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Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Xarelto

rivaroxaban

Procedure no: EMEA/H/C/000944/P46/042

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Abbreviations

AE	Adverse event
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
CIAC	Central independent adjudication committee
CSR	Clinical study report
DVT	Deep venous thrombosis
FAS	Full analysis set
LMWH	Low molecular weight heparin
MAH	Marketing authorisation holder
PD	Pharmacodynamics
PE	Pulmonary embolism
PIP	Paediatric investigation plan
PK	Pharmacokinetics
PT	Prothrombin time
SAE	Serious adverse event
SAS	Safety analysis set
TEAE	Treatment emergent adverse event
TESAE	Treatment emergent serious adverse event
ULOQ	Upper level of quantification
VKA	Vitamin K antagonist

1. Introduction

On 27 September 2017, the MAH submitted a completed paediatric study for Xarelto (rivaroxaban), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the PIP programme for Xarelto (Rivaroxaban EMEA-000430-PIP01-08-M10) as follow up measure 7.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Rivaroxaban, an oral specific, direct factor Xa inhibitor, has been evaluated in adult patients, including treatment of deep vein thrombosis and pulmonary embolism. Rivaroxaban is a therapeutic alternative for treatment of venous thromboembolism (VTE) in children as well and is currently developed in this indication as agreed in a Paediatric Investigational Plan (PIP).

Venous thrombosis in children is about 100 times less common than in adults, however, the incidence is increasing, likely due to higher awareness, improved diagnosis and due to often lifesaving procedures, which may be associated with a higher risk of thrombosis (e.g., use of central lines, cancer treatment).

Based on the current knowledge of the coagulation system in children, it is expected that children will respond to the Factor Xa inhibitor rivaroxaban with a similar PK/PD relationship as compared to adults. Therefore, the rivaroxaban paediatric program follows the concept that exposures in children that are equivalent to exposures observed with the 20 mg dose in adults will also result in similar safety and efficacy for treatment and secondary prevention of VTE in children. The main objectives of the rivaroxaban paediatric program are (1) to establish an age and body weight adjusted dosing regimen to achieve an exposures that is equivalent to the adult exposure following 20 mg rivaroxaban once daily dose, and (2) to demonstrate the safety and efficacy of rivaroxaban in children.

The clinical program in children started with a single dose phase I study (study 12892) in children aged 6 months to < 18 years. This study was followed by two consecutive, 30-day treatment phase II studies (studies 14373 and 14374) and a phase III, 3-month treatment study (study 14372) to evaluate comparative safety and efficacy of rivaroxaban vs. standard of care in children with VTE. The two phase II studies have been completed, and enrolment into the phase III study is currently ongoing. Through modification of the PIP, patients from birth to aged < 2 years will be included in this ongoing phase III study (14372), and the previously planned phase III for this age group (17625) was deleted. Additionally, the ongoing phase I/II study (study 17618) in children aged from birth to <6 months was added to the PIP through this modification

One additional paediatric studies is currently being conducted. A phase I study (study 17992) that investigates the PK/PD of rivaroxaban administered as granules for oral suspension formulation in children aged 6 months <12 years.

This submission concerns the study 14374, 30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis, submitted as a stand-alone study.
No changes to the product information are proposed within this submission.

2.2. Information on the pharmaceutical formulation used in the study

INN	Rivaroxaban
Substance code number	BAY 59-7939
Composition	Oral suspension Active ingredient: rivaroxaban / BAY59-7939 micronized
Strength	1 mg/mL

Based on in vitro dissolution data and information from study 12892, individual doses of the ready-to-use suspension were diluted in a defined volume of liquid to 0.1% before administration in phase II study 14374.

Assessor's comment:

The children in study 14374 received rivaroxaban as oral suspension. Oral suspension has been used in previous paediatric studies, e g. 12892 and 14373.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

• study 14374, titled 30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis.

Rivaroxaban (Xarelto) is an oral, selective direct factor Xa inhibitor. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi.

Rivaroxaban (Xarelto) is indicated in:

- Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.
- Prevention of stroke and systemic embolism in adult patients with non valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age >- 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
- Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.
- Rivaroxaban (Xarelto), co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers.

The goal of the rivaroxaban paediatric program is to make rivaroxaban available to children for treatment and secondary prevention of venous thromboembolism (VTE).

2.3.2. Clinical study 14374 (clinical phase 2)

Description

Study 14374 was designed to evaluate the safety, efficacy and PK/PD profile of a 30-day treatment with age and body weight-adjusted oral rivaroxaban (diluted ready-to use suspension) in children aged between 6 months and < 6 years.

Children who had been treated for at least 2 months or in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA for symptomatic or asymptomatic venous thrombosis were eligible for inclusion.

Children received rivaroxaban according to an age- and body weight-adjusted regimen. The study treatment period was for a total of 30 days followed by an observational period of another 30 days. All suspected clinical study outcomes and baseline and repeat thrombosis imaging tests were assessed by a central independent adjudication committee (CIAC). An independent data monitoring committee (DMC) monitored the children's safety and gave recommendations to the steering committee.

The study was performed in 27 centres in 14 countries, including 6 countries in the EU.

First subject, first visit: 15 Jan 2015
Last subject, last visit: 05 Apr 2017

Methods

Objective(s)

The primary objective was:

- to assess the incidence of major bleeding and clinically relevant non-major bleeding

The secondary objectives were:

- to assess the incidence of recurrent symptomatic venous thromboembolism
- to assess asymptomatic deterioration in the thrombotic burden on repeat imaging
- to characterize the pharmacokinetic/pharmacodynamic profile of a 30-day treatment with oral rivaroxaban.

Study design

The study was initially designed as an open-label, active-controlled, randomized study (original protocol dated 04 March 2014), but was altered to single-arm study in Amendment 4 (see below).

Assessor's comment:

This was an open-label study. This is acceptable because blinding with different comparators is not feasible. The dosing of the oral suspension is based on findings from the phase 1 study 12892.

Substantial protocol changes

Amendment 1 (global, protocol version 2.0) dated 02 September 2014:

- Erroneous dosing information was corrected.

- The suspension information was adjusted and summary of oral suspension preparation was provided.

Amendment 4 (global, protocol version 3.0), dated 14 April 2015:

- The comparator arm was removed. Furthermore, due to the comparator arm removal, the total subject number was reduced.
- Inclusion criterion 1 was changed to enable enrolment of children who are on long-term anticoagulant treatment. Additionally, instructions on how to safely handle the switch from heparin, fondaparinux, and Vitamin K antagonists (VKA) to rivaroxaban and vice versa were made available in the protocol.
- The platelet count threshold for exclusion of children was adjusted from <100x109/L to <50x109/L.

Study population /Sample size

At least 20 children in two cohorts (6 months - ≤ 2 years and 2-6 years) were planned to be treated with rivaroxaban (at least 10 children per age cohort). Before amendment 4 and the removal of comparator arm, the planned number of children was 40 (20 children in each treatment arm).

Assessor's comment:

46 children received at least one dose of the study drug.

Treatments

Subjects in the treatment arm was given age- and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban as an oral suspension twice a day for 30 days.

Age- and body weight-adjusted rivaroxaban was administered twice daily (12 hours apart) as diluted ready-to-use oral suspension based on the results from the phase I study (12892):

Age group	Body weight [kg]		Oral suspension dose (b.i.d.)	Maximum daily dose
	Min	Max		
≥ 6 months to < 6 years	3	<4	0.7 mg	1.4 mg
	4	<5	0.9 mg	1.8 mg
	5	<6	1.4 mg	2.8 mg
	6	<7	1.8 mg	3.6 mg
	7	<8	2.2 mg	4.4 mg
	8	<9	3.2 mg	6.4 mg
	9	<10	3.2 mg	6.4 mg
	10	<12	3.4 mg	6.8 mg
	12	<14	4.0 mg	8.0 mg
	14	<16	4.0 mg	8.0 mg
	16	<20	4.0 mg	8.0 mg
	20	<30	5.0 mg	10.0 mg
	30	<40	7.5 mg	15.0 mg
	40	<50	7.5 mg	15.0 mg

b.i.d. = twice daily

Rivaroxaban was taken in the morning and in the evening within 2 hours after a meal.

Since children with a glomerular filtration rate below 30 mL/min/1.73 m^2 were excluded from the study, a dose adaptation was not indicated.

Before implementation of Amendment 4, children were randomized to receive either rivaroxaban or comparator (low molecular weight heparin [LMWH], fondaparinux or vitamin K antagonist [VKA]) as per standard of care. Children in the comparator groups continued with the anticoagulant treatment that had been used prior to study randomization

Outcomes/endpoints

Efficacy:

- Symptomatic recurrence of venous thrombosis or asymptomatic deterioration (secondary outcome)

Clinical pharmacology:

- The variables for pharmacodynamics were PT, aPTT, and antifactor Xa (secondary outcome).
- Rivaroxaban plasma concentrations were used to assess the pharmacokinetics of rivaroxaban (secondary outcome).

Safety:

- Composite of major and clinically relevant non-major bleeding (primary outcome).
- Adverse events, vital signs, physical examination (including bodyweight and height), and laboratory measures (secondary outcome)

Other:

- A taste and texture questionnaire in the form of a 3-point scale was used to determine the acceptance of the oral suspension in children aged ≥ 4 years.

Statistical Methods

For the demography and baseline characteristics, summary statistics (arithmetic mean, standard deviation, median, minimum and maximum for quantitative variables) were presented by treatment and age group. Frequency tables for qualitative data were provided. Medical history findings were summarized using Medical Dictionary for Regulatory Activities (MedDRA) terms.

All efficacy analyses were performed on the full analysis set population. The occurrence of recurrent venous thromboembolism and asymptomatic deterioration in thrombotic burden were summarized by age group. None of these events occurred in the study.

All safety analyses were performed on the safety analysis set (SAS) population. The analysis primarily focused on bleeding that occurred during or within 2 days after stop of study treatment. Bleeding events observed later were described separately. Individual listings of major and clinically relevant non-major bleeding were provided. The incidence of bleeding was summarized descriptively.

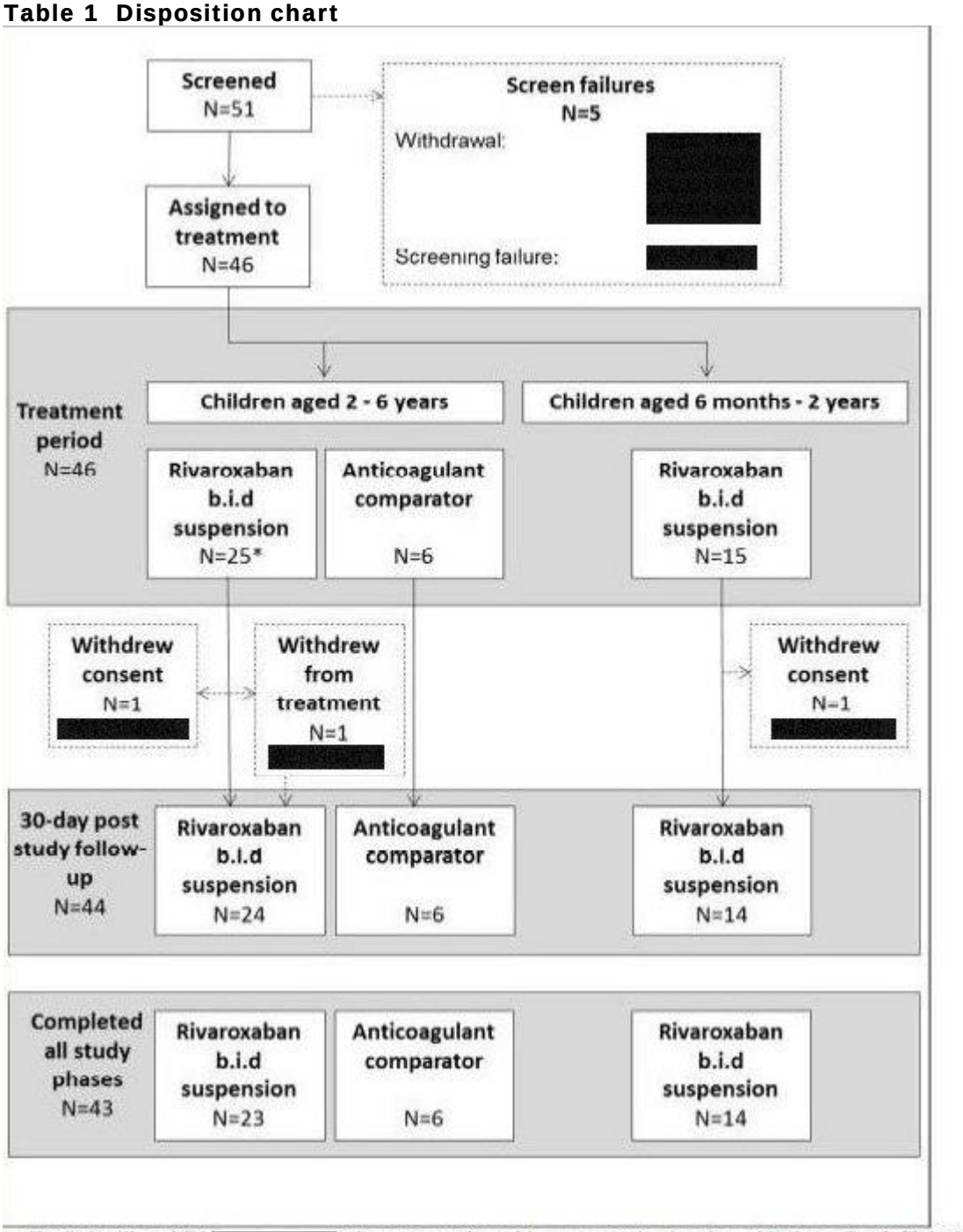
For PD analyses, quantitative data were described by the summary statistics mentioned above, and presented descriptively for the original data as well as for the difference, respectively, ratio to baseline. PK/PD modelling, using population approaches, was used to describe the pharmacokinetics of rivaroxaban, including potential influence of relevant co-variables, and to relate anticoagulant parameters

Results

Recruitment / Number analysed

A total of 51 children were screened in 27 study centres in 14 countries. In total, 46 children were assigned to study treatment and received at least one dose of study medication (Table 1).

Table 1 Disposition chart



*includes the child [redacted] who was assigned to comparator treatment but received diluted rivaroxaban. Source: Table 14.1.1 / 4, Table 14.1.1 / 5, Table 14.1.1 / 6 , Table 14.1.1 / 7, Table 14.1.1 / 10

One child in 2-6 years group was assigned to anticoagulant comparator treatment, but received rivaroxaban. The child completed the study as planned and is included in the rivaroxaban group.

Assessor's comment:

Consent was withdrawn from two subjects. Additionally, one subject was withdrawn from treatment due to the need for a series of lumbar punctures. This child attended to the study follow-up and completed the study.

Baseline data

In this study, children aged between 6 months and < 6 years were included. The mean age of children was 2.94 years (median 3.0 years). Average weight at baseline was 15.45 kg (median 14.05 kg) and average height was 94.69 cm (median 96.00 cm). The demographic characteristics are summarised in Table 2.

Table 2 Demographics (SAS)

	2-6 years group		6 months-2 years group
	Rivaroxaban b.i.d (suspension) N=25 (100%)	Comparator N=6 (100%)	Rivaroxaban b.i.d (suspension) N=15 (100%)
Sex			
Male	13 (52.0%)	3 (50.0%)	6 (40.0%)
Female	12 (48.0%)	3 (50.0%)	9 (60.0%)
Race			
White	23 (92.0%)	6 (100.0%)	10 (66.7%)
Black/African American	1 (4.0%)	0	2 (13.3%)
Asian	0	0	1 (6.7%)
Multiple	0	0	1 (6.7%)
Not reported	1 (4.0%)	0	1 (6.7%)
Age (calculated, years)			
N	25	6	15
Mean (SD)	3.77 (1.03)	3.67 (0.82)	1.26 (0.45)
Median	4.00	3.50	1.33
Range	2.0 - 5.0	3.0 - 5.0	0.5 - 1.9
Baseline Weight (kg)			
N	25	6	15
Mean (SD)	17.48 (5.37)	18.90 (8.39)	10.69 (2.51)
Median	17.00	16.55	10.70
Range	12.5 - 39.6	11.5 - 34.9	5.8 - 14.1
Baseline Height (cm)			
N	25	5	15
Mean (SD)	103.96 (9.66)	100.50 (8.86)	77.31 (7.61)
Median	104.00	97.50	78.60
Range	83.4 - 127.0	90.0 - 112.0	60.8 - 87.0
Baseline Body Mass Index (kg/m^2)			
N	25	5	15
Mean (SD)	16.02 (3.13)	15.39 (1.18)	17.69 (2.65)
Median	15.72	14.76	17.02
Range	11.4 - 29.4	14.2 - 17.0	13.8 - 23.8

Source: Table 14.1.2 / 1

Assessor's comment:

The demographic distribution is accepted.

For all 46 children in FAS, the index event was confirmed by CIAC before start of study treatment (Table 3). Several children had more than one thrombus location, and more than one diagnostic test was performed.

Table 3 Index venous thrombosis - number of children by clot location category (FAS)

Location of event category	2-6 years group		6 months-2 years group
	Rivaroxaban b.i.d (suspension) N=25 (100%)	Comparator N=6 (100%)	Rivaroxaban b.i.d (suspension) N=15 (100%)
Category 1: Lower extremity deep vein thrombosis and/or vena cava thrombosis and/or pulmonary embolism and/or heart atrium	6 (24.0%)	1 (16.7%)	10 (66.7%)
Category 2: Upper extremity deep vein thrombosis and/or subclavian vein thrombosis	4 (16.0%)	2 (33.3%)	0
Category 3: Cerebral vein and sinus thrombosis and/or jugular vein thrombosis	15 (60.0%)	3 (50.0%)	5 (33.3%)

Source: Table 14.1.5 / 4

Note: A subject could have more than one index event location but is allocated to only one category. Only confirmed events are considered in the table and the location is taken from the assessment of the central independent adjudication.

Note: the single child who had thrombi belonging to category 1 (heart atrium) and category 3 (cerebral vein and sinus thrombosis) was assigned to category 3.

Assessor's comment:

The distribution of subjects in the three categories differs between the rivaroxaban and comparator groups in children 2-6 years. This is accepted, as there are only 6 subjects in the comparator group, making statistical comparisons between the groups not meaningful.

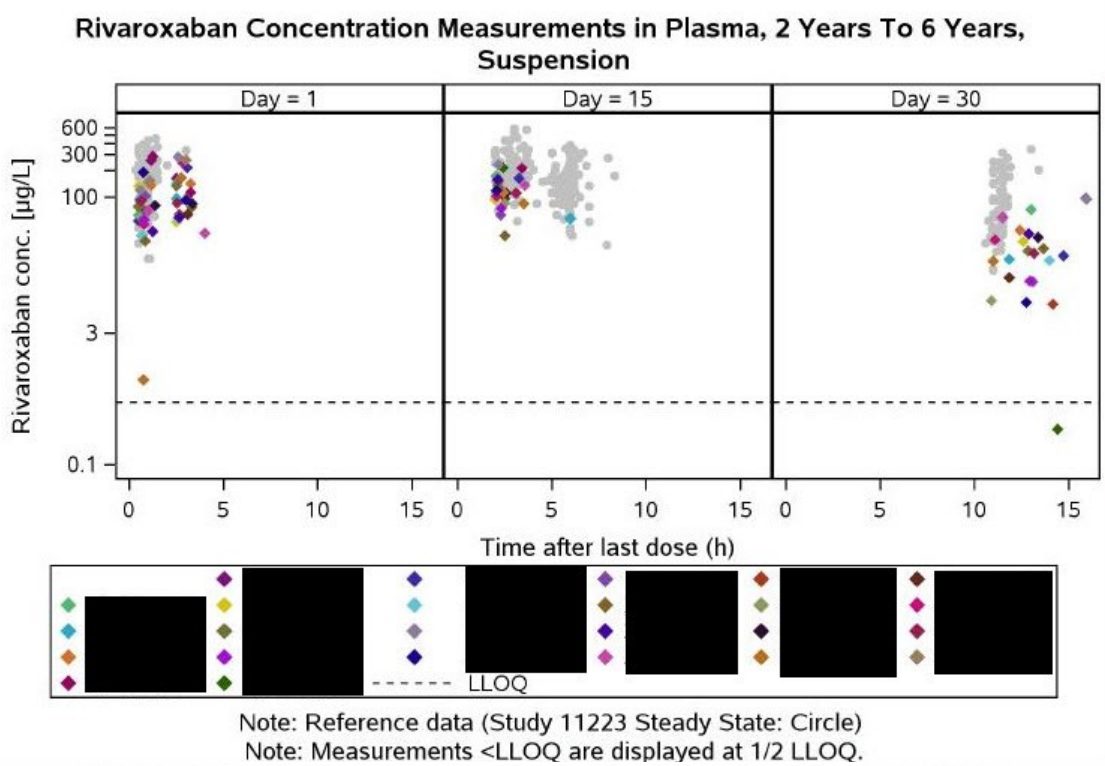
All children in SAS received antithrombotic agent for treatment of index event prior to study drug administration. Most children (45/46, 97.8%) were treated with LMWH/heparin. Vitamin K-antagonists, fondaparinux and enzymes (thrombolytic therapy) were reported for 4/46 (8.7%), 1/46 (2.2%) and 1/46 (2.2%) children, respectively. A child could receive more than one antithrombotic agent as prior medication for index event.

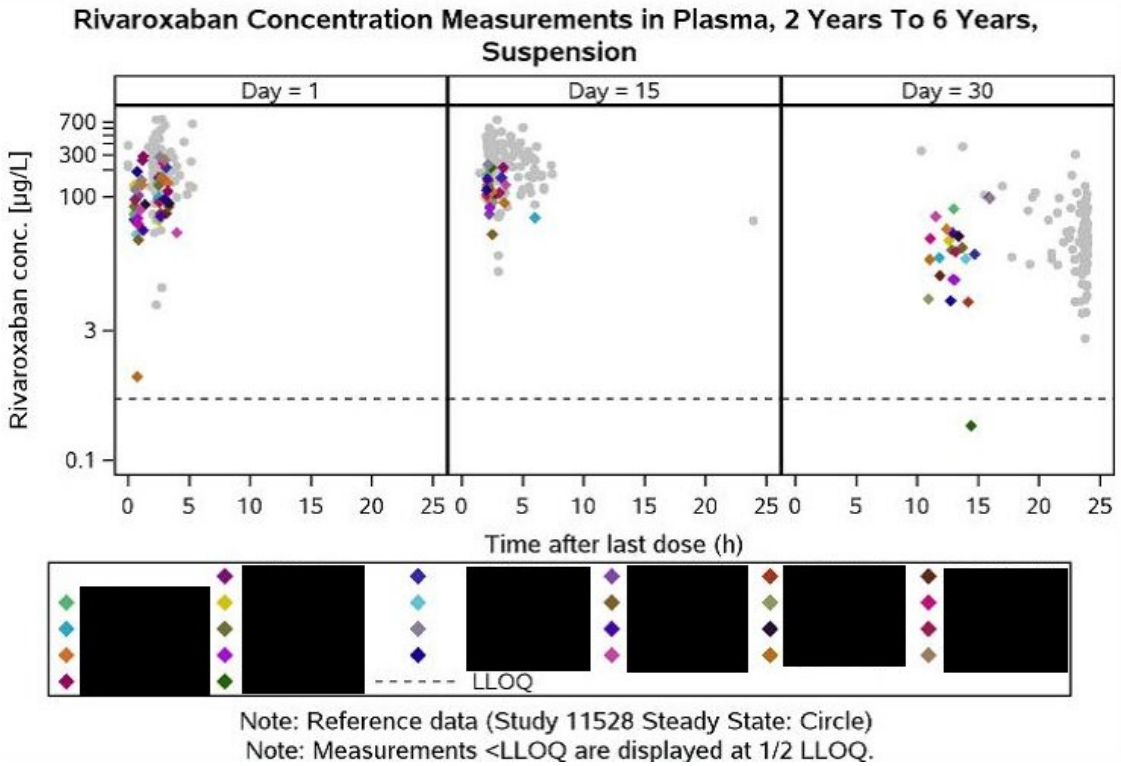
The median for treatment duration for index event prior to treatment assignment in this study was 65.5 days (range: 27-973 days).

Pharmacokinetics

Forty children enrolled in this study were valid for pharmacokinetic analysis. Rivaroxaban pharmacokinetics were evaluated on Day 1 and at steady state following 15 days and 30 days of treatment with 10 mg rivaroxaban dose equivalents b.i.d. as diluted ready-to-use oral suspension. Children were enrolled in age groups 2-6 years (25 children) and 6 months-2 years (15 children). From each child, 4 blood samples were taken: on Day 1 at 0.5-1.5 h and 2.5-4 h post administration, on Day 15, 2-8 h post administration and on Day 30, 10-16 h post administration. The observed concentrations measured 10-16 hours after dosing on Day 30 are labelled “Ctrough”, whereas the population PK estimates of the steady state trough concentrations are labelled “C(12)ss”.

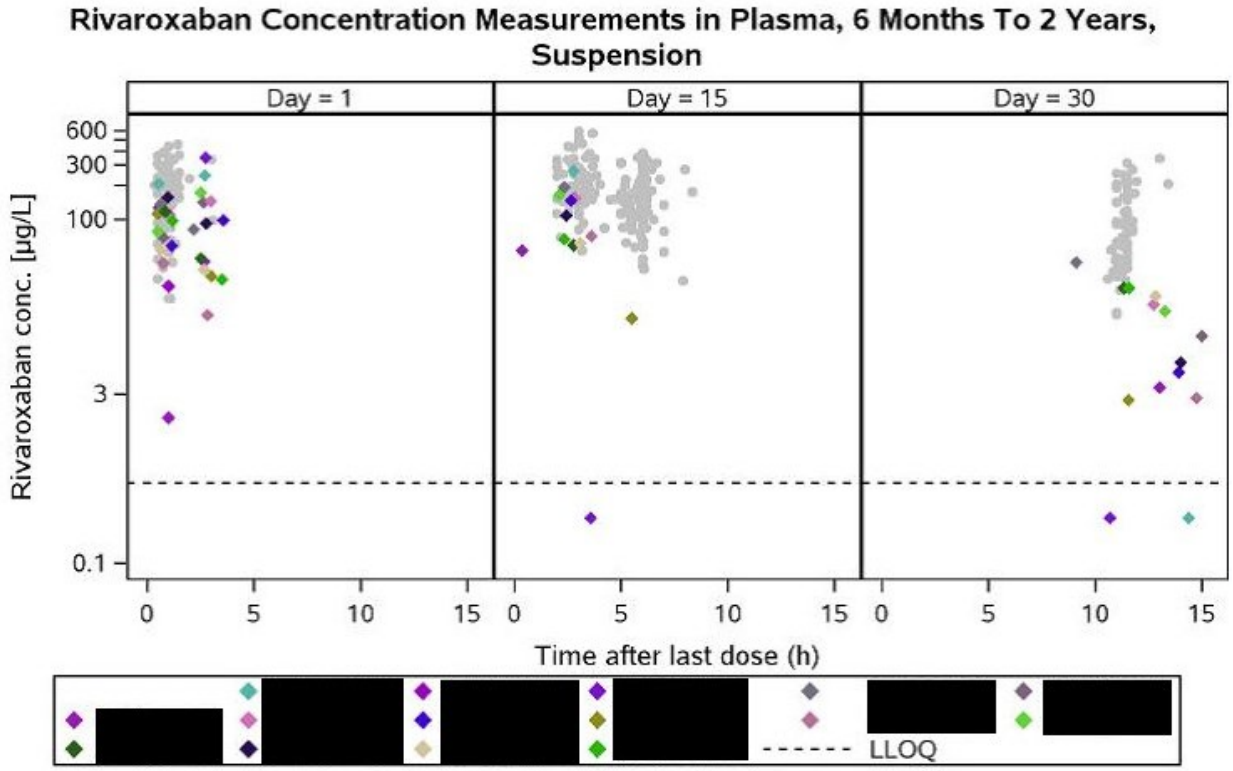
Rivaroxaban plasma concentrations (µg/L) in children 2-6 years of age on Day 1, Day 15 and Day 30 of multiple dose administration of rivaroxaban 10 mg b.i.d. dose equivalents (diluted ready-to-use oral suspension), semilogarithmic scale, PK analysis set, n=25

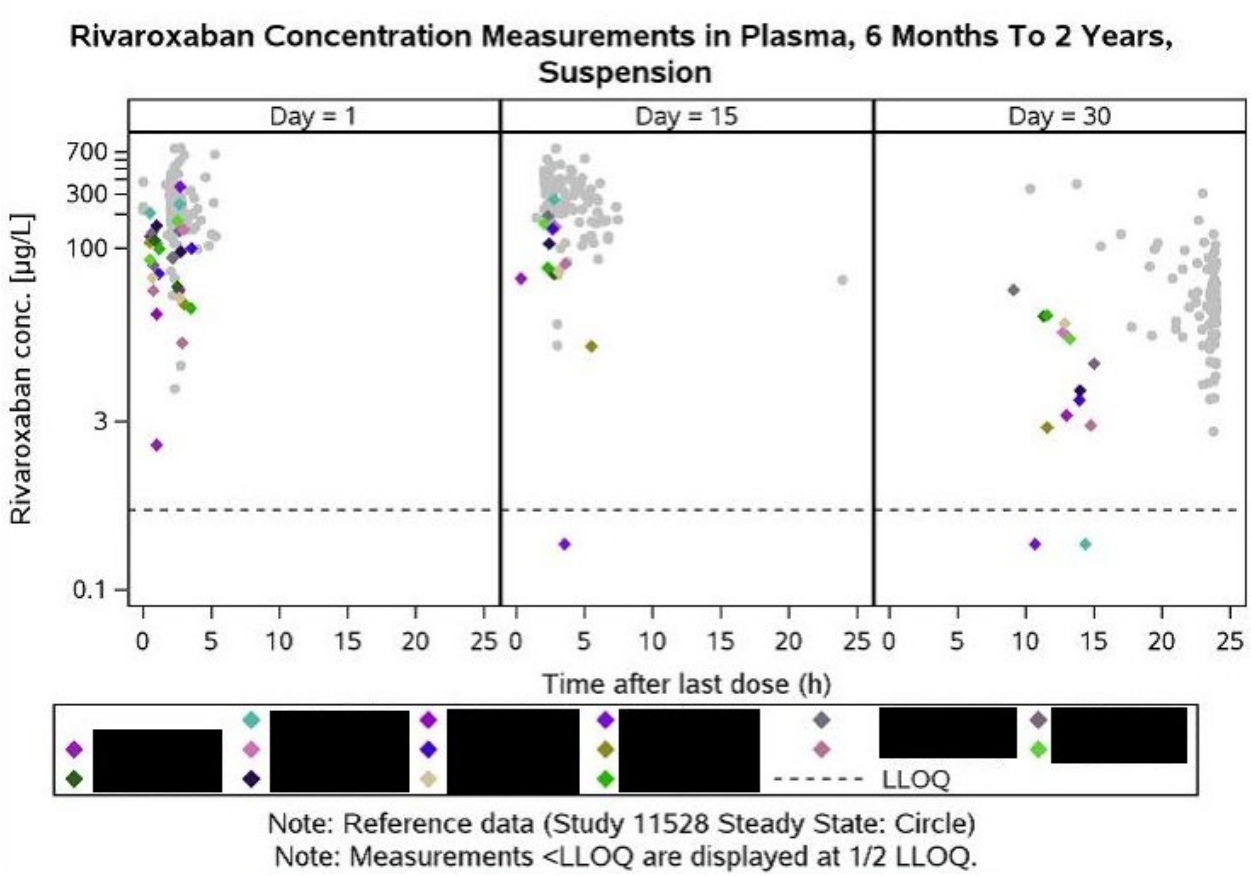




Rivaroxaban plasma concentrations (µg/L) in children 6 months-2 years of age on Day 1, Day 15 and Day 30 of multiple dose administration of rivaroxaban 10 mg

b.i.d. dose equivalents (diluted ready-to-use oral suspension), semilogarithmic scale, PK analysis set, n=15





Reference populations are adult patients aged with VTE aged 20 to 90 years (n=118 receiving 10 mg rivaroxaban b.i.d., Study 11223) and aged 22 to 87 years (n=135 receiving 20 mg rivaroxaban o.d., Study 11528)

Assessor's comment:

Raw data on PK stratified for age has been presented in the graphs above and lower than expected rivaroxaban Ctrough concentrations were seen in children compared to the adult reference range. In order to further visualise the data, the MAH is suggested to plot Day 30 (Ctrough) measurements also vs body weight. Please elaborate whether the observation may be due to biopharmaceutic reasons (e.g. potential difference in bioavailability of the formulations used; suspension in children and tablets in adults) or rather a difference in PK (e.g. maturation factors or a different weight dependence than previously predicted).

Based on the PK observation, the MAH has presented preliminary plan for future studies and on a general level, the plan is supported.

Pharmacodynamics

PD data were available from 39 children treated with rivaroxaban (25 children aged 2-6 years and14 children aged 6 months-2 years).

For each child, Prothrombin time (PT) (in seconds and as INR), activated partial thromboplastin time (aPTT), and anti-Xa were assessed. Three blood samples were scheduled for each child:

- 2.5-4 hours after dosing on Day 1,
- 2-8 hours after dosing on Day 15

- 10-16 hours after dosing on Day 30.

For changes of PD parameters from baseline, the trough level obtained on Day 30 at 10-16 h after the last rivaroxaban dose was used as baseline as the children were pre-treated with other anticoagulants which would have had an impact on baseline determinations prior to the start of the rivaroxaban treatment. It was anticipated, that specifically PT and aPTT levels have returned to baseline or close to baseline at 10-16 hours after the last dose of rivaroxaban due to the limitations of both assays to detect low levels of rivaroxaban.

Mean values of the three sampling intervals in children were generally comparable between both age cohorts (Table 4).

