Scarlet fever			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 162 (0.62%)	6 / 329 (1.82%)	
occurrences (all)	1	6	
Skin infection			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Subcutaneous abscess			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	4 / 162 (2.47%)	5 / 329 (1.52%)	
occurrences (all)	4	5	
Tooth abscess			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Upper respiratory tract infection			
subjects affected / exposed	8 / 162 (4.94%)	10 / 329 (3.04%)	
occurrences (all)	8	13	
Urethritis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	2 / 162 (1.23%)	4 / 329 (1.22%)	
occurrences (all)	2	4	
Varicella			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 162 (0.62%)	4 / 329 (1.22%)	
occurrences (all)	1	4	
Viral pharyngitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Viral rash			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Vulvitis			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Wound infection			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Oral infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Tooth infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Abscess limb			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Cardiac infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Tinea versicolour			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Asymptomatic bacteriuria			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Catheter site infection			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Enteritis infectious			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Implant site infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Sinusitis bacterial			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Adenovirus infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	

Bacterial infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Mastoid abscess			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Ear infection viral			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Parainfluenzae virus infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	2	
Respiratory tract infection			
subjects affected / exposed	0 / 162 (0.00%)	3 / 329 (0.91%)	
occurrences (all)	0	3	
Acarodermatitis			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Device related infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Vulvovaginal mycotic infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	0 / 162 (0.00%)	4 / 329 (1.22%)	
occurrences (all)	0	5	
Gastrointestinal viral infection			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	

Candida infection			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Folate deficiency			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hypercalcaemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hyperchloraemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hyperkalaemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hypernatraemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Hyperuricaemia			
subjects affected / exposed	0 / 162 (0.00%)	1 / 329 (0.30%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 162 (0.00%)	8 / 329 (2.43%)	
occurrences (all)	0	8	
Hypomagnesaemia			

subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	2	
Hyponatraemia			
subjects affected / exposed	1 / 162 (0.62%)	2 / 329 (0.61%)	
occurrences (all)	1	2	
Hypophosphataemia			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	3	
Iron deficiency			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Metabolic acidosis			
subjects affected / exposed	0 / 162 (0.00%)	2 / 329 (0.61%)	
occurrences (all)	0	3	
Selenium deficiency			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Vitamin B12 deficiency			
subjects affected / exposed	1 / 162 (0.62%)	0 / 329 (0.00%)	
occurrences (all)	1	0	
Vitamin D deficiency			
subjects affected / exposed	2 / 162 (1.23%)	1 / 329 (0.30%)	
occurrences (all)	2	1	
Hyperhomocysteinaemia			
subjects affected / exposed	1 / 162 (0.62%)	1 / 329 (0.30%)	
occurrences (all)	1	1	
Decreased appetite			
subjects affected / exposed	0 / 162 (0.00%)	6 / 329 (1.82%)	
occurrences (all)	0	7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2015	- Implementation of dosing regimen for children aged between 6 to <12 years following confirmation of the body weight-adjusted dosing regimen for this age group in the phase II study (14373). - Inclusion of menstruation intensity assessments. The protocol was adjusted throughout to reflect that the intensity of menstruation has to be assessed from visit 2 to visit7. - Information was provided on continuing body weight-adjusted treatment in children who turned 2, 6, 12 and 18. If a child turned to the next highest age group, he/she continued treatment according to age- and body-weight dependent dosing of his/her inclusion age cohort. However, if a child's weight increased (as measured at a visit), the child would be assigned to the appropriate dose group. - Heparins flushes were added to maintain catheter patency. It was decided to allow heparin flushes except for flushes before PK/PD samples. - Instructions for rivaroxaban administration with an o.d. and b.i.d. regimen for children aged between 6 and <12 years were added. - Instructions for handling of missed doses are provided for o.d. and bid dosing in children aged between 6 and <12 years.
20 September 2016	- The timeframe in which randomization can be done was extended from day 1-5 to day 1-9 of the initial treatment. - Information was added for switch from VKA to rivaroxaban. This modification clarified the procedure for children randomized to rivaroxaban, who had already started VKA therapy prior to randomization. - Update of exclusion criterion 1: "high risk for bleeding contraindicating anticoagulant therapy" was modified to read "bleeding risk contraindicating anticoagulant therapy". - Clarification of exclusion criterion 5: it was clarified that children with sustained uncontrolled hypertension should be excluded from the study. - Clarification of concomitant medication in exclusion criteria 7 and 8; The modification indicated that the drugs listed in the exclusion criteria 7 and 8 were considered strong inhibitors of both CYP3A4 and P-gp, and strong inducers of CYP3A4, respectively, but that the lists was not limited to the drugs mentioned. - Collection of body weight was added for Visits 2 and 3. - The assessment of the incidence of post-thrombotic syndrome was added for children of ≥12 years with lower or upper extremity DVT at Visit 4, 5, 6 and 7. - The upper range for children completing the Taste- and Texture questionnaire was changed from <12 to <18 years. - Introduction of additional supplies for preparation and administration of oral suspension; Additional supplies were be provided to prepare, measure and administer the rivaroxaban oral suspension. These supplies included a syringe for measurement of 100 mL of water and liquid dosing devices for measurement of the dose volume. - Enrollment of children aged between 0.5 to <6 years was opened, and the structure of age cohort specific dosing and regiment instructions was resolved and replaced by a consistent description applicable for children aged between 0.5 and <18 years. - The suspension formulation was provided for children in all age cohorts.
11 January 2017	- A visit was added to be scheduled 2+1 days after start of rivaroxaban treatment for children treated according to a t.i.d. regimen. - The dosing table was extended to include dosing information for children with body weight of 6 kg to 12 kg. Children with body weight between 6 and <12 kg were to be treated according to a thrice-daily (t.i.d.) schedule with a time interval of approximately 8 hours between individual doses.
27 September 2017	- New dosing information for children with body weight between 2.6 and <6 kg, and inclusion of children aged between birth and 0.5 year was added.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported