12 November 2020
EMA/647126/2020
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Xarelto

International non-proprietary name: rivaroxaban

Procedure No. EMEA/H/C/000944/X/0074/G

## Note

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

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# List of abbreviations

| | |
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| ALT | Alanine aminotransferase |
| anti-Xa | Anti-factor Xa activity |
| aPTT | Activated partial thromboplastin time |
| ASA | Acetylsalicylic acid |
| CHMP | Committee for Medicinal Products for Human use |
| CLCR | Creatinine clearance |
| CSR | Clinical study report |
| CVC | Central venous catheter |
| CVST | Cerebral vein and sinus thrombosis |
| DVT | Deep vein thrombosis |
| eGFR | Estimated glomerular filtration rate |
| ESRD | End Stage Renal Disease |
| FXa | Factor Xa |
| GFR | Glomerular filtration rate |
| GI | Gastro-intestinal |
| HDPE | High Density Polyethylene |
| HPLC-MS/MS | High pressure liquid chromatography with tandem mass spectrometric detection |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| INR | International normalized ratio |
| IPC | In-process control |
| LMWH | Low-molecular weight heparin |
| NSAIDs | Non-steroid anti-inflammatory drugs |
| PDE | Permitted Daily Exposure |
| PE | Pulmonary embolism |
| P-gp | P-glycoprotein |
| PNA | Postnatal age |
| PT | prothrombin time |
| RH | Relative Humidity |
| SmPC | Summary of Product Characteristics |
| TSE | Transmissible Spongiform Encephalopathy |
| UFH | Unfractionated heparin |
| USP | United States Pharmacopoeia |
| UV | Ultraviolet |

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| VKA | Vitamin K antagonist |
| VTE | Venous thromboembolism |

# 1. Background information on the procedure

## *1.1. Submission of the dossier*

Bayer AG submitted on 22 November 2019 a group of variations consisting of an extension of the marketing authorisation and the following variations:

| Variation requested | | Type |
|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |

Extension application to introduce a new pharmaceutical form, granules for oral suspension, 1 mg/ml.

Extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto 15 and 20 mg tablets.
As a consequence, sections 4.2,4.4,4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly.

In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC is updated for all other dose strengths (2.5/10/ and 15/20 mg initiation packs) of Xarelto and corresponding sections of the Package Leaflet. Section 4.4 has been updated with regards to sodium content according to Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668).

The RMP version 12.1 has also been submitted.

**The legal basis for this application refers to:**

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

## *Information on Paediatric requirements*

At the time of submission of the application, the PIP P/0126/2019 was completed.

The PDCO issued an opinion on compliance for the PIP P/0126/2019.

## *Information relating to orphan market exclusivity*

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

### *Scientific advice*

The MAH received Scientific Advice from the CHMP on 15 September 2016 (EMEA/H/SA/422/13/2016/PED/III).

The Scientific Advice pertained to quality and clinical aspects of the dossier.

## *1.2. Steps taken for the assessment of the product*

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Kristina Dunder

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| The application was received by the EMA on | 22 November 2019 |
| The procedure started on | 2 January 2020 |
| The Rapporteur's first Assessment Report was circulated to all CHMP members on | 23 March 2020 |
| The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on | 23 March 2020 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 17 April 2020 |
| The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on | 30 April 2020 |
| The MAH submitted the responses to the CHMP consolidated List of Questions on | 24 May 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on | 24 June 2020 |
| The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on | 9 July 2020 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the MAH on | 23 July 2020 |
| The MAH submitted the responses to the CHMP List of Outstanding Issues on | 18 August 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 2 September 2020 |
| A SAG was convened to address questions raised by the CHMP on<br>The CHMP considered the views of the SAG as presented in the minutes of this meeting. | 7 September 2020 |
| The CHMP agreed on a list of outstanding issues in writing and/or in an | 17 September 2020 |

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| oral explanation to be sent to the MAH on | |
| The MAH submitted the responses to the CHMP List of Outstanding Issues on | 13 October 2020 |
| The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on | 28 October 2020 |
| The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Xarelto on | 12 November 2020 |

# 2. Scientific discussion

## *2.1. Problem statement*

### 2.1.1. Disease or condition

This application concerns a new, paediatric indication that pertains to treatment of VTE and prevention of VTE recurrence in children and adolescents as well as a new formulation: granules for oral suspension. The application is supported by extrapolation of data from approved adult indications as well as separate paediatric studies as outlined in the PIP.

For the already approved 15 and 20 mg tablets, the sought indication was:

15 mg tablets

*Paediatric population*

*Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and* ***weighing from 30 kg to 50 kg*** *following initiation of standard anticoagulation treatment.*

20 mg tablets

*Paediatric population*

*Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and* ***weighing more than 50 kg*** *following initiation of standard anticoagulation treatment*

For the new granules for oral suspension, the sought indication was:

*Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years following initiation of standard anticoagulation treatment.*

### 2.1.2. Epidemiology and risk factors

Venous thrombosis in children is rare, with an incidence at about 100 times lower than in adults. An annual incidence of VTE of between 53-57 per 100 000 has been reported among hospitalized children and between 1.4-4.9 per 100 000 in the community overall. The distribution of events is bimodal with the majority occurring in neonates/infants and in adolescents. Idiopathic paediatric venous thromboses are very uncommon; more than 90 per cent of children who experience a VTE have been described to have a serious underlying disease including malignancy, congenital heart disease and nephrotic syndrome; a hereditary pro-thrombotic condition; or a precipitating factor such as surgery, infection, trauma or an indwelling catheter such as central venous catheter (CVC). In adolescents, hormonal contraception is a common triggering factor for VTE. The only randomized study on the treatment of venous thrombosis in children conducted so far (the REVIVE study) confirmed that cancer and infections, followed by congenital heart disease, were the most frequently reported risk factors. In the REVIVE study, children with cerebral vein and sinus thrombosis were excluded due to lack of consensus on the need for anticoagulation. Risk factors for recurrent VTE as reported in the European collaborative paediatric database on cerebral venous thrombosis include age at onset, absence of anticoagulant treatment, persistent venous occlusion, or presence of the prothrombin gene mutation.

### 2.1.3. Biologic features, aetiology and pathogenesis

The coagulation system differs in neonates and infants aged < 6 months, as compared to older children and adults. At birth, the plasma levels of vitamin K-dependent coagulation factors (II, VII, IX, X) are only half of the adult values, and increase during the first 6-12 months of life but remain at about 15% lower levels throughout childhood as compared to adults. The capacity to generate thrombin is decreased, whereas the capacity to inhibit thrombin is enhanced throughout childhood as compared to adults. The aetiology of VTE is based on Virchow's triad including stasis, endothelial injury and hypercoagulability. For catheter-related thromboses, intravenous catheters cause endothelial trauma and inflammation and are often placed in patients who are hypercoagulable, leading to venous thrombosis. (Albisetti M et al 2020). For cerebral vein and sinus thrombosis, the pathogenesis has not been fully characterised. The mechanisms that contribute to the clinical features of CVST include obstruction of blood drainage from brain tissue, leading to parenchymal lesions and an increased venous and capillary pressure that could disrupt the blood-brain barrier, and occlusion of dural sinuses resulting in decreased CSF absorption and elevated intracranial pressure. (Ferro J et al 2020).

### 2.1.4. Clinical presentation, diagnosis and prognosis

Paediatric VTE is rarely idiopathic, occurring in subjects with a high additional burden of disease. Location of VTE differs, with neonates and young children more often experiencing upper venous system VTE (most frequently CVC-related VTE), as compared to adolescents and adults. Deep vein thrombosis usually presents in the lower extremities similar to adults. Pulmonary embolism is relatively rare in children as compared to adults. Renal vein thrombosis most commonly occurs secondary to nephrotic syndrome or renal transplantation (Albisetti M 2020). Ultrasonography is the preferred initial diagnostic study; alternative imaging modalities include contrast venography, MRI or CT (Albisetti M 2020).

The risk of recurrence for paediatric VTE ranges from 7 to 20 percent, however, recurrence is uncommon if the underlying cause is removed or resolved. A prothrombotic state appears to be a predictor of VTE recurrence among children with unprovoked VTE, however, recurrence risk relating to a prothrombotic state is uncertain in children <2 years of age. (Albisetti M et al 2020).

### 2.1.5. Management

The aim of VTE therapy is generally to prevent disease progression (including prevention of occurrence of severe manifestations such as pulmonary embolism) prevent VTE recurrence and the development of sequelae such as post thrombotic syndrome.

The current standard of care of paediatric VTE is based upon a moderate level of evidence, including parenteral treatment with unfractionated heparin (UFH) or low molecular heparin (LMWH) and oral anticoagulation with vitamin K antagonists (VKA). The current understanding of PK in children is extrapolated from adult studies, although physiological differences in absorption, distribution and metabolism in children could warrant different doses according to body weight as compared to adults (Monagle P et al 2012).

In the Clinical Overview, the MAH refers to the most recent American College of Chest Physician (ACCP) management guidelines published in 2012 (Monagle et al 2012), which recommend for the initial treatment of VTE in children adjusted-dose unfractionated heparin (UFH), bodyweight-adjusted low-molecular-weight heparin (LMWH) or fondaparinux. For subsequent treatment, either INR-titrated vitamin K antagonist (VKA) or bodyweight-adjusted LMWH is recommended. Suggested treatment durations are 3 months for children with provoked VTE in whom the risk factor has resolved and continued anticoagulant therapy in children who have ongoing risk factors. For children with idiopathic VTE, the suggested treatment duration has a minimum of 3 months and a maximum of 6 to 12 months. Children with recurrent unprovoked VTE are usually treated indefinitely.

In the ACCP guidelines, it is stated that it is suggested that central venous access devices or umbilical venous catheters associated with confirmed thrombosis is to be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ. Either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis is suggested as well as start of anticoagulation if extension occurs in previously untreated patients. Anticoagulation should be with either LMWH or UFH followed by LMWH with a total duration of anticoagulation of between 6 weeks and 3 months.

According to the ACCP guidelines, for children with CSVT without significant intracranial haemorrhage, anticoagulation is suggested, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months. For children with CSVT with significant haemorrhage, either anticoagulation or supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted is recommended. However, according to the American Heart association (AHA) scientific statement (Roach et al 2008), there is currently a consensus that older children without haemorrhage should be anticoagulated (International Pediatric Stroke Study consensus) but few neonates with CVST have been treated with anticoagulants, and such treatment is not recommended in neonates except perhaps in selected patients with clinical deterioration or with radiological evidence of clot propagation.

A retrospective study in neonates and young children by Chan et al (2018), in which paediatricians from 12 institutions in North America, Europe and Israel collected data for children younger than 2 years with VTE and described the diagnosis of VTE, use of anticoagulant therapy and its duration, and incidence of recurrent VTE.

The feasibility of recruiting these children in EINSTEIN-Jr. phase III, was assessed. In total, 227/346 children had CVC-VTE and of these 199 (88%) received anticoagulation and 28 (12%) did not receive anticoagulation. Of the children with CVC-VTE that received anticoagulation 44/199 (22%) received a duration of anticoagulation shorter than 6 weeks. Thus, in total 72/227 (32%) of the subjects with CVC-VTE received either no anticoagulation or anticoagulation shorter than 6 weeks. It was not stated how many of these subjects that received anticoagulation shorter than 1 month i.e. the proposed posology for children <2 years with CVC-VTE in the current application. In that study, rates of symptomatic recurrent VTE in children with CVC-VTE were low, in particular if anticoagulant therapy was used (10/199 children had a symptomatic recurrent VTE during and after anticoagulant therapy); however, though higher, it was low also in the group of children not treated with anticoagulants (4/28 had a symptomatic recurrent VTE).

There is no centrally approved anticoagulant product in the EU for treatment of secondary prevention of VTE in children. There is an unmet need for a new treatment-option with well documented efficacy and safety for treatment of paediatric VTE. In this setting, an orally administered alternative that requires less monitoring than existing standard of care would also be a benefit.

## *About the product*

Rivaroxaban is an oral anticoagulant that selectively targets activated coagulation factor X (Xa), thereby inhibiting thrombin generation and thrombus formation. It is approved in adults in various doses for VTE prevention in adjunction to elective hip or knee replacement surgery; for treatment and prevention of deep vein thrombosis and pulmonary embolism; for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and additional risk factors; and for prevention of atherothrombotic events in addition to certain antiplatelet agents in patients with acute coronary syndrome or coronary artery disease/peripheral artery disease.

## *Type of Application and aspects on development*

A Paediatric Investigation Plan (PIP) for the treatment (secondary prevention) of VTE in children was agreed with EMA/PDCO in 2009 with the approval of the first indication for rivaroxaban. After sequential requests for modification procedures, the most recently agreed PIP (P/0126/2019) contains nine measures which have all been completed. The EMA/PDCO has confirmed positive final compliance check with the PIP in September 2019

Support for efficacy and safety in the claimed indication are derived from 6 studies: 2 phase 1 studies, 1 phase 1/2 study, 2 phase 2 studies and 1 phase 3 study.

In September 2016, a Scientific Advice was adopted by the CHMP on the paediatric EINSTEIN-Jr program (EMEA/H/SA/422/13/2016/PED/III). Questions relating to clinical development included a discussion of the concept to target similar exposures in children and adults for the treatment of VTE; the phase III study design including patient numbers and statistical analysis and the overall rivaroxaban paediatric program. Conclusions from the CHMP included:

- To target similar exposure in children as in adults was a plausible approach given the similarities between the adult and paediatric disease process (coagulation cascade), although with different aetiologies, location and frequency.
- The phase III study design was endorsed with regards to the open label design and the use of active comparators.
- At least 3 months of study period would be required for the treatment indication, and another 3 months of extension phase for the prevention indication. The primary evaluation should be related to the presence of risk factors for recurrent VTE.
- The PDCO had specified that a minimum number of children in each age cohort should be studied in the Phase III, to allow relevant efficacy and safety data to be provided in all the age-subsets 6 yrs. - < 12 yrs., 2 yrs. - < 6 yrs., 6 mo. to < 2 yrs. and from birth to < 6 mo., moreover taking into account the higher variability expected in the lower age-subsets, with the specific paediatric formulation, in particular below 12 yrs. of age. The limitations and the feasibility of performing a study in children of different age cohorts that is adequately powered to provide statistically significant results of efficacy were acknowledged. In the PIP, it was agreed that the number of patients in each age cohort should include at least 150 subjects aged 6 months – 18 years and at least 20 subjects aged <6 months.
- For the endpoints of the phase III study, the inclusion of asymptomatic deterioration of thrombus burden in the composite secondary endpoint was acceptable, given that the expected number of the primary efficacy outcome (symptomatic recurrent VTE) would be low and that asymptomatic thromboses may have clinical sequelae in children.
- An adequate collection of PK/PD data in the phase III studies was discussed, considering the expected limited contribution of clinical outcome data, in particular for children from birth to < 6 months, to further guide in the dose selection, and clarify if further monitoring is needed in the paediatric population.
- A discussion of the clinical relevance of the results both in terms of the size of the treatment effect as well as the corresponding 95% confidence interval were required. Consistency of treatment effects across the different age cohorts as well as across the different components of the composite endpoint was expected to be demonstrated. Paediatric patients < 2 yrs. are of particular concern due to differences in underlying aetiologies and thrombus location, as well as a not fully matured coagulation/fibrinolysis system. The applicant was encouraged to focus collection of clinical data in this age cohort to support the benefit/risk assessment. For safety, in children from birth to < 6 months particular safety considerations were pointed out, including CNS bleeding and inconsistent enteric absorption.
- A POPPK approach was encouraged in particular to judge exposure in the youngest individuals 6 months to < 2 years old. The final proposed doses should be adequately justified in terms of comparative exposure to adults.
- Unless otherwise justified, controlled data on a sufficient number of patients at high risk for recurrent VTE, should be presented. If the intended indication is chronic/indefinite use safety data extending beyond the period of 1 year should be presented.

The clinical programme is overall appropriate for the sought indication and posology. The Scientific Advice and applicable EMA guidelines have overall been adhered to, there are some deviations which are commented in relevant parts of this report.

## *2.2. Quality aspects*

### 2.2.1. Introduction

This application is a line extension to the already approved Xarelto 2.5, 10, 15 and 20 mg film-coated tablets. The scope is to add 1 mg/mL granules for oral suspension and an extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years.

The finished product is presented as granules for oral suspension containing 19.7 mg rivaroxaban per gram as active substance. Following reconstitution as per the instructions provided in section 6.6 of the SmPC, the oral suspension contains 1 mg rivaroxaban per ml.

Other ingredients are: citric acid anhydrous (E 330), hypromellose (2910), mannitol (E 421), microcrystalline cellulose and carmellose sodium, sodium benzoate (E 211), sucralose (E 955), xanthan gum (E 415), flavour sweet and creamy (flavouring substances, maltodextrin (maize), propylene glycol (E 1520) and arabic gum (Acacia gum, E 414).

The product is available in two presentations each consisting of a folding box containing:

- For children weighing less than 4 kg:

- 1 brown 100 mL glass bottle containing 2.625 g granules, corresponding to 51.7 mg rivaroxaban, closed with a child resistant screw cap,

- 2 oral dosing syringes 1 mL (blue syringe, marked as Liquid dosing device – LDD) with 0.1 mL marked graduations,

- 1 adapter for bottles and oral syringes,

- 1 water syringe 50 mL (marked as Omnifix) with 1 mL marked graduations;

or

- For children weighing 4 kg and more:

- 1 brown glass bottle 250 mL containing 5.25 g granules, corresponding to 103.4 mg rivaroxaban, closed with a child resistant screw cap,

- 2 oral dosing syringes 5 mL (blue syringe, marked as Liquid dosing device – LDD) with 0.2 mL marked graduations,

- 2 oral dosing syringes 10 mL (blue syringe, marked as Liquid dosing device – LDD) with 0.5 mL marked graduations,

- 1 adapter for bottles and oral syringes,

- 1 water syringe 100 mL (marked as Omnifix) with 2 mL marked graduations,

as described in section 6.5 of the SmPC.

## 2.2.2. Active Substance

The 1 mg/mL granules introduced with this line extension application contain the same active substance, rivaroxaban, used to manufacture the already-approved film-coated tablets. No new information on the active substance has been provided within this application.

## 2.2.3. Finished medicinal product

***Description of the product and Pharmaceutical development***

Xarelto 1 mg/mL granules for oral suspension are white to off-white granules.

The aim of the pharmaceutical development was to obtain an immediate release oral liquid formulation to offer dose flexibility, high convenience and compliance for paediatric use and for patients with dysphagia (difficulty in swallowing). Nasogastric or gastric tube application is possible for patients unable or not allowed to swallow their medication. To this end, the active pharmaceutical ingredient rivaroxaban is formulated as granules that can be administered as a suspension, at a concentration of 1 mg/mL, after addition of drinking water. After preparing the suspension for use, the patient or caregiver can withdraw multiple doses between 0.8 mL and 10 mL from the bottle with an oral pipette depending on the body weight of the patient.

Based on the QTPP, the critical quality attributes (CQAs) of the product were identified.

The compatibility of the excipients used in the granules formulation with the active substance was demonstrated in stability studies.

The manufacturing process of the granules for oral suspension was developed and optimized at the proposed manufacturing site.

A design of experiment (DoE) was conducted at laboratory scale to systemically explore the manufacturing process parameters and to develop a suitable manufacturing process.

The primary packaging is brown glass type 3 bottles closed with a polypropylene (PP) white opaque child resistant screw cap. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

***Manufacture of the product and process controls***

The manufacturing process consists of four main steps: manufacture of granulation liquid; manufacture of a premix; granulation; and blending. It has been demonstrated that the manufacturing process is capable of

producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this granulation manufacturing process.

***Product specification***

The finished product release specifications include appropriate tests for this kind of dosage form: formulation, colour, appearance of suspension colour, suspendability, appearance of suspension, identity (HPLC, UV), dissolution, pH-value, degradation products, assay and microbial purity.

The proposed specification is considered acceptable.

The information on the control of elemental impurities is satisfactory. The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The finished product is released onto the market based on release specifications, through traditional final product release testing.

A risk assessment concerning the presence of nitrosamine impurities was performed for the finished product based on the combined recommendations from health authorities, including EMA communication EMA/189634/2019. A statement that there is no risk of N-nitrosamine contamination has been provided and it was concluded that there is no risk related to the presence of nitrosamine impurities in the product. Therefore, no changes to the control strategy for Xarelto are necessary to mitigate potential contamination by nitrosamines. The nitrosamine impurities risk assessment of the finished product included evaluating contributions from rivaroxaban active substance, excipients, finished product manufacturing facilities, and packaging components.

Batch analysis results are provided for three representative batches from each packaging configuration (100 mL and 250 mL bottles) manufactured at commercial scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

***Stability of the product***

Stability data from several production scale batches of each packaging configuration stored for up to 24 months under long term conditions (25 ºC / 60% RH and 30 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. Samples were tested for formulation (granulate), colour, appearance of suspension, colour of suspension, suspendability, dissolution, pH-value of suspension, degradation products, assay of rivaroxaban, assay of sodium benzoate, and microbial purity.

In addition, Rivaroxaban granules for oral suspension in 100 mL and 250 mL bottles (one production scale batch from each) and the suspension as prepared prior to administration to the patients packed in brown glass type 3 bottles were exposed to UV-light and visible light radiation exceeding the requirements defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Despite this extended UV-exposure, both the granules and the suspension exposed in closed original brown glass bottle did not show relevant alterations This confirms the expected protective effect of the container.

Therefore, it is concluded that rivaroxaban granules for oral suspension in the original primary container are photostable. Thus, a light protection instruction for the drug product after removing the secondary packaging is not required.

For the suspended granules in the original primary container a light protection advice is also not considered necessary.

A stress test was performed with the finished product Rivaroxaban granules for oral suspension to investigate physical alterations or degradation. In summary, no degradation was observed in the stress studies Additionally, an in-use stability study of Rivaroxaban granules for oral suspension was performed according to the guideline CPMP/QWP/2934/99. Several batches of rivaroxaban granules for oral suspension of each presentation were investigated with one batch at the end of the proposed shelf-life. Defined volumes of the suspension were taken several times daily on each working day for several days. Between sampling, the bottles were stored either in a refrigerator at 2-8 °C or in a temperature-controlled oven at 30 °C. The usability period defined for the suspension is set to 14 days.

Based on available stability data, the proposed shelf-life of 3 years, with a storage restriction "Do not store above 30 °C" and do not freeze as stated in the SmPC (section 6.3) is acceptable. After reconstitution the suspension is stable for 14 days stored upright.

***Adventitious agents***

No excipients derived from animal or human origin have been used.

## 2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of Xarelto 1 mg/mL granules for oral suspension has been presented in a satisfactory manner. This immediate release oral liquid formulation has been developed to offer dose flexibility, high convenience and compliance for paediatric use and also for patients with dysphagia (difficulty in swallowing). The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

## 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

## 2.2.6. Recommendations for future quality development

Not applicable.

## *2.3. Non-clinical aspects*

### 2.3.1. Introduction

No new preclinical data were submitted with this application. In order to support clinical development and market authorisation in paediatric indications, juvenile animal toxicity studies in rats up to 14-week treatment were performed which have been assessed in previous submissions.

In order to support the development of a rivaroxaban liquid dosing device for the administration of rivaroxaban liquid formulation for children, an *in silico* genotoxicity assessment of leachables was submitted.

### 2.3.2. Pharmacology

No new non-clinical pharmacological data were submitted.

### 2.3.3. Pharmacokinetics

The pharmacokinetics of CYP3A4 substrates may differ between paediatric populations and adults. This may be related to changes of CYP3A4 activity during human development, as well as additional clearance contribution of the fetal isoform CYP3A7. Rivaroxaban was shown to be a substrate for CYP3A4 and 3A5, but substrate characteristics towards CYP3A7 were not investigated in the initial CYP reaction phenotyping studies. Therefore, an additional study to support the paediatric submission was performed and is discussed in the clinical aspects section of this report.

### 2.3.4. Toxicology

No new data were submitted in the current procedure. Juvenile toxicity studies were submitted and assessed in a previous procedure (EMEA/H/C/944/X/17). Information on study design and major findings from these studies are presented in **Table 6**.

Dose levels were selected according to results in toxicity studies with adult rats. The maximum dose was selected based on a limit of absorption at 60 mg/kg.

**Table 1.** Main findings form juvenile toxicity studies conducted with rivaroxaban

| **Study type/ Study ID / GLP** | **Species; Number animals/ group** | **Route & dose** | **Dosing period** | **Major findings** | **NOAEL (mg/kg)** |
|---|---|---|---|---|---|
| Pilot study Juvenile Toxicity/ T8080929<br><br>(Report PH-36153)<br><br>Non GLP | Rat (Neonatal) Male and female n=12 (control n=5)<br><br>TK n=3/time point | Oral gavage 0, 6, 20 and 60 mg/kg in 0.5% aqueous tylose | 23 days starting on postnatal day 4 once daily | - At 20 and 60 mg/kg males exhibited lower final bw and a retarded bw gain.<br>- Clinical Chemistry no significant changes except for slightly higher ALAT levels in all dose groups*).<br>- Absolute liver and kidney weights were reduced dos-dependently in males. | M 6 mg/kg<br>F 60 mg/kg |

| Study type/ Study ID / GLP | Species; Number animals/ group | Route & dose | Dosing period | Major findings | NOAEL (mg/kg) |
|---|---|---|---|---|---|
| Juvenile Toxicity/ T1081417<br><br>(Report PH-36347)<br><br>GLP | Rat (Neonatal) Male and female n=12/group (control n=5)<br><br>TK n=3/time point | Oral gavage 0, 6, 20 and 60 mg/kg in 0.5% aqueous tylose | 14 weeks starting on postnatal day 10 once daily | - No mortalities except one 6 mg/ female found dead day 20, (considered to be incidental).<br>- At 60 mg/kg 3 of 10 males exhibited alopecia (this finding was seen in control females in the same frequency).<br>- Hematology: 60 mg/kg <u>males</u> lower mean erythrocyte count and hematocrit and higher mean MCHC and reticulocytes. 60 mg/kg <u>females</u> higher thrombocytes<br><u>≥20 mg/kg</u><br>(M/F) Minor changes in liver function<br><u>60 mg/kg</u><br>(M) Minor decrease in ERY and HCT, increase in RETI and THROM<br>(M) Morphological changes in the pancreas and thyroids<br>(M) Increase in adrenal weights (see also below) | M & F 20 mg/kg<br><br>(60 mg/kg) |
| Juvenile Toxicity/ T8081982<br><br>(Report PH-36480)<br><br>(evaluation of age- & vehicle-dependent effects on systemic exposure)<br>Non GLP | Rat (Neonatal) Female n=18/group | Oral gavage 60 mg/kg<br><br>in 0.5% aqueous tylose (up to PND30) PND31-37 ethanol/Solutol HS15®/tap water (1/4/5) as vehicle. | 4 weeks starting on postnatal day (PND)10 once daily<br><br>(changed vehicle PND 31) | Main aim was to study the effect of the changed vehicle on the PK in treated animals.<br><br>No unscheduled deaths or clinical symptoms occurred during the course of the study. | N/A |
| Juvenile Toxicity/ T2082309<br><br>(Report PH-36598)<br><br>additional study<br><br>GLP | Rat (Neonatal) Male and female n=12/group (control n=5)<br><br>TK n=3/time point | Oral gavage 0, 6, 20 and 60 mg/kg<br><br>in 0.5% aqueous tylose (up to PND28) from PND29 ethanol/Solutol HS15®/tap water (1/4/5) as vehicle. | 13 weeks starting on postnatal day 10 once daily<br><br>(changed vehicle day 20 / PND 29, day 20-94) | None of the animals died pre-scheduled.<br>No adverse effect on the body weight development. In most cases in treated rats higher body weights and increased body weight gain were seen than at 0 mg/kg.<br>Hematology; slightly increased Hepato Quick (starting at 6 mg/kg) and thrombocyte count (at 60 mg/kg) in females (due to the pharmacological mode of action).<br><br>Absolute liver weight at 20 and 60 mg/kg (14% at 60 mg/kg) and relative liver weights at 60 | M & F 60 mg/kg |

| Study type/ Study ID / GLP | Species; Number animals/ group | Route & dose | Dosing period | Major findings | NOAEL (mg/kg) |
|---|---|---|---|---|---|
| | | | | mg/kg (6%) increased in females only. **) | |

*) In males, no relevant changes in exposure on Day 74 were observed as compared to Day 1. In females, a slightly higher exposure was observed (up to a factor of about 1.8). Thus, the change in vehicle at the time of weaning resulted in a relatively constant exposure throughout the study period, so that the high dose of 60 mglkg represents the maximum feasible exposure.

**) In males, a slightly higher means for ALA T were seen in all dose groups. Because the deviations were minimal and exposure relationship did not exist, a toxicological relevance is not assumed.

### *Other toxicity studies*

Chemical structures that were investigated in the *in silico* genotoxicity assessment were selected based on the results of an leachable study (S19001261). In this study, the adapter as well as the 10 mL pipette were exposed to the reconstituted drug suspension. Detected leachable compounds were 4-methoxybenzyl formate or 4-methoxybenzeneacetic acid, oleamide, 2,4,7,8-tetramethyl-5-decyn-4,7-diol, sclareolide, and an unknown compound. The study report for the investigation of potential mutagenic properties using computer-based toxicity prediction system and the VITIC database was provided. The identified leachables showed no alerts for mutagenicity.

## 2.3.5. Ecotoxicity/environmental risk assessment

For the current application no new experimental data on environmental toxicity of rivaroxaban were submitted, as the environmental exposure of rivaroxaban due to the new formulation granules for oral suspension and the new proposed paediatric indication for the treatment and secondary prevention was considered to be negligible compared to the exposure based on the currently approved indications for rivaroxaban.

The prevalence of VTE in children is estimated to be 20-100 times lower than in adult patients (Andrew M et al, 1994, Van Ommen CH et al, 2001, Stein PD et al, 2004, Raskob GE et al, 2014). This would mean that approximately 1 to 5% paediatric cases can be expected compared to adults. Based on the above information, it was estimated that VTE occurs in 0.01 to 0.05 cases per 1000 children each year (Van Ommen CH et al, 2001, Stein PD et al, 2004). According to Eurostat, there are approximately 69 million children<15 years in the EU, which means that 690 to 3400 children are potential VTE patients.

The dose for children is dependent of the weight; daily doses range from 2.4 mg to 20 mg. As a conservative average, 10 mg (children up to 30 kg) was used for the exposure calculation

Based on a maximum potential paediatric patient population of 3400 patients, and a conservative average dose of 10 mg, the $PEC_{surfacewater}$ for this population and assuming 100% treatment with Xarelto is $PEC_{surfacewater}$ = 0.038 ng/L.

Thus, the ERA for rivaroxaban remains unchanged.

## 2.3.6. Discussion on non-clinical aspects

Investigations of rivaroxaban in juvenile rats did not reveal any new toxicity compared to studies in adolescent or adult animals. The toxicological profile in juvenile rats appears to be in line with previous findings. Minor effects on pancreatic peri-insular findings as well as on the thyroid gland seen in the first subchronic toxicity study were not confirmed in the second study showing significantly higher systemic exposure. The numerical increase in pancreatic peri-insular lesions (hemorrhage, hemosiderin, and fibrosis) and colloid alteration in the thyroids in the first juvenile study was therefore considered to be incidental.

In the submitted study on impurities, no structural alerts were detected for the investigated compounds. The study report for the investigation of potential mutagenic properties using computer-based toxicity prediction system and the VITIC database showed no alerts for mutagenicity.

No ERA studies were submitted, and this was considered acceptable as the use of rivaroxaban in the paediatric population is not expected to lead to any significant increase in the combined sales volumes for all rivaroxaban containing products and the exposure of the environment to the active substance.

## 2.3.7. Conclusion on the non-clinical aspects

There are no objections to the approval of rivaroxaban in the proposed paediatric indication from a non-clinical point of view.

# *2.4. Clinical aspects*

## 2.4.1. Introduction

## GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical efficacy and safety studies pertinent to the claimed indication VTE treatment and secondary prevention in paediatric patients

| **Study ID / Report no.**<br>**No. of study centers** | **Study design**<br>**Control type** | **Study/control drugs**<br>**Dose, route & regimen**<br>**Duration** | **Study objective** |
|---|---|---|---|
| 12892 / PH-38444<br>Phase 1<br><br>**18 study centers in 7 countries** | Multinational<br>Multicenter<br><br>Single-dose<br><br>Single-arm<br>Non-controlled<br>Open-label | **Oral rivaroxaban**<br><br>Dose adapted to bodyweight class (per kg)<br><br>Oral administration as tablet (children aged | **Primary objective**<br>PK and PD of single oral doses of rivaroxaban in children in order to obtain weight-adjusted doses with equivalent exposure compared to 10 mg and 20 mg doses in adults<br><br>**Secondary objective** |

| Study ID / Report no.<br>No. of study centers | Study design<br>Control type | Study/control drugs<br>Dose, route & regimen<br>Duration | Study objective |
|---|---|---|---|
| | | ≥ 6 yrs)<br>or suspension (children aged <12 yrs)<br><br>single-dose administration<br><br>**Duration**<br>1 day | Safety and tolerability of rivaroxaban in children<br><br>**Other outcomes:**<br>Palatability and acceptability of the suspension |

| Study ID / Report no.<br>No. of study centers | Study design<br>Control type | Study/control drugs<br>Dose, route & regimen<br>Duration | Study objective |
|---|---|---|---|
| 14373 / PH-38995<br>Phase 2<br><br>**30 study centers in 10 countries** | Multicenter<br>Open-label<br>Active comparator, amended to single-arm (Amendment 6) | **Oral rivaroxaban**<br><br>susp. b.i.d.<br>or<br>tabl. o.d.<br><br>Age- and bodyweight-adjusted dosing<br><br>**Comparator:** UFH, LMWH,fondaparinux, VKA<br><br>as per SoC<br><br>**Duration:**<br>30 days | **Primary objective**<br>Incidence of major and clinically relevant non-major bleeding<br><br>**Secondary objectives**<br>Incidence of recurrent VTE<br><br>Asymptomatic deterioration of thrombotic burden on repeat imaging<br><br>PK/PD profile of a 30-day treatment with oral rivaroxaban |
| 14374 / PH-39333<br>Phase 2<br><br>**27 centers in 14 countries** | Multicenter<br>Open-label<br>Active comparator, amended to single-arm (Amendment 4) | **Oral rivaroxaban**<br><br>susp. bid<br><br>Age- and bodyweight-adjusted dosing<br><br>**Comparator:**<br>LMWH<br>Fondaparinux<br>VKA<br><br>as per SoC<br><br>**Duration**<br>30 days | **Primary objective**<br>Incidence of major bleeding and clinically relevant non-major bleeding<br>**Secondary objectives**<br>Incidence of recurrent symptomatic VTE;<br>asymptomatic deterioration in the thrombotic burden on repeat imaging;<br>PK/PD profile of a 30-day treatment with oral rivaroxaban |
| 14372 / PH-40166<br>Phase 3<br>**ıters in 28 countries** | Multinational<br>Multicenter<br>Open-label randomized<br>Active controlled | **Oral rivaroxaban**<br><br>Granules for susp.<br><br>Age- and bodyweight-adjusted dosing<br><br>**Comparator:**<br>LMWH<br>Fondaparinux<br>VKA<br><br>as per SoC<br><br>**Duration**<br>3 to 12 months, except:<br>1 to 3months for children <2 yrs with CVC-VTE | To assess the incidence of symptomatic recurrent VTE<br><br>To assess the incidence of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging.<br><br>To assess the incidence of symptomatic recurrent VTE<br><br>To assess the incidence of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging.<br><br>To characterize the pharmacokinetic/pharmacodynamic profile of rivaroxaban**.** |

| Study ID / Report no.<br>No. of study centers | Study design<br>Control type | Study/control drugs<br>Dose, route & regimen<br>Duration | Study objective |
|---|---|---|---|
| 17618 / PH-39733<br>Phase 1/2<br><br>**9 centers in 7 countries** | Multicenter<br>Open-label | **Bodyweight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for venous thromboembolism (VTE) with 20 mg rivaroxaban once daily**<br><br>**Oral**<br><br>**Duration:**<br>7 days | **Primary objective:**<br>Characterize the PK/PD profile of a 7-day treatment with oral rivaroxaban<br>**Secondary objectives:**<br>Assess the incidence of major bleeding and clinically relevant non-major bleeding<br>Assess the incidence of symptomatic recurrent VTE and<br>Assess asymptomatic deterioration in the thrombotic burden on repeat imaging |
| 17992 / PH-38996<br>Phase 1<br><br>**21 centers in 8 countries** | Multicenter<br>Single-dose<br>Open-label<br>Cohort study | **Bodyweight-adjusted single administration of granules for oral suspension:**<br><br>**Group A:** Dosing as in Study 12892<br><br>**Group B:** Dosing as in studies 14373 and 14374.<br><br>**Group C:** Dosing of 0.4 mg/kg bodyweight for children weighing 3 to <12 kg | **Primary objective:**<br>Characterize the PK profile of rivaroxaban administered as granules for oral suspension<br><br>**Secondary objective:**<br>Document safety and tolerability |

## 2.4.2. Pharmacokinetics

The pharmacokinetic properties of rivaroxaban have been extensively characterised in adults. Relevant subject covariates such as age (elderly), bodyweight, gender, ethnicity as well as renal and hepatic function have been investigated in detail in adults and were reported in previous submissions. Food affects the bioavailability of rivaroxaban which is reduced in the fasted state. This effect is more pronounced at doses of 15 mg and above. A dose-dependent decrease in relative bioavailability has been detected in adult studies. Time-dependencies in rivaroxaban PK have been studied in adults and did not reveal any undue accumulation beyond steady-state, nor alterations in rivaroxaban absorption or elimination behaviour between morning and evening/night PK profiles. Based on the data obtained in adults, concomitant use of strong inhibitors of both CYP3A4 and P-gp is not recommended; strong inducers of CYP3A4 should be co-administered with caution. Based on the physicochemical properties of rivaroxaban and based on PK data obtained in adults, in all studies children received the rivaroxaban IR tablet or the oral suspension during or closely after feeding or

meal intake and with a typical serving of drink to ensure reliable dosing in children. Children younger than 0.5 years were required have oral / (naso)gastric tube feeding for at least 10 days.

A bodyweight-adjusted dosing scheme, resulting in rivaroxaban exposure similar to that observed in adult deep vein thrombosis (DVT) patients treated with 20 mg o.d., was developed and evaluated in a comprehensive program comprised of six Phase 1, 2 and 3 studies in children from birth (term neonates) to 18 years.

Different rivaroxaban formulations were used throughout the clinical paediatric program. The final to-be-marketed granules for oral suspension, that was used in the pivotal phase-III study, was evaluated in two bioequivalence (BE) studies in healthy adults. At both 10 mg in the fasted state and 20 mg in the fed state the granules for suspension were equivalent with the respective 10 and 20 mg IR tablets using standard BE criteria.

In healthy adults a similar effect of food was seen with the 20 mg suspension as with the 20 mg IR tablets, i.e. a reduced bioavailability in the fasted state compared to the fed state. In all paediatric studies rivaroxaban was administered during or closely after feeding or meal intake this is also recommended in the paediatric posology in the SmPC.

CYP3A activity changes during human development. CYP3A4 activity is negligible in the first days after birth, increasing activity up to an age of 12 months. The fetal isoform CYP3A7 have peak activities in the first days after birth, deceasing activity to negligible levels up to 12 months of age. An i*n vitro* study was performed which indicates that rivaroxaban is a poor substrate for the fetal isoform CYP3A7 compared to CYP3A4. A relevant contribution of CYP3A7 to the hepatic clearance of rivaroxaban in the paediatric population is unlikely.

*Methods*

An adequately validated HPLC-MS/MS method with a calibration range of 0.50 µg/L to 500 µg/L was used to detect rivaroxaban in plasma.

Physiologically-based pharmacokinetic (PBPK) modelling was used to predict the initial doses to be used in the paediatric studies and to support further dosing recommendations during the running program.

Population pharmacokinetic (popPK) modelling was used for the evaluation of rivaroxaban PK in children of various age groups and, additionally, to further support dosing recommendations required in the course of this program. A comprehensive popPK model was developed based on mainly sparse PK sampling collected in seven phase I/II/III trials (12892, 14372, 14373, 14374, 17992, 17618, and preliminary data of the first part of the UNIVERSE study). The median age was 9 years (SD 5.9 years, min 0 years, max 18 years), the median body weight was 29.5 kg (SD 28 kg, min 2.7 kg, max 194 kg). In total, 524 patients and 1988 PK samples were included in the final population PK analysis. In the final dataset, 62% of the patients and the PK samples were collected in the phase III study (study 14372).

The comprehensive (final) population PK model for rivaroxaban in the paediatric population was a two-compartment model with first-order absorption and first-order elimination from the central compartment. A lower rate of absorption was estimated for undiluted suspension when compared to the other tested formulations (tablet, granules for oral suspension, and diluted suspension). The dose dependent effect on relative bioavailability was described using a previously reported adult F1 function, in which dose was replaced by dose/weight ratio, with decreasing F1 with increasing dose/weight ratio. The relative oral

bioavailability of 100% as a reference value was assumed for a dose/weight of 0.12 mg/kg and decreased gradually to 79.1% at 0.30 mg/kg and 68.1% at 0.50 mg/kg.

*Rivaroxaban exposure in the paediatric population*

The underlying dosing strategy of this paediatric program was to achieve a rivaroxaban exposure in children that is similar to that observed in adult DVT patients receiving 20 mg rivaroxaban o.d. The bodyweight-adjusted rivaroxaban dosing schedule for children aged birth (term neonates) to < 18 years (**Table 7**) was developed based on the comprehensive Phase 1 and 2 data and was confirmed in the subsequent Phase 3 Study 14372.

**Table 2.** Bodyweight-adjusted rivaroxaban dosing scheme for children aged birth to < 18 years

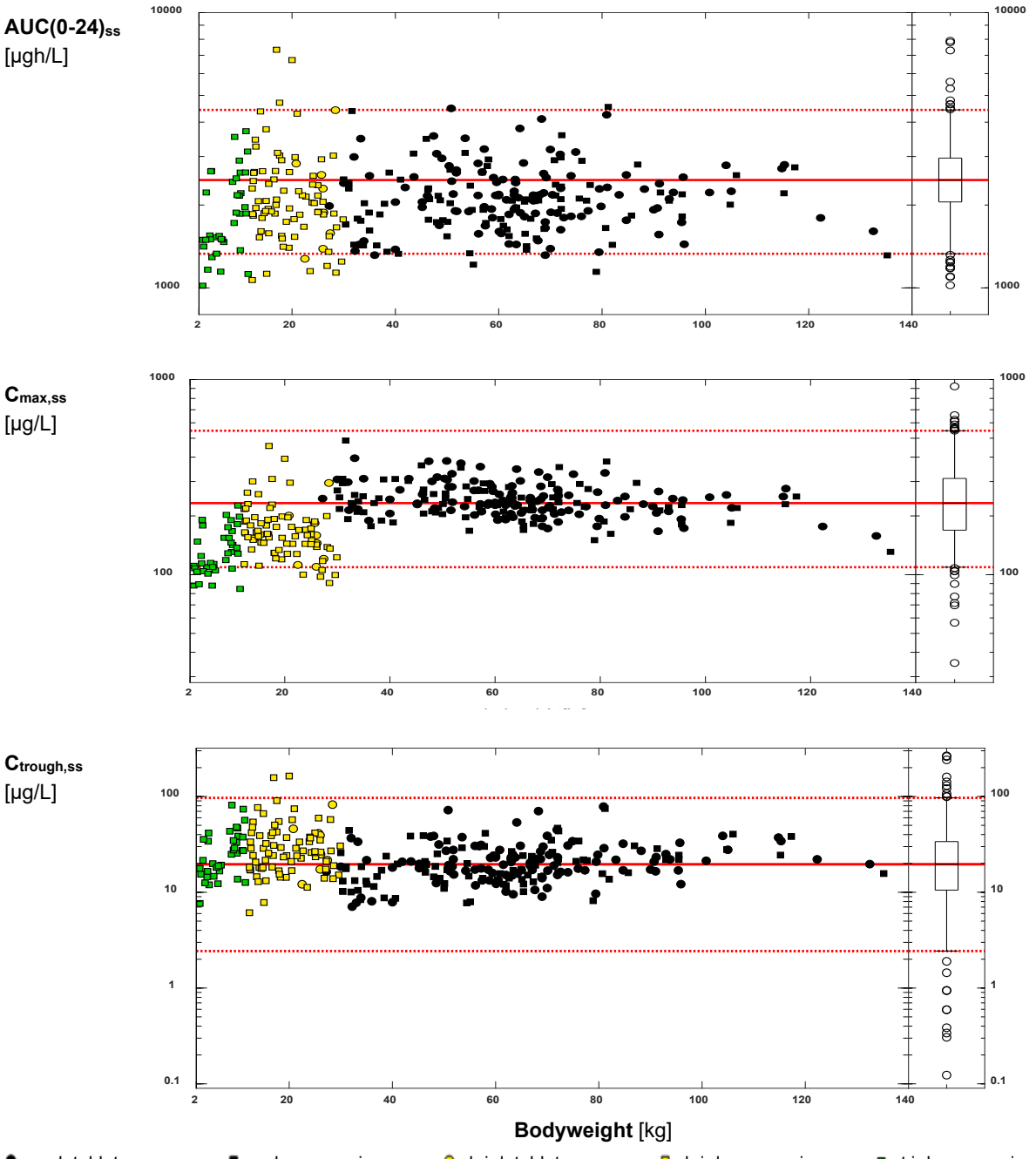
| | Bodyweight (kg) | | Regimen | | | Total daily dose |
|---|---|---|---|---|---|---|
| | Min | Max | o.d. once a day | b.i.d. 2 times a day | t.i.d. 3 times a day | |
| **Oral suspension** | 2.6 | < 3 | | | 0.8 mg | 2.4 mg |
| | 3 | < 4 | | | 0.9 mg | 2.7 mg |
| | 4 | < 5 | | | 1.4 mg | 4.2 mg |
| | 5 | < 7 | | | 1.6 mg | 4.8 mg |
| | 7 | < 8 | | | 1.8 mg | 5.4 mg |
| | 8 | < 9 | | | 2.4 mg | 7.2 mg |
| | 9 | < 10 | | | 2.8 mg | 8.4 mg |
| | 10 | < 12 | | | 3.0 mg | 9.0 mg |
| | 12 | < 30* | | 5 mg | | 10 mg |
| **Tablets or oral suspension** | 30 | < 50 | 15 mg | | | 15 mg |
| | ≥ 50 | | 20 mg** | | | 20 mg |

* In Study 14372, children weighing 12 to < 30 kg received either tablets or oral suspension (5 mg b.i.d.)

** In Japan, 15 mg was applicable also for subjects ≥ 50 kg bodyweight.

The individual values for main PK parameters $AUC(0\text{-}24)_{ss}$, as a measure for daily exposure, and $C_{max,ss}$ and $C_{trough,ss}$ within a dosing interval are shown as a function of bodyweight and in comparison to the corresponding adult exposure levels in **Figure 1**.

**Figure 1.** Bodyweight dependence of AUC(0-24)$_{ss}$, $C_{max,ss}$ and $C_{trough,ss}$ (popPK) for children aged < 18 years for the 20 mg daily dose equivalent on a semi-log scale (Study 14372).




*Individual exposure metrics based on final popPK model.*
*AUC(0-24)$_{ss}$ = Area under the curve from zero to 24h at steady state; $C_{max,ss}$ = maximum drug concentration at steady state; $C_{trough,ss}$ = trough concentration at steady state; DVT = deep vein thrombosis; popPK = population pharmacokinetics; VTE = venous thromboembolism; o.d. = once daily; b.i.d. = twice daily; t.i.d. = three times daily*

*PK Parameters were derived by PopPK. On the right-hand side, popPK results for adult DVT patients (20 mg o.d.) are shown as box whisker plot, which indicate the percentiles 5, 25, 50, 75, and 95 and individual values beyond the 5th - 95th percentile as open circles.*

*PK related to intrinsic and extrinsic factors*

Exploratory PK analyses did not indicate relevant differences between male and female children nor between either Japanese, Chinese, or Asian children outside Japan and China compared to the respective overall paediatric population. Furthermore, no relevant impact of underweight or obesity on rivaroxaban PK in children was found. No influence of renal function on rivaroxaban PK was found. No data was available in children with hepatic impairment. The exploratory analyses did not indicate a relevant impact of concurrent functional gastrointestinal disorders, certain malignant diseases on rivaroxaban PK in children, neither for the acute and chronic GI diseases nor for neoplasms with high prevalence in childhood. Limited results from clinical studies in children did not indicate new drug-drug interaction potential not already known from adults. No additional analyses on the impact of food on rivaroxaban absorption in children were conducted, hence the recommendation of administration with food is based on the PK data obtained in adults.

## 2.4.3. Pharmacodynamics

The pharmacological effects of rivaroxaban have been extensively characterised in adults. A dose-dependent inhibition of Factor Xa was observed across the complete dose range, closely following the pharmacokinetic profiles of rivaroxaban. The other global clotting tests prothrombin time (PT) and activated partial thromboplastin time (aPTT) were also affected in a dose-dependent way.

In children, the blood coagulation system is distinctly different from adults and matures with age – a phenomenon that is described as 'developmental haemostasis'. The following studies of relevance for primary pharmacology have been provided:

**12892:** Phase 1. Multicentre, single-arm single-dose study of oral rivaroxaban in suspension or tablets adapted to bodyweight. Primary objective: PK/PD. Secondary objective: safety/tolerability. Other outcomes: palatability and acceptability of suspension. 59 treated subjects aged 0.5 years-<18 years.

**14373:** Phase 2. Multicentre, single-arm 30 days study of oral age- and bodyweight-adjusted rivaroxaban in suspension or tablets. Primary objective: major/CRNM bleeding. Secondary objective: recurrent VTE; asymptomatic deterioration of thrombotic burden on repeat imaging; PK/PD profile of 30 days oral rivaroxaban treatment. 68 enrolled, 63 treated subjects aged 6-18 years.

**14374:** Phase 2. Multicentre, single-arm 30 days study of oral age- and bodyweight-adjusted rivaroxaban in suspension. Primary objective: major/CRNM bleeding. Secondary objective: recurrent VTE; asymptomatic deterioration of thrombotic burden on repeat imaging; PK/PD profile of 30-day oral rivaroxaban treatment. 51 enrolled, 46 treated subjects aged 0.5-6 years.

**14372:** Phase 3. Multicentre, open-label, randomised, active controlled study of age- and bodyweight-adjusted rivaroxaban in granules for suspension or tablets, with a study duration of 3 to 12 months (1-3 months for children < 2 years with CVC-VTE). Study objectives were to assess the incidence of symptomatic recurrent VTE, asymptomatic deterioration, and PK/PD profile of rivaroxaban. 335 enrolled subjects in rivaroxaban group (165 comparator); 329 rivaroxaban treated subjects aged birth - <18 years. 313 children were valid for PD analysis.

**17618:** Phase 1/2. Multicentre, open-label 7 days study of oral bodyweight adjusted rivaroxaban in suspension given b.i.d. or t.i.d. Primary objective: PK/PD profile. Secondary objectives: major/CRNM bleeding; recurrent VTE, asymptomatic deterioration. 11 enrolled, 10 treated subjects aged 0-6 months.

**Results of PD parameters**

***Ex-vivo* experiments**

*Ex-vivo* spiking experiments with increasing rivaroxaban concentrations were performed that investigated the correlation of prothrombin time, aPTT, inhibition of anti-factor Xa activity and thrombin generation to rivaroxaban plasma concentrations in children aged birth to 16 years as compared to adults. Age-specific plasma pools were created (i.e. birth to 28 days, 28 days to 23 months, 2 to 6, 7 to 11, 12 to 16 years and adults) and spiked with increasing concentrations of rivaroxaban (0–500 ng/ml). In children older than 28 days, the effects of rivaroxaban on in vitro coagulation tests were similar across all age cohorts and similar to the effects observed in adults. In children younger than 28 days, prothrombin time and thrombin generation (lag time), showed a significantly more pronounced effect as compared to adults for all plasma concentrations. A similar effect was also observed for aPTT at low plasma concentrations, which was not significant at higher plasma concentrations. No age-related differences were observed for the inhibition of anti-factor Xa activity assays. Whereas in general a dose and dosing regimen in children was chosen that targeted the exposure range of the adult reference population, in younger children (weighing less than 12 kg, which corresponds to an age of approximately 2 years and younger), a match with the lower 30% of the adult exposure range was targeted.

**Results from clinical studies**

Anti-Xa-activity

In the anti-factor Xa activity assay, a linear correlation to plasma concentrations as determined by HPLC-MS/MS was observed in a pooled analysis of all multiple dose studies in children (studies 14374, 14373, 17618 and 14372). After exclusion of outliers originating from study 14372, which were potentially influenced by storage and/or processing/analysis deviations, the correlation between anti-factor Xa activity and plasma concentrations has a slope of 0.961 and an intercept of 0.655 µg/L.

The dosing regimen (o.d., b.i.d. and t.i.d.) did not influence the correlation of anti-factor Xa activity versus plasma concentrations in children (data not shown).

Global clotting tests (PT and aPTT):

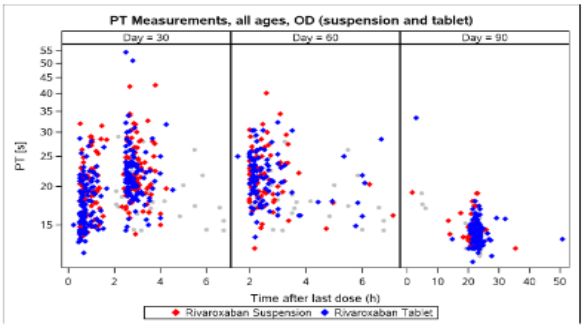
PT or aPTT data (absolute values) from the Phase 3 study in children were compared to the adult reference population (patients being treated for DVT who received a 20 mg once daily dose. A pooled analysis from all treatment studies in children (studies 14373, 14374, 17618, 14372) investigated the correlation of PT/aPTT versus plasma concentrations. PT and aPTT were determined as ratio to the individual baseline and correlated to plasma concentrations determined by HPLC-MS/MS. These data were compared to the adult data from patients who were treated for DVT and received a 20 mg once daily dose. These adult data are depicted as the 99% prediction interval of adult DVT patients.

*Prothrombin time (PT)*

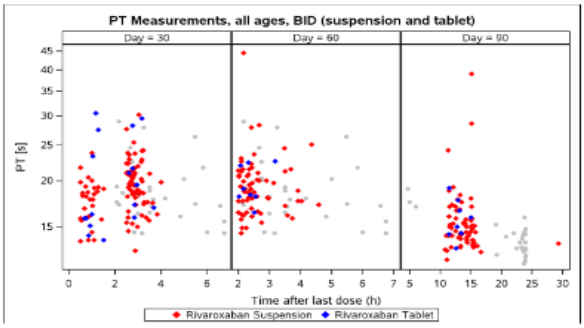
The paediatric data are very similar to the adult data independent of the dosing regimen (once, twice and three times daily) as well as independent of the formulation used (tablet or oral suspension) **(Figure 2).**

**Figure 2.** Prothrombin time profiles in children

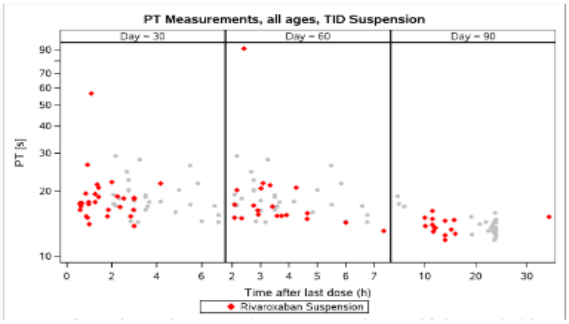
o.d. treatment




b.i.d. treatment



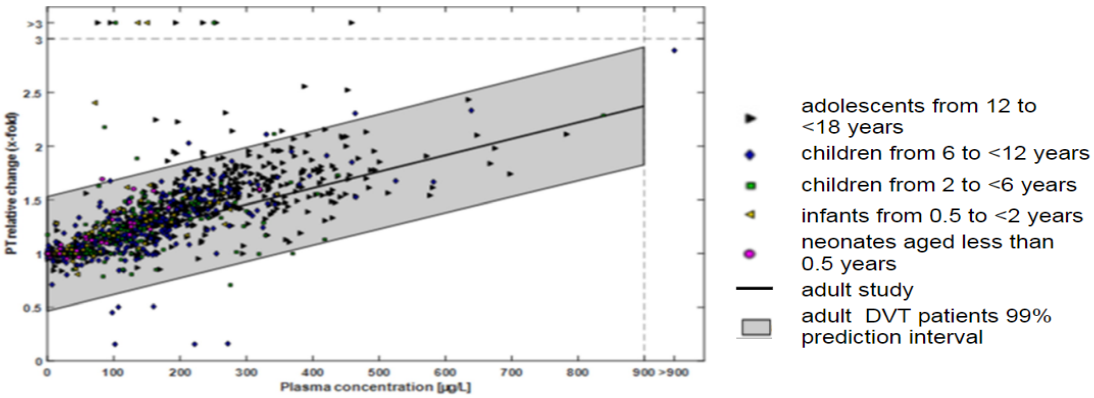

t.i.d treatment




Blue symbols: tablet, red symbols: suspension, grey circles: reference population PT change to baseline (x-fold) is individual PT divided by individual PT at baseline (Day 90) A linear relationship was assumed for the concentration-response curve of the reference populations. 99% prediction intervals were used to depict the variability in the reference population (dashed lines). Grey symbols: Reference population: adult DVT patients treated with 20 mg tablets once daily

The correlation of PT prolongation versus plasma concentration was visually close to linear in children, not different from adults, and not different between the individual age groups (**Figure 3**).

**Figure 3.** Correlation of PT prolongation versus plasma concentration in children treated with multiple doses of rivaroxaban by age




PK-PD: Prothrombin time relative change to baseline (x-fold) for children of study 14372, 14373, 14374, 17618 of all age groups. Lines indicate the 99% prediction interval from adult DVT patients receiving a 20 mg once daily dose of rivaroxaban

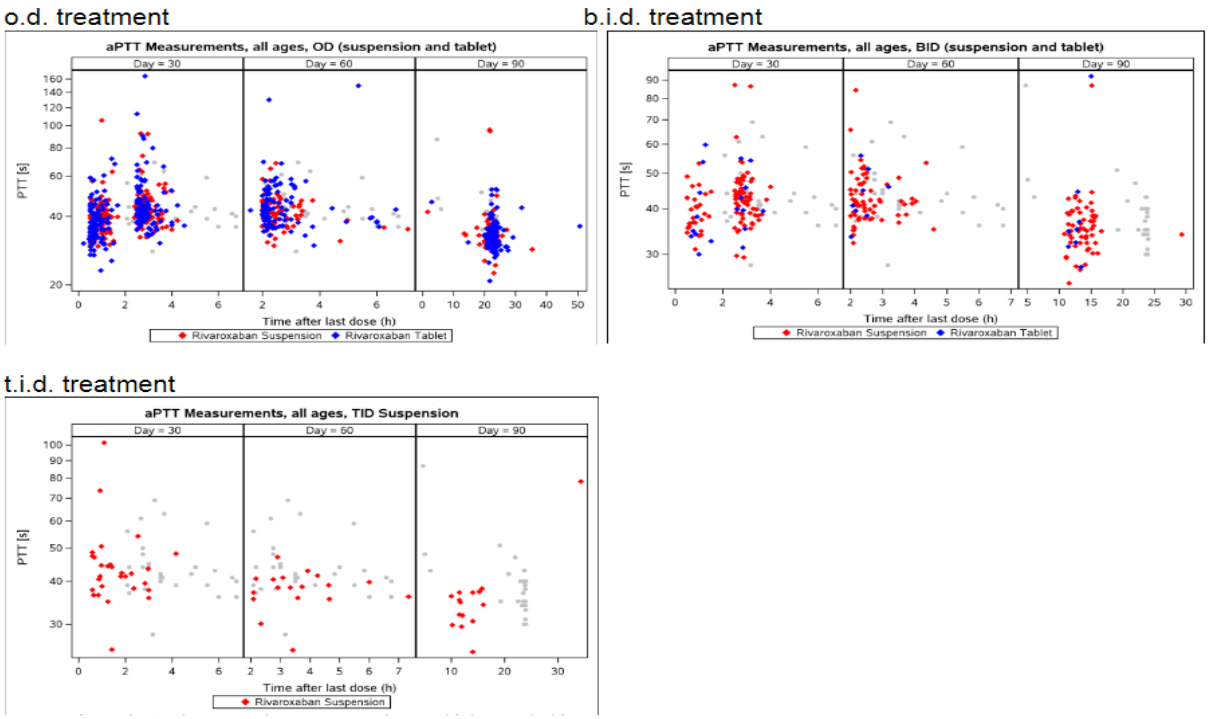
Different dosing regimens did not influence the correlation of PT versus plasma concentrations (data not shown).

The relationship between the PT and measured plasma concentrations of rivaroxaban was explored using regression analysis of PT data from all paediatric studies. The relationship between PT and plasma concentration was best described by a modulated power model, described by a baseline and slope parameter, plus an exponent that modulates plasma concentration as the dependent variable. The exponent depends on the plasma concentration in a way that it approaches 1 for low rivaroxaban concentrations (i.e. approaching a linear model) and is smaller than 1 for high rivaroxaban concentrations. This exponential modulation of the plasma concentrations leads to a flattening of the linear relation between PT and plasma concentrations at high concentrations, in line with the observed PT data.

*Activated partial thromboplastin time (aPTT)*

Individual aPTT values in children from the Phase 3 study 14372 were compared to adult DVT patients receiving 20 mg rivaroxaban once daily. The paediatric data are very similar to the adult data independent of the dosing regimen or the formulation used (**Figure 4**).

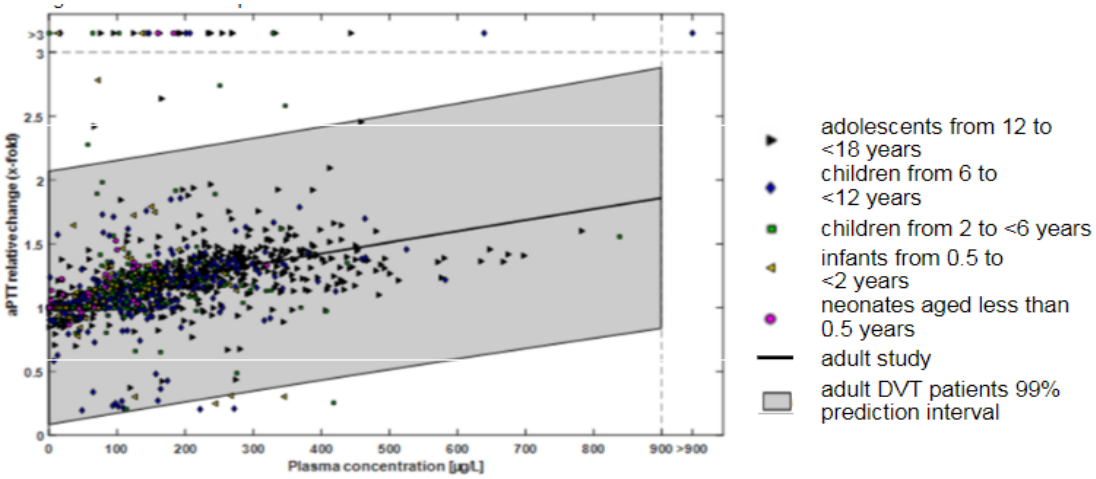
**Figure 4.** Activated partial thromboplastin time profiles in children




Blue symbols: tablet, red symbols: suspension, grey circles: reference population aPTT change to baseline (x-fold) is individual aPTT divided by individual aPTT at baseline (Day 90). A linear relationship was assumed for the concentration-response curve of the reference populations. 99% prediction intervals were used to depict the variability in the reference population (dashed lines). Reference population: adult DVT patients treated with 20 mg tablets once daily

The correlation of aPTT prolongation versus plasma concentration is visually close to linear but less steep than observed for PT, but not different from adults, and not different between the individual age groups (**Figure 5**). Likewise, different dosing regimens do not influence the correlation of aPTT versus plasma concentrations.

**Figure 5.** Correlation of aPTT prolongation versus plasma concentration in children treated with multiple doses of rivaroxaban by age




aPTT relative change to baseline (x-fold) for children of study 14372, 14373, 14374, 17618 of all age groups. Lines indicate the 99% prediction interval from adult DVT patients receiving a 20 mg once daily dose of rivaroxaban

The relationship between aPTT and measured plasma concentrations of rivaroxaban was explored using regression analysis with PT data from all pediatric studies. The relationship between PT and plasma concentration was best described by a modulated power model, described by a baseline and slope parameter, plus an exponent that modulates plasma concentration as the dependent variable. Similar to the model for PT, the exponent depends on the plasma concentration in a way that it approaches 1 for low rivaroxaban concentrations (i. e. approaching a linear model) and is smaller than 1 for high rivaroxaban concentrations. This exponential modulation of the plasma concentrations leads to a flattening of the linear relation between PT and plasma concentrations at high concentrations, in line with the observed aPTT data.

The concentration-effect relationship was graphically explored to test for potential age or weight dependencies. No correlation was observed with the slope parameter of the PK/aPTT relationship. Additional analysis showed that the weighted residuals for aPTT are equally distributed around zero for each age group individually, indicating that the aPTT model describes the concentration-effect relationship adequately for all children irrespective of their age.

**Effect of intrinsic factors on PD**

No effect of age, weight, gender, acute or chronic GI disorders, mild renal impairment or children with and without neoplasms were observed for the correlation of the pharmacodynamic tests PT, aPTT, or anti-factor Xa activity versus plasma concentrations based on pooled data of studies 14373, 14374, 17618, 14372. No data is available in children with hepatic impairment.

## 2.4.4. Discussion on clinical pharmacology

Extensive PBPK and popPK analyses have been performed throughout the paediatric rivaroxaban development program. PBPK modelling has been used to predict the initial doses to be used in the paediatric studies and to support further dosing recommendations during the running program, however as the dosing regimens have been studied in clinical trials the PBPK analyses are not perceived as pivotal from a regulatory perspective.

Population PK modelling was used throughout the EINSTEIN-Jr program to analyse the sparse PK samples collected in the clinical trials. A comprehensive popPK model based on pooled paediatric data from all ages (seven studies all together) was developed and this analysis is viewed as the pivotal rivaroxaban population PK analysis in the paediatric population. The approach of a pooled data analysis is endorsed, and the data handling is acceptable. Furthermore, standard software and methods have been used in the model development and evaluation. Formulation was tested as a covariate in an exploratory PK model, and no statistical difference was detected between the tablet and prediluted suspension.

In general, the simulation-based evaluations of the model indicate that the model describes the paediatric data fairly well. Apart from the expected body weight dependence, no major differences between adult and paediatric PK properties of rivaroxaban were detected.

In comparing paediatric and adult exposure levels, a reference range for adult patients aged ≤ 45 years with acute symptomatic DVT receiving 20 mg o.d. was targeted. The adult reference range is based on the knowledge that renal insufficiency affects rivaroxaban PK. As such the exposure range the paediatric population is expected to be more similar to the exposure range in the young adult population. For most part, predicted values for $AUC(0\text{-}24)_{ss}$, $C_{max,ss}$ as well as $C_{trough,ss}$ were within the adult reference ranges irrespective of formulation and for all age groups, bodyweight categories and treatment regimens. For children weighing less than 12 kg, a match with the lower 30% of the adult exposure range was targeted. As a result, most $AUC(0\text{-}24)_{ss}$ values in children receiving rivaroxaban in t.i.d. regimen were located below the median of the adult reference range. As expected, for $C_{max,ss}$ a clear trend is seen by regimen, with decreasing $C_{max,ss}$ with less frequent dosing regimen. $C_{trough,ss}$ a minor trend towards higher values in b.i.d. and t.i.d. regimen compared to o.d. regimen is evident. As such, the exposure predictions from the phase III trial indicate that an adequate dosing regimen was achieved.

For pharmacodynamics, the PD endpoints anti-Xa activity, prothrombin time (PT) and activated partial thromboplastin time (aPTT) are deemed relevant, although the clinical relevance is somewhat limited, in particular for aPTT for which it was concluded in the adult SPAF studies that although aPTT was prolonged dose-dependently, the slope was too flat to allow a sufficient discrimination at the relevant plasma concentrations. Therefore, aPTT was not considered to be adequate for following the PD effects.

The ex-vivo spiking experiments are of interest, given the differences noted between children from birth to 28 days as compared to older children. The effect on PD markers (prothrombin time and thrombin generation) showed a significantly more pronounced effect as compared to adults for all plasma concentrations, and for aPTT a similar effect was shown at low plasma concentrations (not significant at higher plasma concentrations). However, no such effect was demonstrated in the clinical PD studies. For the clinical PD studies, the numbers of children in each age cohort is in line with the agreed PIP, and results indicate similar PD effects as in adults across the individual age groups and different dosing regimens. Of note, the sources of the adult reference data and prediction intervals originate from a limited number of subjects (N = 130) and not from the adult VTE population in the adult pivotal studies. A modulated power model could be fitted for both PT and aPTT versus measured plasma concentrations of rivaroxaban.

No effect of age, weight, gender, acute or chronic GI disorders, mild renal impairment or children with and without neoplasms was demonstrated on the PD tests.

Pharmacodynamic interactions with other medicinal products relate primarily to other antithrombotic agents, for which concomitant use could increase the risk of bleeding. This has been extensively studied in adults, and a similar risk is likely in children, although use of additional antithrombotic agents such as antiplatelet agents for e.g. cardiovascular disease could be expected to be lower in children. There were no major bleedings or clinically relevant non major bleedings in children concomitantly treated with rivaroxaban and other antithrombotic agents during the main treatment period of study 14372; however, two of the three clinically relevant non-major bleeding events during extension phase occurred in children concomitantly treated with acetylsalicylic acid or ibuprofen.

The pharmacokinetic parameters $AUC(0\text{-}24)_{ss}$, $C_{max,ss}$ and $C_{trough,ss}$ did not correlate with efficacy or safety defined as thrombotic events or bleeding events. Consequently, there is no established correlation between any of the PD markers and clinical efficacy or safety.

### 2.4.5. Conclusions on clinical pharmacology

Overall, the CHMP considered that the clinical pharmacology data provided with this application were adequate to support this application.

A pooled population PK analysis of all paediatric PK data demonstrated that acceptable plasma concentration levels were reached across all weight and age groups, and that the exposure was comparable to the exposure measured in reference population of young adults.

Similar to adults, an increased risk of bleeding if other antithrombotic agents are used concomitantly with rivaroxaban would be expected in children.

## *2.5. Clinical efficacy*

### 2.5.1. Main study

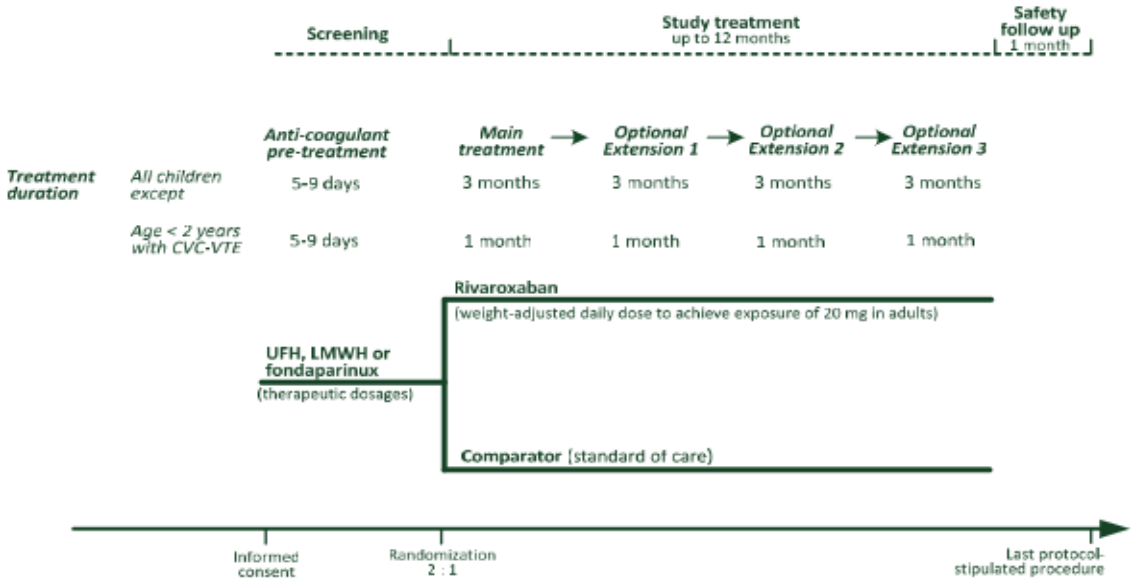
### Title of study

**Study 14372** (also referred to as **EINSTEIN Junior**)**:** A multicenter, open-label, active-controlled, randomized phase III study to evaluate the efficacy and safety of an age- and bodyweight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism.

### *Methods*

The study design in depicted in **Figure 6**.

**Figure 6.** Study design schematic (Study 14372)




CVC = central vein catheter; LMWH = low-molecular-weight heparin; UFH = unfractionated heparin; VTE = venous thromboembolism

## *Study Participants*

Main inclusion criteria:

- Children aged birth to <18 years with confirmed VTE who received initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and required anticoagulant therapy for at least 90 days. However, children aged younger than 2 years with CVC-VTE required anticoagulant therapy for at least 30 days. VTE could affect the lower extremity, caval vein, portal vein, renal vein, right side of the heart, lungs, upper extremity (including axillary and subclavian vein), jugular vein, and cerebral vein and sinuses, and be either catheter-related or non-catheter-related.

- For children younger than 6 months: Gestational age at birth of at least 37 weeks; oral feeding/(naso)gastric for at least 10 days; body weight ≥2600 g.

Main exclusion criteria:

- Active bleeding or bleeding risk contraindicating anticoagulant therapy.

- eGFR <30mL/min/1.73 m2 (in children younger than 1 year, serum creatinine results above 97.5$^{th}$ percentile excluded participation)

- Hepatic disease which was associated either: with coagulopathy leading to a clinically relevant bleeding risk, or ALT >5x ULN, or total bilirubin >2x ULN with direct bilirubin >20% of the total.

- Platelet count <50 x 109/L.

- Sustained uncontrolled hypertension defined as systolic and/or diastolic blood pressure >95thage percentile.

- Life expectancy <3 months.

- Concomitant use of strong inhibitors of both CYP3A4 and P-gp, including but not limited to all human immunodeficiency virus protease inhibitors and the following azole-antimycotics agents: ketoconazole, itraconazole, voriconazole, posaconazole, if used systemically (fluconazole is allowed)

- Concomitant use of strong inducers of CYP3A4, including but not limited to rifampicin, rifabutin, phenobarbital, phenytoin, and carbamazepine

- Childbearing potential without proper contraceptive measures, pregnancy or breast feeding.

## *Treatments*

Initial treatment with UFH, LMWH or fondaparinux was administered for at least 5 days and a maximum duration of 9 days. Randomization was done during the first 9 days of initial treatment and was done in a 2 (rivaroxaban): 1 (standard of care) fashion. Children randomized to receive rivaroxaban had a body weight-adjusted 20 mg equivalent dose given once-daily, twice-daily or thrice-daily for bodyweights of ≥30, ≥12 to <30, and <12 kg, respectively (dosing regimens adjusted if body weight changed during study). No dose reduction for impaired renal function was required (children with impaired renal function with eGFR <30mL/min/1.73 m2 were excluded as described above). 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; see **Table 8**.

**Table 3.** Body weight-adjusted rivaroxaban dosing schedule for children aged birth to <18 years in Study 14372

| Body weight (kg) | | Formulation | o.d. Dose | b.i.d. Dose | t.i.d. Dose | Total Daily Dose |
|---|---|---|---|---|---|---|
| Min | Max | | | | | |
| 2.6 | <3 | Oral suspension | | | 0.8 mg | 2.4 mg |
| 3 | <4 | Oral suspension | | | 0.9 mg | 2.7 mg |
| 4 | <5 | Oral suspension | | | 1.4 mg | 4.2 mg |
| 5 | <6 | Oral suspension | | | 1.6 mg | 4.8 mg |
| 6 | <7 | Oral suspension | | | 1.6 mg | 4.8 mg |
| 7 | <8 | Oral suspension | | | 1.8 mg | 5.4 mg |
| 8 | <9 | Oral suspension | | | 2.4 mg | 7.2 mg |
| 9 | <10 | Oral suspension | | | 2.8 mg | 8.4 mg |
| 10 | <12 | Oral suspension | | | 3.0 mg | 9 mg |
| 12 | <20 | Oral suspension | | 5 mg | | 10 mg |
| 20 | <30 | Tablet or oral suspension | | 5 mg | | 10 mg |
| 30 | <50 | Tablet or oral suspension | 15 mg | | | 15 mg |
| ≥ 50 | | Tablet or oral suspension | 20 mg ** | | | 20 mg ** |

** 15 mg in Japan

Note: Dosing regimen, including dosing frequency, will be adjusted if the child's body weight changes during the study.

For switching from UFH/heparin/fondaparinux to rivaroxaban, the first administration of rivaroxaban was 1) 4 hours after stopping the infusion of UFH, 2) 12 hours after the last injection of LMWH with a twice-daily regimen, or 3) 24 hours after the last injection of fondaparinux or LMWH with a once-daily regimen.

Children randomised to comparator received standard of care anticoagulation, either continuous UFH, LMWH or fondaparinux or switch to VKA therapy, target therapeutic range 2.0-3.0, according to **Table 9**.

**Table 4.** Overview of comparator treatment in Study 14372

| Generic name | Dosage | |
|---|---|---|
| Warfarin | INR 2.0-3.0 | |
| Acenocoumarol | INR 2.0-3.0 | |
| Phenprocoumon | INR 2.0-3.0 | |
| Enoxaparin | 1 mg/kg b.i.d. | |
| Fondaparinux | 0.1 mg/kg o.d. | |
| Tinzaparin | 2-12 mo | 250 u/kg o.d. |
| | 5 yr | 240 u/kg o.d. |
| | 5-10 yr | 200 u/kg o.d. |
| | 10-16 yr | 175 u/kg o.d. |
| Dalteparin | 129 ± 43 u/kg/dose o.d. | |
| UFH | aPTT 1.5-2.5 prolongation | |

b.i.d.: twice daily; o.d.: once daily; u: units; this comparator list is not all-inclusive.[10]

In all children, except those aged < 2 years with catheter-related thrombosis, the main study treatment period was 3 months. After that, up to the discretion of the treating physician, study treatment was stopped or continued for an additional 3 months. In children who completed 6 months of treatment, study treatment was stopped or continued for an additional 3 months. In children who completed 9 months of treatment, study treatment was stopped or continued for an additional 3 months. Thereafter, no prolongation of study treatment could take place.

In children aged < 2 years with catheter-related thrombosis, the main study treatment period was 1 month. After that, up to the discretion of the treating physician, study treatment was stopped or continued for an additional 1 month. In children who completed 2 months of treatment, study treatment was stopped or continued for an additional 1 months. Thereafter, no prolongation of study treatment could take place.

After cessation of study treatment with rivaroxaban, it was at the investigator's discretion to continue with anticoagulation, as needed.

## *Objectives*

The efficacy objectives were:

- To assess the incidence of symptomatic recurrent VTE
- To assess the incidence of symptomatic recurrent VTE and asymptomatic deterioration on repeat imaging

The safety objective was:

- To assess the incidence of overt major and clinically relevant non-major bleeding.

## *Outcomes/endpoints*

The primary efficacy outcome was symptomatic recurrent VTE.

The secondary efficacy outcome was the composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging at the end of the main treatment period.

Further efficacy outcomes:

-Composite of symptomatic recurrent VTE and major bleeding

-Composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in thrombotic burden assessment on repeat imaging at the end of the main treatment period

-Composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging at the end of the main treatment period (symptomatic recurrent VTE, asymptomatic deterioration, no relevant change, uncertain, improved, normalized)

-Normalization of thrombotic burden assessment on repeat imaging at the end of the main treatment period without confirmed symptomatic recurrent VTE

-Fatal or non-fatal pulmonary embolism

-Composite of symptomatic recurrent VTE and other clinically significant thrombosis.

## *Sample size*

A properly powered non-inferiority study was not feasible due to the low incidence of VTE in children, and the lack of well-documented information on recurrence rate and treatment effect with standard of care in children. Hence, there was no formal sample size calculation.

At least 170 children were planned to be included: 80 in the age group 12 to < 18 years, 30 in the age group 6 to < 12 years, 20 in the age group 2 to < 6 years, and 20 in the age group birth to < 2 years, with at least 12 aged birth to < 6 months.

Enrolment was conducted staggered by age, starting with children aged 12 to <18 years, and opening each subsequent age cohort via a substantial amendment once the body weight-adjusted dose regimen had been determined in Phase 2 for the respective age groups.

## *Randomisation*

Randomisation was in a 2 (rivaroxaban): 1 (standard of care [SOC]) fashion. Allocation to treatment was done centrally using an interactive voice/web response system (IxRS) and was stratified by two types of baseline presentation of venous thrombosis as diagnosed by the investigator for each age group, separately:

a) lower extremity DVT, caval vein thrombosis, upper extremity DVT, subclavian thrombosis, right atrial thrombosis, pulmonary embolism and catheter related thrombosis and

b) cerebral vein and sinus thrombosis, jugular vein thrombosis, mesenteric vein thrombosis, portal vein thrombosis and renal vein thrombosis

Children randomised to rivaroxaban were to start rivaroxaban the day following the last administration of initial therapy with UFH, LMWH, or fondaparinux but with a minimal duration of initial therapy of 5 days and a maximum duration of 9 days.

Children randomised to the comparator group had to continue with UFH, LMWH or fondaparinux or switch to VKA therapy.

### *Blinding (masking)*

This was an open label study.

### *Statistical methods*

Incidence proportions were calculated for the efficacy outcomes by treatment group at the end of the main treatment period for the combined data over all children and by classification of index event. Cumulative incidences (time to first event; Kaplan-Meier) were calculated for the primary efficacy outcome and for the composite of all symptomatic recurrent VTE and major bleeding by treatment group at the end of the main study treatment period for pooled data over all children. Incidence proportions were calculated for each age stratum, weight group (seven level grouping) and dosing formulation assignment at the end of the main treatment period for SAF and PPS populations and by presentation of index event. Incidence proportions were also calculated for the primary outcome by treatment group for each age stratum, and pooled data excluding children <2 years with CVC-VTE in the extended study treatment period at 6, 9 and 12 months.

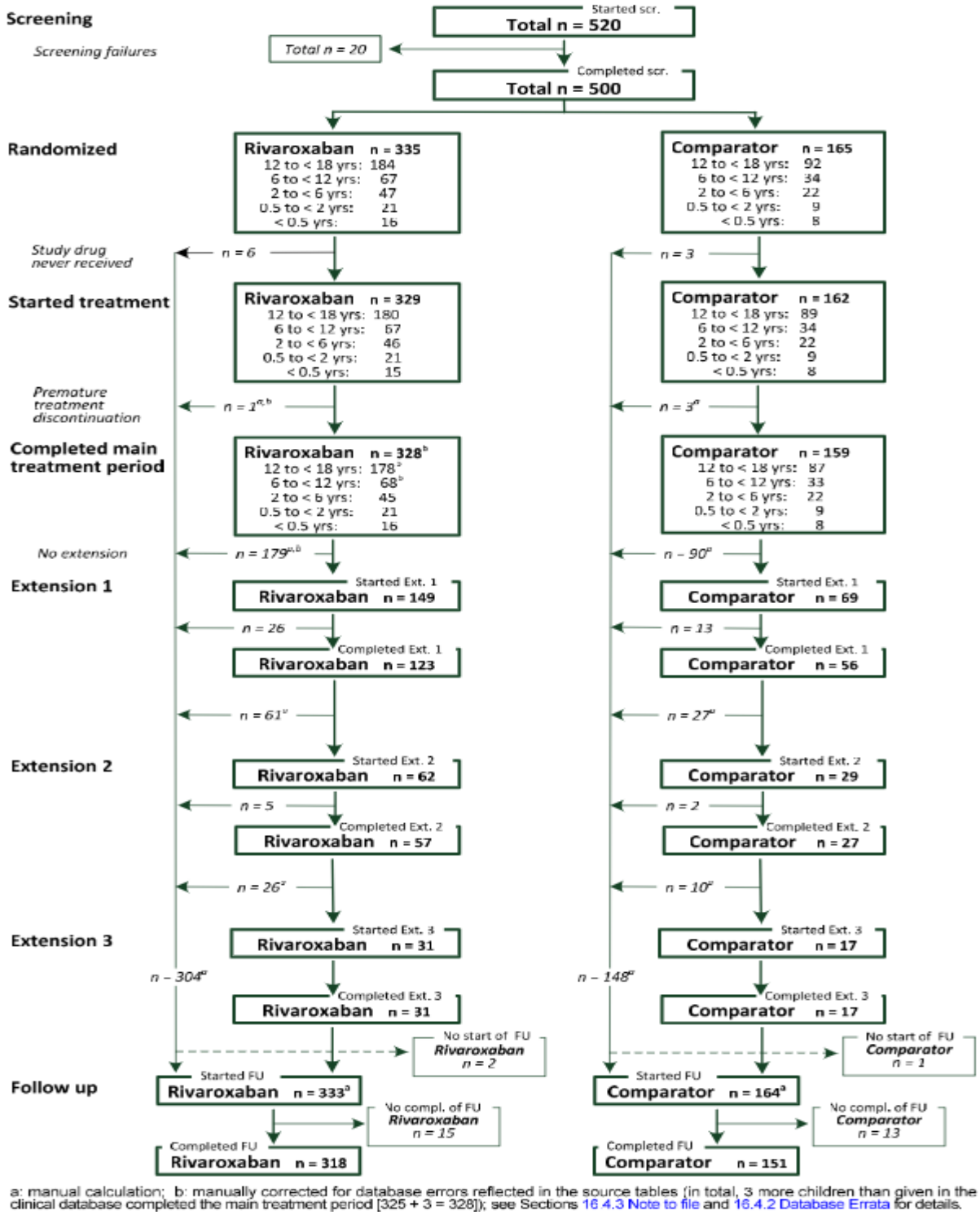
Counts of composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging at the end of the main treatment period were reported by classification and presentation of index event. The counts were also calculated for subjects with anticoagulants that were prolonged after the main treatment period versus subjects without any anticoagulants after the main treatment period. Incidence proportions in the extended treatment period for children <2 years with CVC-VTE were presented separately at 2 and 3 months. Denominators were the number of patients at risk at the start of the respective period.

Two-sided 95% confidence intervals for the frequency efficacy outcomes were calculated by applying the method of Blyth-Still-Casella. For time-to-event analyses, the censoring mechanism was assumed to be non-informative. These analyses included events up to the end of study periods per subject regardless of the actual stop date of study medication. Events that occurred more than 2 days after stop of study medication up to 30 days were to be listed.

### *Results*

## Participant flow

**Table 5.** Disposition chart, Study 14372




a: manual calculation; b: manually corrected for database errors reflected in the source tables (in total, 3 more children than given in the clinical database completed the main treatment period [325 + 3 = 328]); see Sections 16.4.3 Note to file and 16.4.2 Database Errata for details.

The primary reason for not completing the main treatment period in children was withdrawal by subject (11/500, 2.2%, manually calculated), 5 (1.0%, manually calculated) of whom received, and 6 (1.2%) did not receive any study medication.

After completion of the main treatment period and at the discretion of the investigator, study treatment could be continued three times with blocks of 3 months each (maximum duration of study treatment, 12 months). However, for children with CVC-VTE aged < 2 years, study treatment could be continued two times with blocks of 1 month each (maximum study treatment duration, 3 months) (see Section 7.1). Of the 500 randomized children, 218 (43.6%) entered and 179 (82.1%) completed the first block of extended treatment, 91 (18.2%) entered and 84 (92.3%) completed the second block of extended treatment, and 48 (9.6%) entered and all (100%) completed the third block of extended treatment. Although some children with CVC-VTE aged < 2 years were included before Amendment 12 (and therefore had a main study treatment period of 3 months rather than 1 month), the main treatment duration was considered to be 1 month for all of these children. If the actual main treatment period for these children exceeded 1 month, the children were considered as having a subsequent treatment extension.

A total of 469/500 (93.8%) children completed the 30-day post-study treatment follow up period. Three children did not enter, and 28 (5.6%) children did not complete the follow-up. The most common reasons for not completing the follow up were withdrawal by subject and lost to follow-up. There was no relevant difference between the treatment groups or age groups. Of the 491 children in SAF, 248 (50.5%) continued with study medication after the main treatment period, or received local anticoagulant treatment within 7 days after the main treatment period, for at least 7 days.

## Recruitment

Study start: 13 November 2014 (First subject, first visit).

Study ginish:30 January 2019 (Last subject, last visit).

## Conduct of the study

The study protocol was amended 17 times, including 4 global amendments. The main amendments included

- implementation of dosing regimen for children aged 6 to <12 years following the conformation of the body-weight adjusted dosing regimen for this age group in the phase II study (14373);
- enrolment in the study of children aged 0.5 to <6 years was opened;
- the dosing table was extended to include dosing information for children with body weight of 6-12 kg. Children with body weight between 6 and 12 kg were to be treated according to a three times daily schedule with a time interval of approximately 8 hours between individual doses.
- New dosing information for children with body weight between 2.6 and < 6 kg, and inclusion of children aged birth -0.5 year was added.

Minor protocol deviations were reported for 345 (69.0%) of the 500 children: 72.2% in the rivaroxaban group and 62.4% in the comparator group (Table 14.1.1 / 44). Major protocol deviations were reported for 33 (6.6%) of the children: 7.8% in the rivaroxaban group and 4.2% in the comparator group; 22 had major protocol deviations related to PK/PD (rivaroxaban group only), 9 treatment deviations, and 6 other protocol deviations.

## Baseline data

Demographics and baseline characteristics were well balanced between the treatment groups. Of the 500 randomized children, 255 (51.0%) were male and 245 (49.0%) were female, 395 (79.0%) were white, 25 (5.0%) were black, 28 (5.6%) were Asian, 2 (0.4%) were American Indian or Alaska native, 1 (0.2%) was native Hawaiian or other pacific islander, and 4 (0.8%) were of multiple races. For 45 (9.0%) children, no race was reported. The mean age of children was 11.12 years (median 13.23 years). Average weight was 46.35 kg (median 48.30 kg) and average height was 140.93 cm (median 156.00 cm).

Demographics for the smaller group of patients aged between birth to two years of age are presented in **Table 11**.

**Table 6.** Demographics for children aged birth to <2 years (FAS, Study 14372)

| | 0.5 - <2 years | | Birth - <0.5 year | |
|---|---|---|---|---|
| | Rivaroxaban N=21 (100%) | Comparator N=9 (100%) | Rivaroxaban N=16 (100%) | Comparator N=8 (100%) |
| Sex | | | | |
| Male | 11 (52.4%) | 4 (44.4%) | 11 (68.8%) | 7 (87.5%) |
| Female | 10 (47.6%) | 5 (55.6%) | 5 (31.3%) | 1 (12.5%) |
| Race | | | | |
| White | 12 (57.1%) | 7 (77.8%) | 10 (62.5%) | 4 (50.0%) |
| Black | 2 (9.5%) | 0 | 1 (6.3%) | 0 |
| Asian | 4 (19.0%) | 1 (11.1%) | 2 (12.5%) | 2 (25.0%) |
| Not reported | 3 (14.3%) | 0 | 3 (18.8%) | 2 (25.0%) |
| Multiple | 0 | 1 (11.1%) | 0 | 0 |
| Age (months) | | | | |
| n | 21 | 9 | 16 | 8 |
| Mean (SD) | 12.85 (5.77) | 15.71 (5.68) | 2.23 (1.88) | 0.95 (0.56) |
| Median | 12.16 | 15.61 | 1.61 | 0.82 |
| Range | 6.1 – 22.4 | 6.3 – 23.5 | 0.2 – 5.6 | 0.4 – 1.8 |
| Weight (kg) | | | | |
| n | 21 | 9 | 16 | 8 |
| Mean (SD) | 9.40 (2.37) | 9.99 (2.69) | 3.94 (0.92) | 3.60 (0.85) |
| Median | 9.40 | 8.80 | 3.90 | 3.20 |
| Range | 5.4 – 15.1 | 7.0 – 14.0 | 2.7 – 6.0 | 3.0 - 5.5 |
| Height (cm) | | | | |
| n | 19 | 9 | 16 | 7 |
| Mean (SD) | 72.99 (7.99) | 77.41 (6.58) | 53.81 (4.51) | 51.29 (4.81) |
| Median | 72.00 | 78.00 | 53.55 | 51.00 |
| Range | 59.00 – 87.00 | 66.00 – 86.00 | 46.0 – 62.0 | 42.5 – 58.5 |
| BMI (kg/m²) | | | | |
| n | 19 | 9 | 16 | 7 |
| Mean (SD) | 16.93 (2.62) | 16.42 (2.39) | 13.43 (1.46) | 13.41 (2.41) |
| Median | 16.25 | 16.07 | 13.18 | 12.30 |
| Range | 13.6 – 24.2 | 13.4 – 20.3 | 10.4 – 16.1 | 10.6 – 17.2 |

FAS = full analysis set; BMI = body mass index; SD = standard deviation

Index events

The index VTE was confirmed in 99.0% (495/500) of children: 99.7% (334/335) of children in the rivaroxaban group and 97.6% (161/165) of children in the comparator group. The index events were classified by the CIAC as thrombosis of the 1) lower extremity, 2) caval vein, 3) renal vein, 4) portal vein, 5) right side of the heart, 6) lungs, 7) upper extremity (including the axillary and subclavian veins), 8) jugular vein, and 9) cerebral vein or sinuses. For children who presented with VTE in multiple locations, the CIAC assessed the main presentation of VTE, and grouped the child in a single class.

The most common index events were lower extremity VTE (rivaroxaban 112/335, 33.4% and comparator 53/165, 32.1%), CVST (rivaroxaban 74/335, 22.1% and comparator 43/165, 26.1%), and pulmonary

embolism (rivaroxaban 49/335, 14.6% and comparator 31/165, 18.8%). CVC-VTE was found in 127/500 (25.4%) children (90/335, 26.9% in rivaroxaban group and 37/165, 22.4% in comparator group).

Index event by location, age and treatment allocation is reported in **Table 12**.

**Table 7.** Index venous thrombosis-main clot location by age (FAS, Study 14372)

| Location of Event | 12-<18 years | | 6-<12 years | | 2-<6 years | | birth -<2 years | |
|---|---|---|---|---|---|---|---|---|
| | Rivaroxaban | Comparator | Rivaroxaban | Comparator | Rivaroxaban | Comparator | Rivaroxaban | Comparator |
| **All** | **N =184** | **N = 92** | **N = 67** | **N = 34** | **N = 47** | **N = 22** | **N = 37** | **N =17** |
| Lower extremity | 77 (41.8 %) | 31 (33.7 %) | 11 (16.4 %) | 8 (23.5 %) | 9 (19.1 %) | 5 (22.7 %) | 15 (40.5 %) | 9 (52.9 %) |
| Caval vein | 2 (1.1 %) | 0 | 1 (1.5 %) | 0 | 0 | 0 | 0 | 1 (5.9 %) |
| Portal vein | 1 (0.5 %) | 0 | 2 (3.0 %) | 1 (2.9 %) | 1 (2.1 %) | 0 | 1 (2.7 %) | 0 |
| Renal vein | 0 | 0 | 1 (1.5 %) | 0 | 0 | 0 | 3 (8.1 %) | 0 |
| Right side of the heart | 3 (1.6 %) | 2 (2.2 %) | 3 (4.5 %) | 2 (5.9 %) | 2 (4.3 %) | 1 (4.5 %) | 1 (2.7 % ) | 0 |
| Lung | 46 (25.0 %) | 29 (31.5 %) | 3 (4.5 %) | 0 | 0 | 2 (9.1 %) | 0 | 0 |
| Upper extremity | 27 (14.7 %) | 15 (16.3 %) | 7 (10.4 %) | 4 (11.8 %) | 4 (8.5 %) | 0 | 0 | 1 (5.9 %) |
| Jugular vein | 12 (6.5 %) | 6 (6.5 %) | 8 (11.9 %) | 2 (5.9 %) | 8 (17.0 %) | 2 (9.1 %) | 13 (35.1 %) | 1 (5.9 %) |
| Cerebral vein and sinus | 16 (8.7 %) | 9 (9.8 %) | 31 (46.3 %) | 17 (50.0 %) | 23 (48.9 %) | 12 (54.5 %) | 4 (10.8 %) | 5 (29.4 %) |
| **All CVST*** | **N = 16** | **N = 9** | **N = 31** | **N = 17** | **N = 23** | **N = 12** | **N = 4** | **N = 5** |
| CVST | 16 (100.0 %) | 9 (100.0 %) | 31 (100.0 %) | 17 (100.0 %) | 23 (100.0 %) | 12 (100.0 %) | 4 (100.0 %) | 5 (100.0 %) |
| **All non-CVC-VTE**** | **N = 139** | **N = 72** | **N = 20** | **N = 9** | **N = 5** | **N = 3** | **N = 7** | **N = 1** |
| Lower extremity | 76 (54.7 %) | 31 (43.1 %) | 9 (45.0 %) | 6 (66.7 %) | 3 (60.0 %) | 1 (33.3 %) | 2 (28.6 %) | 0 |
| Caval vein | 1 (0.7 %) | 0 | 1 (5.0 %) | 0 | 0 | 0 | 0 | 0 |
| Portal vein | 1 (0.7 %) | 0 | 1 (5.0 %) | 1 (11.1 %) | 1 (20.0% ) | 0 | 1 (14.3 %) | 0 |
| Renal vein | 0 | 0 | 1 (5.0 %) | 0 | 0 | 0 | 3 (42.9 %) | 0 |
| Right side of the heart | 1 (0.7 % ) | 1 (1.4 % ) | 1 (5.0 %) | 0 | 0 | 0 | 0 | 0 |
| Lung | 46 (33.1 %) | 29 (40.3 %) | 3 (15.0 %) | 0 | 0 | 2 (66.7 %) | 0 | 0 |
| Upper extremity | 9 (6.5 %) | 9 (12.5 %) | 2 (10.0 %) | 2 (22.2 %) | 0 | 0 | 0 | 1 (100.0 %) |
| Jugular vein | 5 (3.6 %) | 2 (2.8 %) | 2 (10.0 %) | 0 | 1 (20.0 %) | 0 | 1 (14.3 %) | 0 |
| **All CVC-VTE** | **N = 29** | **N = 11** | **N = 16** | **N = 8** | **N = 19** | **N = 7** | **N = 26** | **N = 11** |
| Lower extremity | 1 (3.4 %) | 0 | 2 (12.5 %) | 2 (25.0 %) | 6 (31.6 %) | 4 (57.1 %) | 13 (50.0 %) | 9 (81.8 %) |
| Caval vein | 1 (3.4 %) | 0 | 0 | 0 | 0 | 0 | 0 | 1 (9.1 %) |
| Portal vein | 0 | 0 | 1 (6.3 %) | 0 | 0 | 0 | 0 | 0 |
| Renal vein | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Right side of the heart | 2 (6.9 %) | 1 (9.1 %) | 2 (12.5 %) | 2 (25.0%) | 2 (10.5 %) | 1 (14.3 %) | 1 (3.8 %) | 0 |
| Lung | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Upper extremity | 18 (62.1 %) | 6 (54.5 %) | 5 (31.3%) | 2 (25.0 %) | 4 (21.1 %) | 0 | 0 | 0 |
| Jugular vein | 7 (24.1 %) | 4 (36.4 %) | 6 (37.5 %) | 2 (25.0%) | 7 (36.8 %) | 2 (28.6 %) | 12 (46.2 %) | 1 (9.1 %) |