Table 4 Summary statistics of PT values and changes from baseline (sec) on Day 1, Day 15 and Day 30 by age group and sampling interval, n, mean ± SD (range), (PD analysis set), n=39

Day	Scheduled time interval	N	2-6 years rivaroxaban b.i.d. suspension	N	6 months-2 years rivaroxaban b.i.d. suspension	N	All 6 months-6 years rivaroxaban b.i.d. suspension
1	2.5-4 h post	24	18.6 ± 4.25 (14.4-35.5)	14	17.2 ± 3.23 (14.1-23.6)	38	18.0 ± 3.92 (14.1-35.5)
15	2-8 h post	23	19.0 ± 4.08 (15.0-32.1)	14	19.4 ± 4.70 (16.1-35.1)	37	19.2 ± 4.26 (15.0-35.1)
30	10-16 h post	23	15.8 ± 2.54 (13.3-21.0)	14	14.6 ± 1.69 (11.7-18.6)	37	15.4 ± 2.30 (11.7-21.0)
1	2.5-4 h post - baseline	22	2.78 ± 4.85 (-4.50-19.2)	14	2.51 ± 3.53 (-3.60-7.80)	36	2.68 ± 4.33 (-4.50-19.2)
15	2-8 h post - baseline	22	2.59 ± 2.39 (-4.00-6.80)	14	4.76 ± 4.74 (0.60-20.5)	36	3.43 ± 3.59 (-4.00-20.5)

PT: prothrombin time; SD: standard deviation sec: seconds
PD: pharmacodynamic(s) b.i.d.: *bis in die* (twice daily)
Baseline: Day 30 / 10-16 h post dose
Source: Table 14.4.1.1 / 1

No obvious impact of body weight on changes of the coagulation parameters PT was observed, as there is a substantial imbalance in subject numbers between the weight categories that add on the effect of differences in individual t_{max}.

Individual PT data in children aged 2-6 years and 6 months-2 years were in line with reference data from adult VTE patients treated with 10 mg rivaroxaban b.i.d. or with 20 mg rivaroxaban once daily as tablets. Correlations were also comparable between older and younger children.

Two PT values observed in children were above the 99% prediction intervals of the adult population. However, results above the limits of the 99% prediction interval were also observed in adult patients. No effect of developmental haemostasis on PT was observed in children aged 6 months-6 years as compared to adult VTE patients.

Assessor's comment:

The MAH believes that the difference between the age group 2- 6 years and 6 months-2 years in the time interval 2 to 8 hours is probably due to differences of timing of sampling between the groups as well as differences in t_{max}. This is accepted.

It is agreed that the small number of subjects in some weight classes, e.g. 2 subjects in the 0-7.5 kg weight class, in part can explain the variations in PT between the weight classes.

Table 5 shows summary statistics for absolute aPTT and the change of aPTT prolongations from baseline levels (Day 30, 10-16 h post). Mean values of aPTT were distorted by outliers, i.e. values above 180 sec, the upper level of quantification (ULOQ) of the assay. These values were reported as '180 sec' for summary statistics. Outliers were observed on Day 1 (1 child [2-6 years]), on Day 15 (2 children [6 months-2 years]) and on Day 30 (1 child [6 months-2 years]). Since median values are more robust with regard to outliers, it appeared more suitable to look at medians and this is why they are presented for aPTT.

Table 5 Summary statistics of aPTT values and changes from baseline (sec) on Day 1, Day 15 and Day 30 by age group and sampling interval, n, mean ± SD, median (range), (PD analysis set), n=39

Day	Scheduled time interval	N	2-6 years rivaroxaban b.i.d. suspension	N	6 months-2 years rivaroxaban b.i.d. suspension	N	All 6 months-6 years rivaroxaban b.i.d. suspension
1	2.5-4 h post	24	48.0 ± 31.1 41.0 (28.6-180)	14	42.2 ± 12.0 41.0 (30.0-77.4)	38	45.8 ± 25.7 41.0 (28.6-180)
15	2-8 h post	23	42.4 ± 11.2 40.1 (31.5-89.9)	14	66.6 ± 50.4 44.1 (31.8-180)	37	51.6 ± 33.8 41.2 (31.5-180)
30	10-16 h post	23	37.0 ± 7.99 34.8 (28.4-60.5)	14	45.6 ± 39.0 34.5 (29.9-180)	37	40.3 ± 24.6 34.8 (28.4-180)
1	2.5-4 h post - baseline	22	6.46 ± 17.0 5.30 (-21.2-73.4)	14	-3.48 ± 40.4 5.55 (-135-47.4)	36	2.59 ± 28.4 5.40 (-135-73.4)
15	2-8 h post - baseline	22	2.81 ± 6.38 3.80 (-20.7-10.7)	14	21.0 ± 66.8 6.00 (-124-150)	36	9.89 ± 42.0 4.00 (-124-150)

aPTT: activated partial thromboplastin time; SD: standard deviation sec: seconds
PD: pharmacodynamic(s) b.i.d.: *bis in die* (twice daily)
Baseline: Day 30 / 10-16 h post dose
Values >180 sec (ULOQ of the assay) were replaced by 180 sec
Source: Table 14.4.1.2 / 1

In general, individual aPTT values of children were within the range of the adult reference populations of VTE patients. The distribution of aPTT measurements in the population of children 2-6 years of age was well comparable to the population of younger children aged 6 months-2 years.

However, four children showed aPTT values >180 sec which is the ULOQ. aPTT values above 180 sec are not covered by the range of aPTT results obtained in the adult reference populations that is used for comparison, which represents a subset of the overall population. In general, such values were observed in adults as well. When assessing the outlying aPTT values in connection with PT, anti-Xa values and plasma concentrations, it is evident, that not all parameters are affected to a similar extent. Therefore, an artefact of the assay is considered the most likely explanation for these outliers. Median values of aPTT values at the three sampling intervals are more robust against outliers and are used for the assessment. These median aPTT values were well comparable between both paediatric age cohorts. A weight based analysis of aPTT displays the same limitations mentioned for PT – low number of subjects in two of the 4 weight cohorts which makes an assessment impossible. Individual correlations between aPTT changes to baseline versus plasma concentrations were also affected by the outliers, however in general there is a good agreement between paediatric and adult data. 2 children showed aPTT values above the range of the adult reference population(s). No effect of developmental

haemostasis was observed for aPTT in children aged 6 months-6 years as compared to adult VTE patients.

Assessor's comment:

The measurements of aPTT are distorted by four outliers, according to the MAH possibly artefacts. This, in combination with small populations, complicates the interpretation of the results.

Table 6 shows the summary statistics for absolute anti-Xa concentrations and anti-Xa increases from baseline levels (Day 30, 10-16 h post).

Table 6 Summary statistics of anti-Xa values and changes from baseline (µg/L) on Day 1, Day 15 and Day 30 by age group and sampling interval, n, mean ± SD (range), (PD analysis set), n=39

Day	Scheduled time interval	N	2-6 years rivaroxaban b.i.d. suspension	N	6 months-2 years rivaroxaban b.i.d. suspension	N	All 6 months-6 years rivaroxaban b.i.d. suspension
1	2.5-4 h post	22	128 ± 69.6 (40.6-275)	14	87.8 ± 84.2 (7.25-278)	36	113 ± 77.1 (7.25-277)
15	2-8 h post	22	103 ± 58.3 (21.6-232)	13	131 ± 96.5 (29.1-332)	35	114 ± 74.7 (21.6-332)
30	10-16 h post	22	19.1 ± 17.5 (7.25-62.7)	14	17.0 ± 19.7 (7.25-81.9)	36	18.2 ± 18.1 (7.25-81.9)
1	2.5-4 h post - baseline	19	94.9 ± 57.4 (-10.2-226)	14	70.9 ± 74.5 (0.00-212)	33	84.7 ± 65.2 (-10.2-226)
15	2-8 h post - baseline	21	77.3 ± 50.5 (14.3-196)	13	114 ± 91.0 (18.4-325)	34	91.2 ± 69.9 (14.3-325)

anti-Xa: anti-factor Xa activity SD: standard deviation
PD: pharmacodynamic(s) b.i.d.: *bis in die* (twice daily)
Baseline: Day 30 / 10-16 h post dose
Source: Table 14.4.1.3 / 1

Assessor's comment:

Mean trough anti-Xa levels 10 to 16 hours after the last rivaroxaban dose on Day 30 were similar between the age groups at 19.1 and 17.0 µg/L. Mean anti-Xa increases from baseline differed between the age groups, but not in a consistent way.

Anti-Xa concentrations are different in the weight categories specifically on Day 1 of the rivaroxaban treatment. Means were 43.9, 50.1, 93.9 and 129 µg/L in the weight categories 0-7.5, 7.5-12, 12-20 and 20- 40 kg. This may be indicative of differences in tmax in addition to the difference in subject numbers in the individual weight groups. During multiple dosing, i.e. on Day 15 / 2-8 h post dose results do not show a consistent dependence of anti-Xa concentrations from weight categories.

As the anti-Xa assay with rivaroxaban specific calibrators and controls was developed after the adult VTE treatment trial was completed, there are no adult reference data available for this assay.

Correlation of anti-Xa with plasma concentrations determined by HPLC was linear, however it has to be noted that outliers were observed. This needs to be considered when the anti-Xa assay is used in clinical practice.

Efficacy results

In total, 46 children were valid for FAS.

None of the 46 children treated with study medication had a confirmed symptomatic recurrent VTE (composite of DVT or fatal of non-fatal PE) during the treatment period or during the 30-day post treatment period. One child (rivaroxaban 6 months- 2 years group) had a suspected recurrent venous thrombosis in the lower extremity as reported by the investigator but the event was not confirmed by the CIAC.

At the end of the 30-day treatment period (Visit 4), a repeat imaging of the thrombus was performed. The images of the index event and repeat imaging were adjudicated by the CIAC. The thrombotic burden at the time of the index event was compared to the thrombotic burden at the time of repeat imaging. The outcome of the adjudication was classified as “normalized”, “improved”, “no relevant change”, “deteriorated”, or “not evaluable”.
Repeat imaging was available for 22/25 (88.0%) children in the rivaroxaban 2-6 years group, for 5/6 (83.3%) children in the comparator 2-6 years group and for 11/15 (73.3%) children in the rivaroxaban 6 months-2 years group (Table 4).

Table 7 Thrombotic burden assessment by treatment group up to visit 4 (FAS, children with repeat imaging available)

Assessment	2-6 years		6 months-2 years
	Rivaroxaban b.i.d (suspension) n=22 (100%)	Comparator n=5 (100%)	Rivaroxaban b.i.d. (suspension) n=11 (100%)
Assessment available	22 (100%)	5 (100%)	11 (100%)
Normalized	6 (27.3%)	1 (20.0%)	4 (36.4%)
Improved	15 (68.2%)	3 (60.0%)	4 (36.4%)
No relevant change	1 (4.5%)	1 (20.0%)	3 (27.3%)
Deteriorated	0	0	0

Source: Table 14.2 / 2, Listing 16.2.6 / 3

Assessor's comment:

The low number of subjects in the comparator group does not allow for comparisons between the groups in children 2-6 years. In both groups, most subjects were improved by treatment.

Among the children 6 months-2 years, there was a higher number of subjects with no relevant change at follow up than among the older children.

For the secondary efficacy endpoints there seem to be no major efficacy differences between rivaroxaban and comparator treatment in this open label study.

Safety results

Safety evaluations were performed for the 46 children who received at least one dose of study medication. Of these, 40 received treatment with rivaroxaban.

Overall, study treatment duration in children in the rivaroxaban 2-6 years group was 8 to 35 days (mean 28.6 days). In the comparator 2-6 years group, overall treatment duration was 28 to 34 days (mean 30.7 days) and in the rivaroxaban 6 months-2 years group, children were treated 1 to 35 days (mean 27.1 days).

Assessor's comment:

Two children in the rivaroxaban 2-6 years group discontinued the study after 8 and 21 treatment days respectively. One child 6 months-2 years group discontinued the study after one day of treatment. None of the subjects discontinued the study due to adverse events.

There were no cases of death, major bleeding or discontinuation of study medication due to AEs.

The number of AEs/TEAEs in the different groups are summarised in Table 5.

Table 8 Overall summary of number of subjects with treatment-emergent adverse events (safety analysis set)

	Rivaroxaban 2-6 years	Rivaroxaban 0.5 -2 years	Rivaroxaban 0.5-6 years (pooled)	Comparator
	N=25 (100%)	N=15 (100%)	N=40 (100%)	N=6 (100%)
Treatment-emergent AE (TEAE)	14 (56%)	11 (73%)	25 (62%)	4 (67%)
TEAE considered related by investigator	1 (4%)	1 (7%)	2 (5%)	0
Maximum intensity for related TEAE:				
Mild	1 (4%)	1 (7%)	2 (5%)	N/A
Death	0	0	0	0
Any serious AE (SAE)	0	7 (47%)	7 (18%)	1 (17%)
Treatment-emergent SAE (TESAE)	N/A	2 (14%)	2 (5%)	1 (17%)
TESAE considered related by investigator	N/A	0	0	0
Discontinuation due to any AE	0	0	0	0

(Based on Table 14.3.2/4 in the CSR)

There were no treatment-emergent clinically relevant non-major bleeding events in the rivaroxaban groups. However, one child in the comparator group presented with a clinically relevant non-major rectal haemorrhage. Treatment-emergent trivial bleedings were reported for 3/46 children. 2 children in the rivaroxaban 2-6 years group and 1 child in the rivaroxaban 6 months-2 years group had at least one trivial bleeding. No trivial bleedings were reported for children in the comparator group

In 2/46 children at least one TEAE was reported as drug-related by the investigators (diarrhoea and constipation).

In 1/6 child in the comparator group and in 2/15 children in the rivaroxaban 6 months-2 years group, at least one treatment emergent SAE (TESAE) was reported (Headache and Optic atrophy; Pyrexia; Respiratory disorder). For all children, the reason for seriousness was hospitalization. Additionally, for one child in the comparator, the reason of seriousness was persistent or significant disability (Optic atrophy). All TESAE were assessed as not related to the study drug by the Investigator.

Assessor's comment:

No cases of death, major bleeding or discontinuation of study medication due to AEs were reported. One event of clinically relevant non-major bleeding was reported in the comparator group. 3 TESAEs were reported, 2 in the rivaroxaban 6 months – 2 years group and 1 in the comparator group.

The subject reporting respiratory distress (a nine months old male) had concomitant symptoms of fever, inflammation of throat and diarrhoea. The investigator considered the event respiratory disorder to be unrelated to the study drug and study procedure and provided intercurrent disease as an alternative explanation for the event. This is agreed.

The subject reporting pyrexia (a 23 months old male) had a medical history of sickle cell anaemia and acute lymphoblastic leukaemia, both ongoing. The final day of study treatment, the subject presented with oral herpes. The next day, the subject was noted with severe fever and was hospitalized. The investigator considered the event (fever) unrelated to the study drug and protocol required procedures. Alternative possible explanation for the event to be underlying disease further specified as leukaemia. This is agreed.

Adverse events of special interest were reported for 2/46 (4.4%) children in SAS, one in the comparator group and one in the treatment (6 months to 2 years group). Both events regarded thrombocytopenia.

The event in the rivaroxaban group is summarised below:
A 20-months old girl with ongoing Langerhans' cell histiocytosis developed thrombocytopenia, anaemia and febrile leukocytopenia during rivaroxaban treatment. The event assessed unrelated to the study drug as concurrent treatment with chemotherapy and the Langerhans cells histiocytosis may plausibly explain the event occurrence.

Other evaluations

16 children over 4 years old treated with rivaroxaban oral suspension were asked to respond to the taste and texture questionnaire. The results are summarised below (Table 9).

Table 9 Taste and texture questionnaire – Expression assessment (SAS)

	Comfortable N (%)	Indifferent N (%)	Displeased N (%)	Total N (%)
Expressions concerning the appearance	12 (75.0%)	4 (25.0%)		16 (100.0%)
Expressions concerning the smell	11 (68.8%)	4 (25.0%)	1 (6.3%)	16 (100.0%)
Expressions concerning the taste	12 (75.0%)	3 (18.8%)	1 (6.3%)	16 (100.0%)

Source: Table 14.3.7 / 1

Assessor's comment:

The taste and texture of the oral suspension was acceptable to most children.

2.3.3. Discussion on clinical aspects

Study 14374 was designed to evaluate the safety, efficacy and PK/PD profile of a 30-day treatment with age and body weight-adjusted oral rivaroxaban (diluted ready-to use suspension) in children aged

between 6 months and < 6 years. Children who had been treated for at least 2 months or in case of catheter-related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA for symptomatic or asymptomatic venous thrombosis were eligible for inclusion.
The study was initially designed as an open-label, active-controlled, randomized study, but was altered to single-arm study in Amendment 4.

46 children received at least one dose of the study drug. Children in the rivaroxaban group received age- and body weight-adjusted rivaroxaban was administered twice daily (12 hours apart) as diluted ready-to-use oral suspension based on the results from the phase I study (12892). 6 subjects (aged 2-6 years) were included in the comparator arm before Amendment 4. The subjects in the rivaroxaban groups were divided into two cohorts based on age (6 months - ≤ 2 years and 2-6 years). The demographic distribution between the groups was acceptable.

Correlations between individual changes of PT/aPTT and individual plasma concentrations were in the range of the adult VTE patients receiving a 10 mg rivaroxaban dose b.i.d (Study 11223) or 20 mg rivaroxaban once daily (Study 11528) In general, a linear relationship of anti-Factor Xa activity as determined by anti-Xa assay versus plasma concentrations measured by HPLC were observed, however outliers were observed.

No obvious influence of body weight on PD parameters was observed. No apparent influence of developmental haemostasis was observed in children aged 6 months - 6 years when data were compared to the adult VTE population studies in the adult dose ranging studies.

Regarding PK, PK data stratified for age has been presented and lower than expected rivaroxaban Ctrough concentrations were seen in children compared to the adult reference range. In order to further visualise the data, the MAH is suggested to plot Day 30 (Ctrough) measurements also vs body weight. Please elaborate whether the observation may be due to biopharmaceutical reasons (e.g. potential difference in bioavailability of the formulations used; suspension in children and tablets in adults) or rather a difference in PK (e.g. maturation factors or different weight dependence than previously predicted).

Based on the PK observation, the MAH has presented preliminary plan for future studies and on a general level, the plan is supported.

The number of subjects in the comparator arm was too low to allow statistical comparisons regarding the effect of the study drugs. For the secondary efficacy endpoints there seem to be no major efficacy differences between rivaroxaban and comparator treatment in this open label study.

No new safety issues were observed during the cause of this study. There were no cases of death, major bleeding or discontinuation of study medication due to AEs in the rivaroxaban groups. One event of non-major bleeding of clinical significance was reported in the comparator group.

The taste and texture of the oral suspension was acceptable to most children.

3. Additional clarification requested

1) PK stratified for age has been presented and lower than expected rivaroxaban Ctrough concentrations were seen in children compared to the adult reference range. In order to further visualise the data, the MAH is suggested to plot Day 30 (Ctrough) measurements also vs body weight.

2) Please elaborate whether the observation may be due to biopharmaceutic reasons (e.g. potential difference in bioavailability of the formulations used; suspension in children and tablets in adults) or

rather a difference in PK (e.g. maturation factors or a different weight dependence than previously predicted).

Assessment of questions

1) PK stratified for age has been presented and lower than expected rivaroxaban Ctrough concentrations were seen in children compared to the adult reference range. In order to further visualise the data, the MAH is suggested to plot Day 30 (Ctrough) measurements also vs body weight.

REPLY

The applicant would like to explain that the study report displays the paediatric data in comparison to two adult dose regimens, i.e. 10 mg rivaroxaban administered twice daily (Study 11223), representing the equivalent regimen, and 20 mg rivaroxaban administered once daily (Study 11528), which is the approved regimen for VTE treatment in adults and represents, the targeted exposure range in terms of $AUC(0\text{-}24)_{ss}$ and C_{trough}

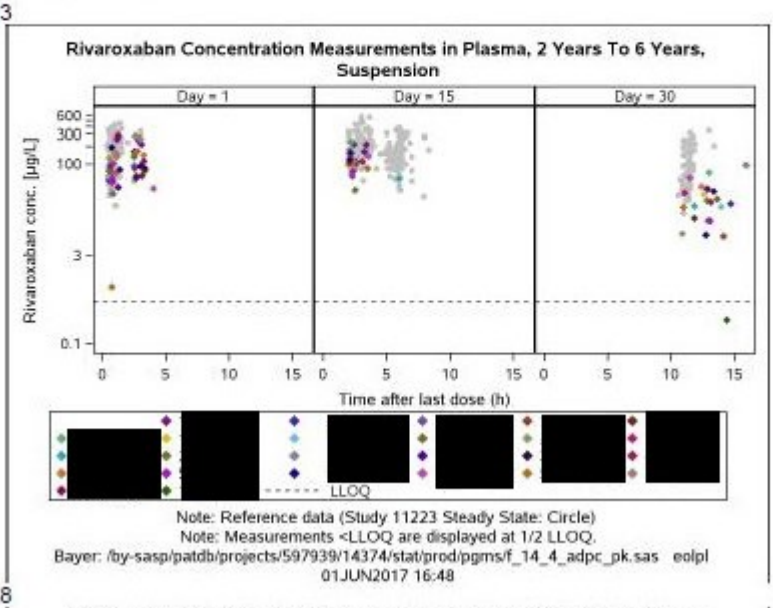
We agree with the Rapporteur, that the paediatric trough concentrations for children aged 6 months to 2 years are at the lower end of the C_{trough} values of adult VTE treatment patients receiving the 10 mg bid dose (upper part of figures 11-13 and 11-14 of the study report PH-39333, study 14374 – copied below for your reference). For children aged 2 to 6 years, concentrations observed in the trough interval scatter in the lower half of the C_{trough} values of adult VTE treatment patients receiving rivaroxaban in 10 mg bid regimen. However, when the paediatric data for C_{trough} $(C(12)_{ss})$ are compared to the 20 mg once daily treatment in adult VTE patients $(C(24)_{ss})$, the observed concentrations are mainly within the concentration range of the adult data, with the exception of one data point being below the LLOQ in children aged 2 to 6 years and two data points <LLOQ for children aged 6 months to 2 years, (lower part of figures 11-13 and 11-14 of the study report PH-39333, study 14374, copied below for your reference).

As the approved and clinically used adult VTE treatment dosing scheme is 20 mg od in the maintenance phase, we consider the C_{trough} values of children aged 6 months to 6 years to be within the targeted range of the adult VTE reference population, with a trend towards lower than expected trough concentrations particularly for children <2 years.

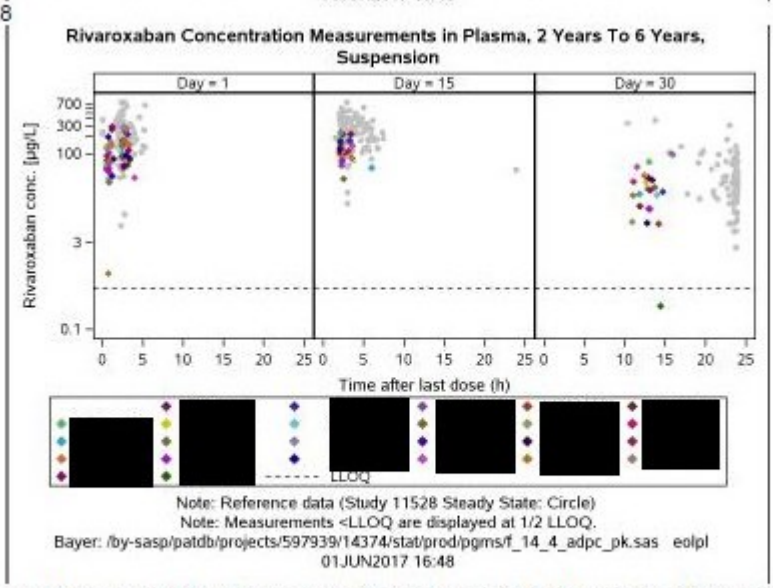
Figure 11-13 copied from the study report (PH-39333, study 14374):

Figure 11-13: Rivaroxaban plasma concentrations (µg/L) in children 2-6 years of age on Day 1, Day 15 and Day 30 of multiple dose administration of rivaroxaban 10 mg b.i.d. dose equivalents (diluted ready-to-use oral suspension), semilogarithmic scale, PK analysis set, n=25

Study 11223



Study 11528



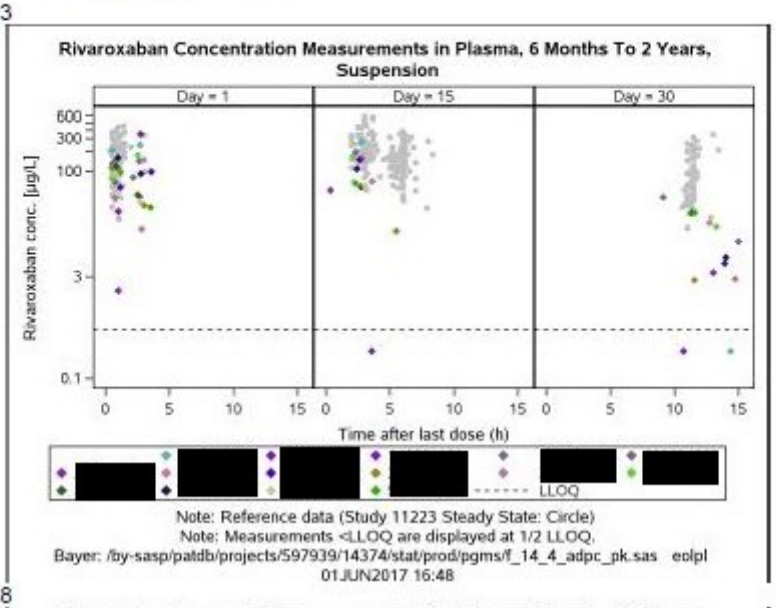
Reference populations are adult patients aged with VTE aged 20 to 90 years (n=118 receiving 10 mg rivaroxaban b.i.d., Study 11223) and aged 22 to 87 years (n=135 receiving 20 mg rivaroxaban o.d., Study 11528)

Source: Figure 14.4.2 / 1 and Figure 14.4.2 / 4

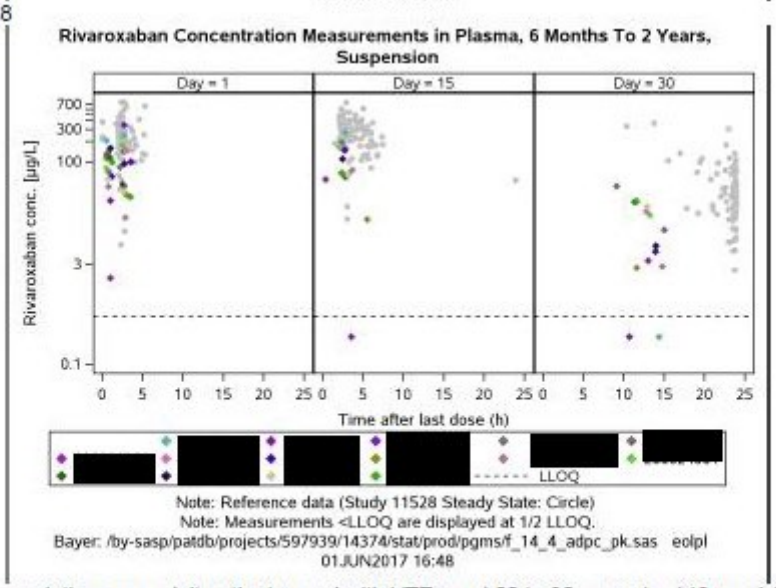
Figure 11-14 copied from the study report (PH-39333, study 14374):

Figure 11-14: Rivaroxaban plasma concentrations (µg/L) in children 6 months-2 years of age on Day 1, Day 15 and Day 30 of multiple dose administration of rivaroxaban 10 mg b.i.d. dose equivalents (diluted ready-to-use oral suspension), semilogarithmic scale, PK analysis set, n=15

Study 11223



Study 11528



Reference populations are adult patients aged with VTE aged 20 to 90 years (n=118 receiving 10 mg rivaroxaban b.i.d., Study 11223) and aged 22 to 87 years (n=135 receiving 20 mg rivaroxaban o.d., Study 11528)

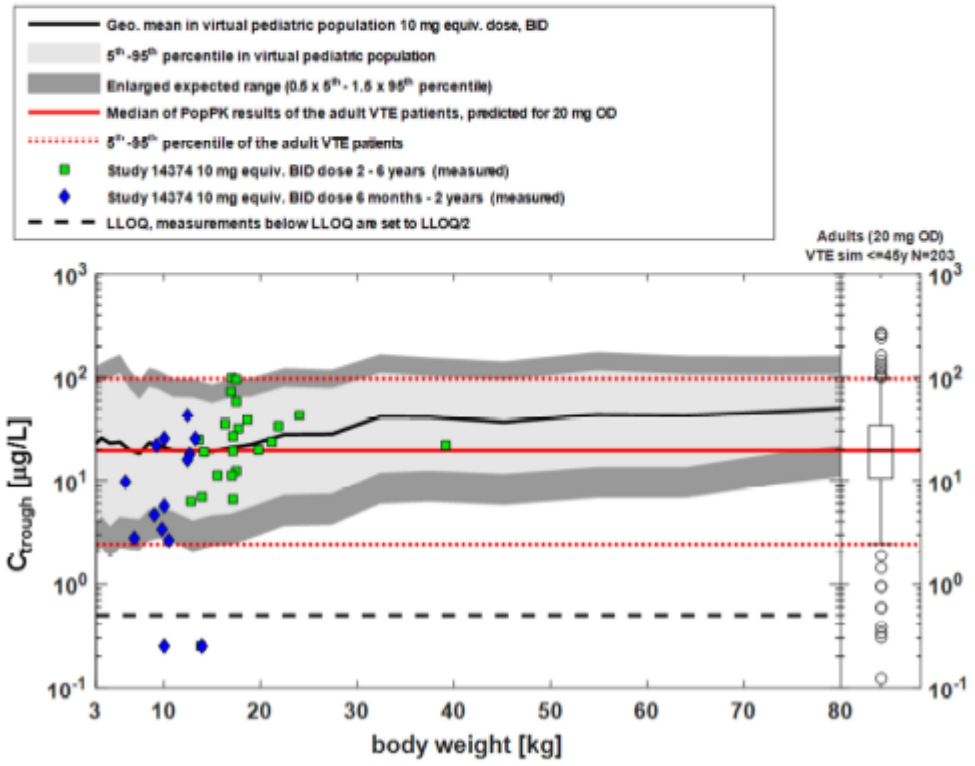
Source: Figure 14.4.2 / 2 and Figure 14.4.2 / 5

For a visual inspection of C_{trough} in dependence of body weight, we kindly refer to Figure 11-19 (copied from the study report PH-39333, study 14374 for your reference). This figure shows the observed trough concentrations (10 to 16 hours after dosing) on day 30 for children receiving 10 mg dose equivalent b.i.d. in comparison to the adult reference range (red horizontal lines, adult VTE patients receiving 20 mg od, simulated via population PK modelling) and the PBPK predictions (grey shaded area, children/adolescents between 6 months and 18 years of age receiving 10 mg equivalent dose bid). Green symbols represent children aged 2 to 6 years and blue symbols represent children aged 6 months to 2 years. This graph shows that the trough concentrations that were measured in children aged 2 to 6 years were right within the range for C_{trough} of the adult VTE population receiving 20 mg od

(indicated by red horizontal lines in Figure 11-19), whereas for children of the age group 6 months to 2 years, there is a trend towards lower than expected trough concentrations, with values that were <LLOQ, and even below the 5th percentile of the adult range (indicated by red dotted line in Figure 11-19). The figure also shows that the PBPK model tends to overestimate C_{trough} values in children below 2 years of age (corresponding approximately to body weights below 12 kg), which is even more obvious in the corresponding concentration-time plot (please refer to the semilogarithmic scale of Figure 11-16 of the study report PH-39333, study 14374 copied below for your reference). As mentioned above, for. one child in the age group 2 to 6 years and for two children in the age group 6 months to 2 years, C_{trough} concentrations were below LLOQ on day 30, and were thus below the prediction range of the PBPK model.

Figure 11-19 copied from the study report (PH-39333, study 14374):

Figure 11-19: Measured trough concentrations (C_{trough}) 10-16 hours after dosing on Day 30 for children and adolescents receiving rivaroxaban 10 mg dose equivalent b.i.d. in comparison to the corresponding PBPK predictions (10 mg equivalent dose b.i.d.) for children/adolescents between 6 months and 18 years of age (grey shaded area) and for adult VTE patients (20 mg o.d.) simulated via population PK modeling (box-whisker plot indicating the percentiles 5, 25, 50, 75, and 95; open circles show individual values beyond the 5th-95th percentile range).

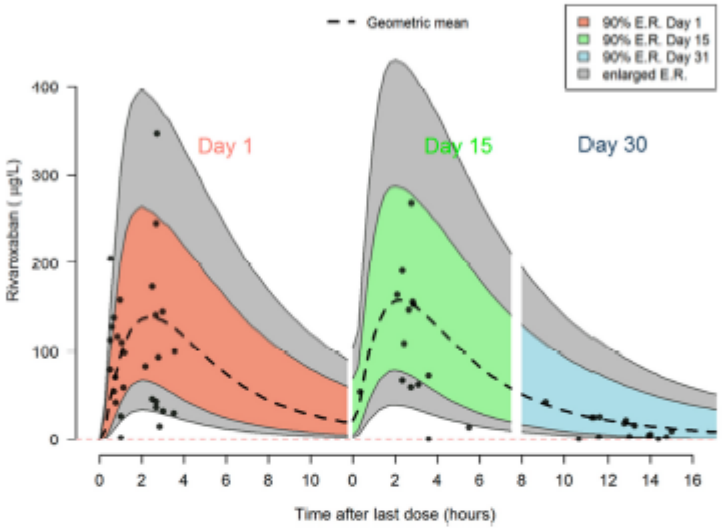


Source: M&S Report [21]

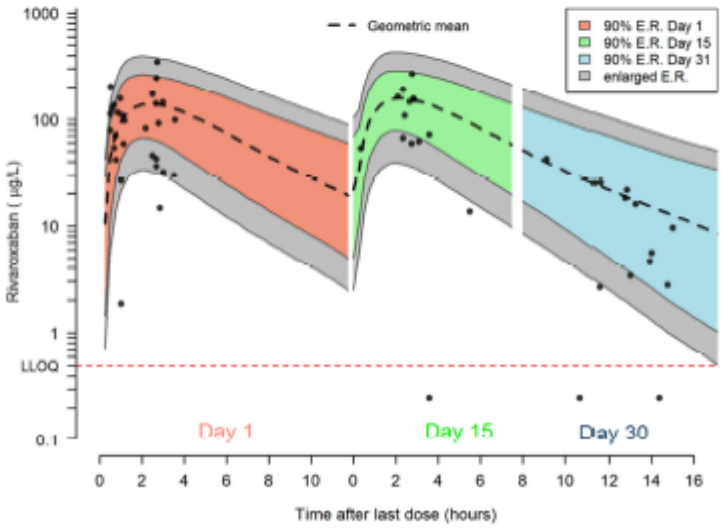
Figure 11-16 copied from the study report (PH-39333, study 14374):

Figure 11-16: Observed plasma concentration vs. time profiles for children aged 6 months-2 years receiving rivaroxaban 10 mg b.i.d. dose equivalents as diluted ready-to-use oral suspension in comparison to the PBPK model predictions for a population aged 0.5 to <2 years (linear [upper graph] and semilogarithmic [lower graph] scale). Individual subjects are shown as black dots.

Linear scale



Semilogarithmic scale



E.R.expected range (=predicted PBPK range)
The colored area represents the interval between the 5th and 95th percentiles of the PBPK prediction (90% prediction range). The light grey area represents the enlarged expected range, with the lower line representing 0.5 times the 5th percentile and the upper line representing 1.5 times the 95th percentile of the PBPK prediction.
Source: M&S Report [21]

Assessor's comment:

The applicant has provided the requested information. Since earlier, the MAH has clarified that the observation with lower than expected exposure will be accounted for in the planning of future studies.

Issue resolved.

2) Please elaborate whether the observation may be due to biopharmaceutic reasons (e.g. potential difference in bioavailability of the formulations used; suspension in children and tablets in adults) or rather a difference in PK (e.g. maturation factors or a different weight dependence than previously predicted).

REPLY

Rivaroxaban PK data observed in children below 2 years or approximately 12 kg in study 14374 indicate a tendency towards lower than expected trough values and (according to exploratory population PK analyses) shorter half-life in plasma compared to older children and adults. Consistent observations have been made in the other rivaroxaban phase I and II paediatric trials involving children below 2 years, in particular study 17618 (neonate phase I/II study). There is no evidence or indication that these observations are related to biopharmaceutical aspects or absorption properties of rivaroxaban.

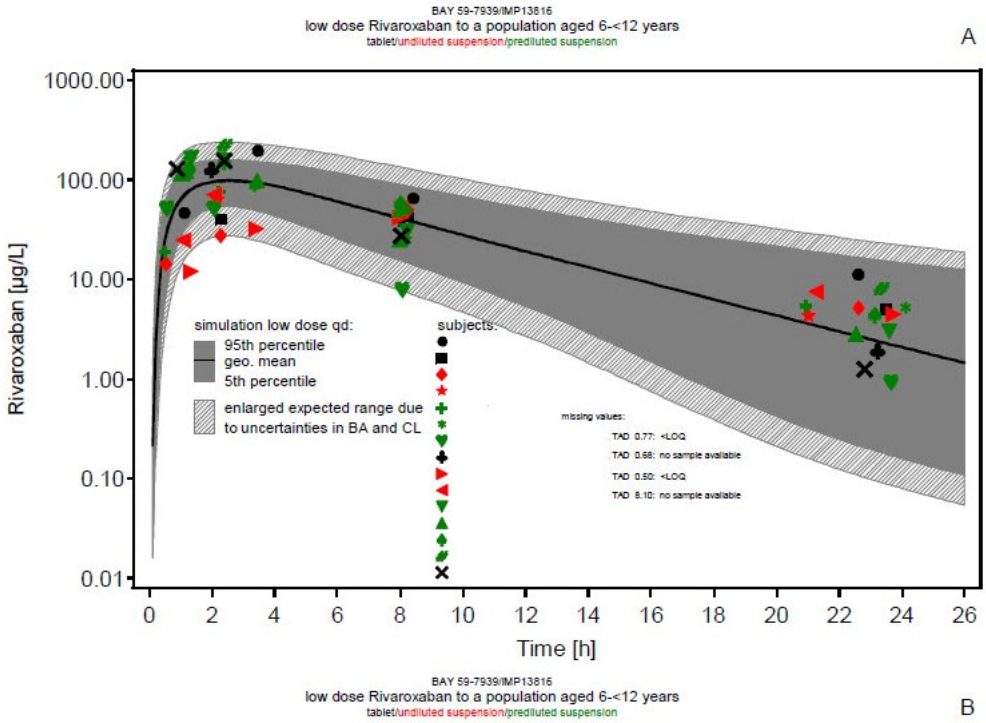
Prior to its use in children, the relative bioavailability of the ready-to-use oral suspension, in comparison to the marketed tablet formulation, was investigated in adults, as requested in the ICH E11 guideline for the development of paediatric formulations. In this study (study number 14022), PK characteristics of 10 mg rivaroxaban were observed to be comparable when the drug was given as oral suspension or as standard IR tablet in the fasted state. Criteria for bioequivalence (90% confidence interval of ratio '10 mg suspension / 10 mg tablet' contained in [0.80, 1.25]) were met for dose normalized AUC, i.e. AUC/D (90% CI: 0.85 to 1.01). The 90% confidence interval of the ratio '10 mg suspension / 10 mg tablet' for C_{max}/D ranged from 0.77 to 0.98. Comparison of the dose normalized PK parameters AUC/D and C_{max}/D indicated PK linearity between the 10 mg standard IR tablet / oral suspension in the fasted state and the 20 mg oral suspension taken with food. This is in line with data from the tablet formulation, where a food effect was also observed between the 10 and the 20 mg dose and administration of the 20 mg dose with food restored dose linearity. Despite the slightly lower C_{max} in fasted state, the ready-to-use oral suspension was thus considered to be adequate for use in children with the recommendation to administer the drug with food.

The first paediatric study in which the ready-to-use suspension was used was a phase I PK/PD study (PH 38444, study 12892. As specified in the protocol for study 12892, children aged 12 to <18 years as well as children aged 6 to <12 years received tablets (each with two dose cohorts). In the age group 6 to <12 years, the oral suspension was given in addition to the cohorts for the tablet. All children <6 years of age received rivaroxaban oral suspension. In the course of the study, it was noted that PK profiles following administration of the ready-to-use oral suspension to children aged 6 to <12 years demonstrated a delayed increase of rivaroxaban plasma concentrations when compared to the PBPK predictions and the PK profiles observed after tablet administration (see Figure 9-30 copied from the study report PH 38444, study 12892). Plasma concentrations obtained in the first 4 hours after administration of rivaroxaban suspension (red symbols) were in the lower range of the PBPK prediction interval, whereas the concentrations obtained during the first 4 hours after administration of the tablet (black symbols) were right within the prediction interval. Plasma concentrations around 8 hours were comparable between tablet and oral suspension. Similarly, plasma concentrations taken around 24h after administration were comparable between tablet and oral suspension. Based on subsequent *in vitro* dissolution data, it was concluded that the delay in absorption could have been caused by excipients of the oral suspension which limit dissolution of rivaroxaban particles at low pH. The in vitro results further indicated that dilution of the oral suspension with a defined volume of liquid prior to administration may overcome this delayed absorption, which was subsequently confirmed in vivo. The diluted oral suspension displayed a similar spread of C_{max} values as the tablet, while also not differing at later time points, i.e. around 8 hours and 24 hours after drug administration. Plasma concentrations

were completely within the prediction range of the paediatric PBPK model regardless of the formulation used.

Figure 9-30 copied from the study report (PH-38444, study 12892)

Figure 9–30 Observed plasma concentration vs. time profiles for subjects aged 6 to <12 years receiving rivaroxaban 10 mg dose equivalent as either tablets (black symbols), undiluted suspension (red symbols) or diluted suspension (green symbols) in comparison to the PBPK model predictions for a population aged 6 to <12 years (semi-logarithmic (A) and linear (B) scale). Individual subjects are shown as symbols, with the patient IDs being indicated in the figure legend.

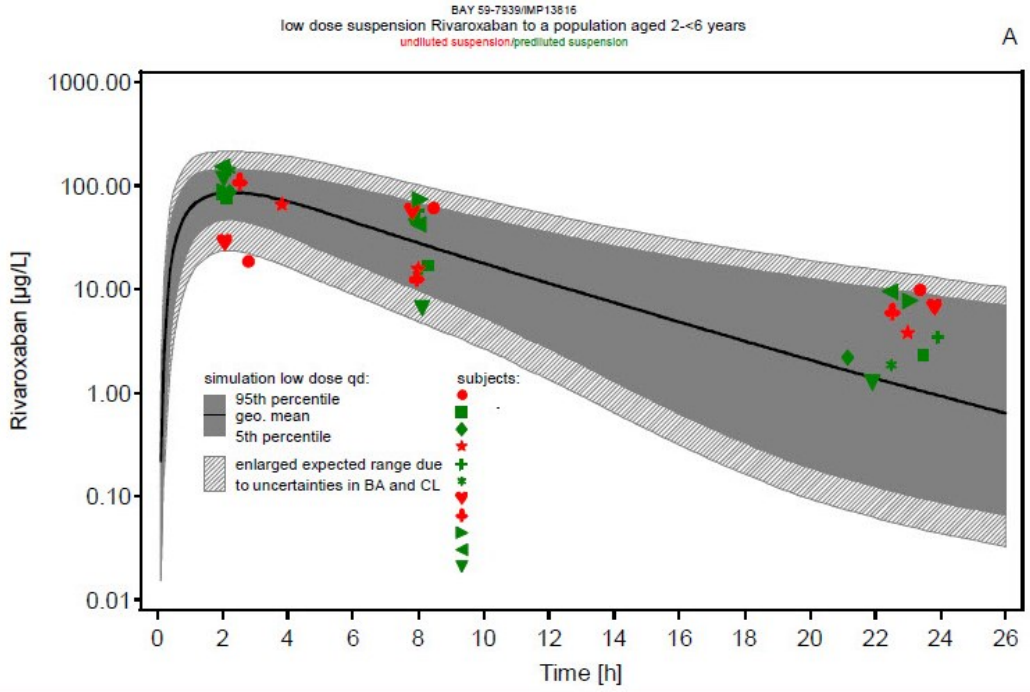


The grey shaded areas show PBPK model predictions for children taking the growth and variability in anthropometrics (body height, weight and body mass index), anatomy (e.g. organ weight) and physiology (e.g. blood flow rates) for the respective ages into account – split in the 5^{th}/95^{th} percentile of the prediction interval (dark grey) and the enlarged $0.5x5^{th}$ percentile to $1.5x95^{th}$ percentile prediction interval (light grey). The enlarged range accounts for uncertainty in the absorption and clearance.

Subsequently, 'tablet-like' concentration vs. time profiles were also observed for diluted suspension in 2 to <6 years old children (10 mg dose equivalent cohort, see Figure 9-32 copied from study report PH-38444, study 12892).

Figure 9-32 copied from the study report (PH-38444, study 12892)

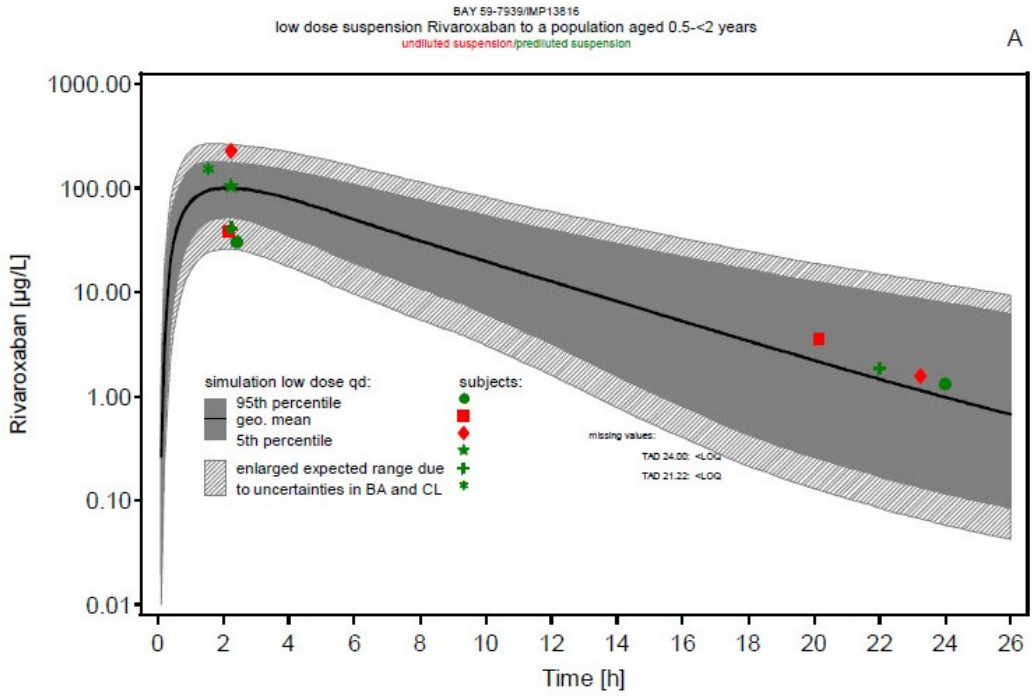
Figure 9–32 Observed plasma concentration vs. time profiles for subjects aged 2 to <6 years receiving rivaroxaban 10 mg equivalent as either undiluted suspension (red symbols) or diluted suspension (green symbols) in comparison to the PBPK model predictions for a population aged 2 to <6 years (semi-logarithmic (A) and linear (B) scale). Individual subjects are shown as symbols, with the patient IDs being indicated in the figure legend



In children aged 0.5 to <2 years, no such clear trend could be observed due to the small number of data points. In agreement with children older than 2 years, the observed plasma concentration time values were within the ranges expected based on PBPK modelling (see Figure 9-34 copied from study report 384444, study 12892).

Figure 9-34 copied from the study report (PH-38444, study 12892)

Figure 9–34 Observed plasma concentration vs. time profiles for subjects aged 0.5-<2 years receiving rivaroxaban 10 mg equivalent as either undiluted suspension (red symbols) or diluted suspension (green symbols) in comparison to the PBPK model predictions for a population aged 0.5 to <2 years (semi-logarithmic (A) and linear (B) scale). Individual subjects are shown as symbols, with the patient IDs being indicated in the figure legend



The dilution step was subsequently also introduced in the phase II studies 14373 and 14374. However, in agreement with PDCO, the ready-to-use suspension was not considered ideal for the use in children, as the dilution step prior to each administration is not convenient, may introduce dosing errors and, thus, may not be acceptable as a marketed product (for details see EMA/PDCO Modification Summary Report, May 8 2015, EMA/547579/2015). Therefore, in parallel to phase II, a new oral suspension formulation was developed ("granules for oral suspension"), which is now used in the ongoing phase III study 14372.

Extensive and continuous modelling activities have been performed in order to support optimizing doses and dosing schemes to be used in children using PBPK and PopPK approaches. Two preliminary population PK analyses of the paediatric PK data of rivaroxaban have been conducted so far: (i) an interim PopPK/PD analysis using PK data from paediatric trials 14372, 14373, 14374, 17992 and 12892, including children ≥ 6 months [R-11836] and (ii) an exploratory population PK analysis in patients below two years including data from studies 12892, 17618, 17992, and 14374 [PH-39769]. The sponsor is aware that results of the PopPK model below 2 years have to be treated with caution, as the model is exploratory, based on a small number of observations, and as the standard errors of the model parameters are very high (as stated previously). Nevertheless, the results of the two PopPK analyses are more in line with the assumption that maturational changes in the elimination process of rivaroxaban are causing the apparent difference in PK when compared to adult VTE treatment patients.

Absorption is predicted to be fairly rapid with maximum concentrations reached around 1.2 to 1.5 hours after dose and complete in the small children (see e.g. Figure 11.2-1 of the modelling report PH-39769 copied below for your reference).

Figure 11.2.1 copied from the modelling report (PH-39769):

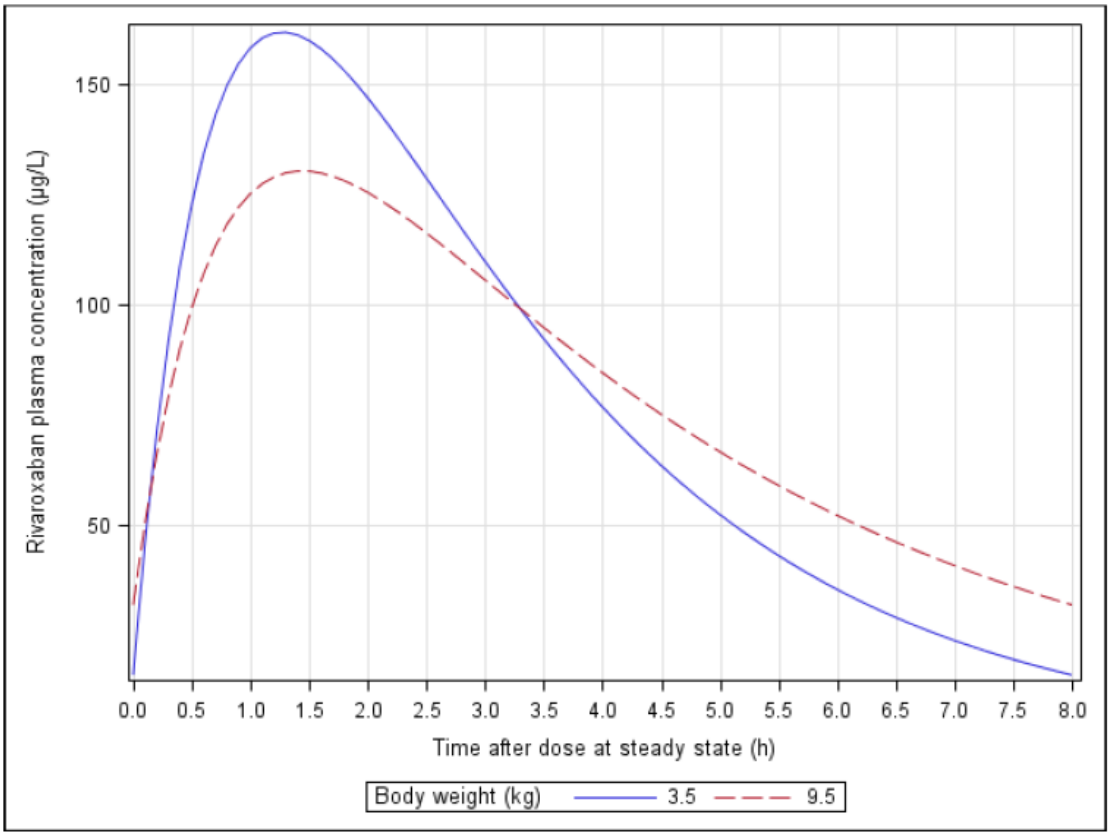


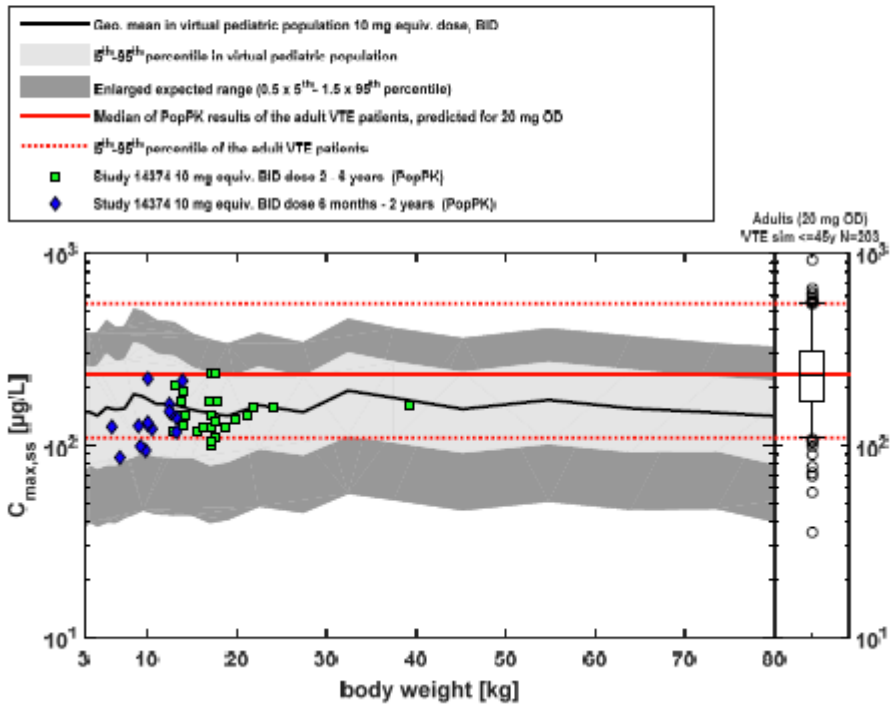
Figure 11.2-1: Typical plasma concentration-time profiles at steady state for children with different body weight

blue solid line: profile for a child with 3.5 kg
red dashed line: profile for a child with 9.5 kg

This is in line with PBPK modelling results: in children older than 2 years, the PBPK model is able to predict rivaroxaban pharmacokinetic behaviour very well (PBPK report PH-35614, PBPK report PH-38803). Although peak plasma concentrations in children below 2 years are also well predicted by the PBPK model, C_{trough} values are less well predicted. However, no literature data are available which could explain this phenomenon. A sensitivity analysis with the paediatric PBPK model indicated that the unexpectedly low trough concentrations in small children are better described via an adaptation of elimination parameters rather than assuming delayed or reduced absorption behaviour (which would also considerably affect the well-predicted C_{max}, see Figure 11-18 of the study report PH-399333, study 14374 below for your reference).

Figure 11-18 copied from the study report (PH-39333, study 14374):

Figure 11-18: Population PK modeling parameter $C_{max,ss}$ for children and adolescents receiving rivaroxaban 10 mg dose equivalent b.i.d. in comparison to the corresponding PBPK predictions (10 mg equivalent dose b.i.d.) for children/adolescents between 6 months and 18 years of age (grey shaded area) and for adult VTE patients (20 mg o.d.) simulated via population PK modeling (box-whisker plot indicating the percentiles 5, 25, 50, 75, and 95; open circles show individual values beyond the 5th-95th percentile range.



Source: M&S Report [21]

Due to the lack of literature data which could explain the increased elimination rate with decreasing age detailed above, our hypothesis - based on a very limited amount of data – is, that so far unaccounted maturational changes may alter the PK in children below 2 years. It is planned to perform an integrated population PK analysis for children on the basis of the pooled data covering the age range from neonates to adolescents to further test if inclusion of maturation functions leads to a better description of the observed age- or body weight dependent changes in rivaroxaban PK.

Assessor's comment:

The applicant has elaborated regarding the potential underlying cause. Since earlier, the MAH has clarified that the observation with lower than expected exposure will be accounted for in the planning of future studies.

Issue resolved.

4. Overall conclusion and recommendation

Overall conclusion

Study 14374, 30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis, was an open-label, single-arm, multicentre study in children 6 months to 6 years with documented venous thrombosis.

The study report was submitted in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. These data are also submitted as part of the PIP programme for Xarelto (Rivaroxaban EMEA-000430-PIP01-08-M10) as follow up measure 7.

There was no new safety concerns found in this study.

The benefit/risk profile for Xarelto remains unchanged.

Recommendation

☒ **Fulfilled:**

No regulatory action required.