FAS = full analysis set; CVC-VTE = catheter-related venous thromboembolism; CVST = cerebral vein and sinus thrombosis
*All children with CVST had their clot not in relation to the use of catheters.
** Excluding CVST

Risk factors at baseline

VTE was provoked by a single risk factor in 48.0%, by 2 risk factors in 29.2%, and by more than 2 risk factors in 10.4% of children. The most common persistent risk factors were major organ disease (16.6%) and active cancer (11.2%). Most common transient risk factors were major infectious disease (28.4%) and use of central venous catheter (25.2%)

Kidney function at baseline

Children were ineligible for the study if they had an eGFR less than 30 mL/min/1.73 m2, or, in children younger than 1 year, if they had a serum creatinine above the 97.5th percentile. Renal function was categorized as ≥80 mL/min, 50 to <80 mL/min, and 30 to <50 mL/min to allow comparisons to adult data from VTE rivaroxaban treatment studies. However, in children younger than 1 year, GFR estimating formulas have never been validated. For the purpose of analyses, a serum creatinine level below the 90$^{th}$ percentile, between the 90$^{th}$ and the 97.5$^{th}$ percentile, and above the 97.5$^{th}$ percentile were classified as a GFR of≥80 mL/min, 50 to <80 L/min, and <50 mL/min, respectively (Boer et al 2010). 465/500 children (rivaroxaban 310/335, 92.5% and comparator 155/165, 93.9%) had a creatinine clearance ≥80 ml/min, 23/500 children

(rivaroxaban 17/335, 5.1% and comparator 6/165, 3.6%) had creatinine clearance 50 to <80 ml/min, and 4/500 children (rivaroxaban 2/335, 0.6% and comparator 2/165,1.2%) <50 ml/min.

Initial anticoagulant therapy for index event

All children received initial parenteral anticoagulant treatment for the index event prior to study drug administration. Initial parenteral anticoagulant had a duration of at least 5 days in 97.4% of children.

Comparator study medication type

106/162 subjects in the SAF comparator group received LMWH/Fondaparinux, and 56/162 received vitamin K-antagonist (VKA). Distribution by age group is presented in **Table 13**.

**Table 8.** Comparator study medication type up to the end of main treatment period by age group (SAF, study 14372)

| Age Group | | Comparator |
|---|---|---|
| 12 - <18 years | n | 89 (100.0%) |
| | Study medication type: | |
| | LMWH / FONDAPARINUX | 48 ( 53.9%) |
| | VITAMIN K-ANTAGONIST | 41 ( 46.1%) |
| 6 - <12 years | n | 34 (100.0%) |
| | Study medication type: | |
| | LMWH / FONDAPARINUX | 26 ( 76.5%) |
| | VITAMIN K-ANTAGONIST | 8 ( 23.5%) |
| 2-<6 years | n | 22 (100.0%) |
| | Study medication type: | |
| | LMWH / FONDAPARINUX | 17 ( 77.3%) |
| | VITAMIN K-ANTAGONIST | 5 ( 22.7%) |
| < 2 years | n | 17 (100.0%) |
| | Study medication type: | |
| | LMWH / FONDAPARINUX | 15 ( 88.2%) |
| | VITAMIN K-ANTAGONIST | 2 ( 11.8%) |
| 0.5 -< 2 years | n | 9 (100.0%) |
| | Study medication type: | |
| | LMWH / FONDAPARINUX | 8 ( 88.9%) |
| | VITAMIN K-ANTAGONIST | 1 ( 11.1%) |
| Birth -< 0.5 years | n | 8 (100.0%) |
| | Study medication type: | |
| | LMWH / FONDAPARINUX | 7 ( 87.5%) |
| | VITAMIN K-ANTAGONIST | 1 ( 12.5%) |

Notes: LMWH / FONDAPARINUX category includes subjects who received LMWH and/or fondaparinux and/or unfractionated heparin only as study medication up to the end of main treatment period.

Of the 91 available children who received comparator, treatment compliance for the main treatment period could not be calculated for 1 child because dispensed medication was not returned. Of the 90 remaining children with compliance calculations, 1 child (1.1%) had a compliance <50%, 4 (4.4%) had a compliance between 50 and 80%, and 85 (94.4%) had a compliance ≥80%.

For the entire (main and extended) treatment period, treatment compliance could not be addressed for 1 of the 91 available children who received comparator because dispensed medication was not returned. Of the remaining 90 children in the comparator group, 2 (2.2%) had a treatment compliance <50%,8 (8.9%) had a compliance between 50 and 80%, and 79 (87.8%) had a compliance≥80%.

## Numbers analysed

The full analysis set (FAS) included all randomised children, 335 children in the rivaroxaban group and 165 patients in the comparator group. The safety analysis set (SAF, n=491)) included all randomised children who had received at least one dose of study medication. The per-protocol set (PPS, n=485) included all children included in FAS without major protocol deviations.

## Outcomes and estimation

**Primary efficacy outcome (recurrent VTE):**

Main treatment period

**Table 9.** Incidences of primary efficacy outcomes during the main treatment period (FAS, study 14372)

| | | Rivaroxaban | | Comparator | |
|---|---|---|---|---|---|
| Index event | Location | Incidence | 95% CI | Incidence | 95% CI |
| Any | Any | 1.2% (4/ 335) | 0.4 - 3.0% | 3.0% (5/ 165) | 1.2 - 6.6% |
| | lower extremity | 1.8% (2/ 112) | | 5.7% (3/ 53) | |
| | lung | 2.0% (1/ 49) | | 3.2% (1/ 31) | |
| | upper extremity* | 2.6% (1/ 38) | | 0.0% (0/ 20) | |
| | CVST | 0.0% (0/ 74) | | 2.3% (1/ 43) | |
| CVST | Any | 0.0% (0/ 74) | 0.0 - 4.8% | 2.3% (1/ 43) | 0.1 - 11.8% |
| CVC-VTE | Any | 0.0% (0/ 90) | 0.0 - 3.9% | 0.0% (0/ 37) | 0.0 - 8.3% |
| Non-CVC-VTE | Any | 2.3% (4/ 171) | 0.8 - 5.6% | 4.7% (4/ 85) | 1.6 - 11.2% |
| (excluding CVST) | lower extremity | 2.2% (2/ 90) | | 7.9% (3/ 38) | |
| | lung | 2.0% (1/ 49) | | 3.2% (1/ 31) | |
| | upper extremity | 9.1% (1/ 11) | | 0.0% (0/ 12) | |

CI = confidence interval; CVC = central venous catheter; CVST = cerebral vein and sinus thrombosis; FAS = full analysis set; VTE = = venous thromboembolism
Incidence = number of subjects having the event in the time window / number at risk
number at risk = number of subjects in reference population
*Upper extremity venous thrombosis includes axillary and subclavian vein thrombosis.

In the safety analysis set, the primary efficacy outcome occurred in 1.2% (4/329) in the rivaroxaban group (95% CI 0.4-3.0%) and in 3.1% (5/162) in the comparator group (95% CI 1.2%-6.7%) in the main study treatment period.

Analysed by per protocol set, the primary efficacy outcome occurred in 1.2% (4/327) in the rivaroxaban group (95% CI 0.4-3.1%) and in 3.2% (5/158) in the comparator group (95% CI 1.3%-6.9%) in the main study treatment period.

All recurrent VTEs in the rivaroxaban group occurring during the main treatment period occurred in children aged between 12 and 18 years (4/184; 2.2%;95% CI 0.7 - 5.3%). In the comparator group, recurrent VTE

occurred in 3 of the 92 children aged between 12 and 18 years (3.3%; 95% CI 0.9 - 8.6%), in 1 of the 34 children aged between 6 and 12 years (2.9%; 95 CI 0.2% - 15.1%) and in 1 of the 22 children aged between 2 and 6 years (4.5%; 95% CI 0.2 - 20.7%). Details of these events are summarised in **Tables 15** and **16**.

**Table 10.** Listing of children with primary recurrent efficacy events during main treatment in the rivaroxaban group (FAS, study 14372)

| | | | | Recurrent VTE | | |
|---|---|---|---|---|---|---|
| Age/Sex/Weight* | Index Event | Index event location | Risk factors | Day of occur-rence | Presentation of occurrence | Treatment at time of occurrence |
| 16.1yr/F/56 kg | non-CVC-VTE | Lower extremity | Persistent and transient risk factors | 22 | Lower extremity | Heparins |
| 14.3yr/F/62.8 kg | non-CVC-VTE | Upper extremity | Unprovoked | 28 | Upper extremity | Rivaroxaban tablet o.d. ** |
| 16.7yr/M/110.4 kg | non-CVC-VTE | Lower extremity | Persistent risk factor | 6 | Lower extremity | Rivaroxaban suspension o.d. ** |
| 13.2yr/M/58.6 kg | non-CVC-VTE | Lung | Persistent and transient risk factors | 5 | Lung | Heparins |

CVC = central venous catheter; F = female; yr = years; M = male; o.d. = once daily; VTE = venous thromboembolism;
*Body weight at the time of an event is presented. If not available, baseline weight is used.
** General term used in table; original term: QD

**Table 11.** Listing of children with primary recurrent efficacy events during main treatment in the comparator group (FAS, study 14372)

| | | | | Recurrent VTE | | |
|---|---|---|---|---|---|---|
| Age/Sex/Weight* | Index Event | Index event location | Risk factors | Day of occur-rence | Presentation of occurrence (location) | Treatment at time of occurrence |
| 16.9yr/F/55 kg | non-CVC-VTE | Lower extremity | Persistent and transient risk factors | 6 | Lower extremity | VKA** |
| 16.0yr/F/70 kg | non-CVC-VTE | Lower extremity | Unprovoked | 12 | Lower extremity | Tinzaparin |
| 17.2yr/F/95 kg*** | non-CVC-VTE | Lower extremity | Transient risk factor | 6 | Lower extremity | Enoxaparin |
| 6.7yr/F/23 kg | CVST | CVST | Transient risk factor | 30 | CVST | VKA |
| 3.4yr/M/15.5 kg | non-CVC-VTE | Lung | Persistent risk factor | 5 | Lung | Dalteparin |

CVC = central venous catheter; CVST = cerebral vein and sinus thrombosis; F = female; yr = years; M = male; VTE = venous thromboembolism; VKA = vitamin K antagonist therapy
*Body weight at the time of an event is presented. If not available, baseline weight is used.
** Treatment was 'missing' for the day of occurrence and is thus blank in Table 14.2.1 / 96, however treatment with VKA was documented in Listing 16.2.5 / 5
*** Child also had a recurrent VTE in the extended treatment period. An additional (secondary) index event location was lung.

The incidence of recurrent VTE during the main treatment period was 0.5% (1/204; 95% CI 0.0 - 2.5%; location lower extremity) in children who received rivaroxaban as suspension and 2.4% (3/125; 95% CI 0.7 - 6.6%; location lower extremity, lung, upper extremity) in children who received rivaroxaban as tablets.

Primary efficacy outcome during extended treatment:

A total of 135 subjects in the rivaroxaban group and 63 subjects in the comparator group participated in the first extended treatment period. Only 2 subjects <2 years of age were incluced in the rivaroxaban group, and only 1 subject in the comparator group.

During Extension 1 (month 3 to 6), 1/46 children (2.2%; 95% CI 0.1-10.9%) in the comparator group had recurrent VTE. During Extension 2 (month 6 to 9), 1/38 children (2.6%; 95% CI 0.1-13.4%) in the rivaroxaban group and 1/19 children (5.3%; 95% CI 0.3-24.4%) in the comparator group had recurrent VTE. During Extension 3 (month 9 to 12), no recurrent VTE occurred.

Primary efficacy outcome after stop of study treatment

During the post-study treatment period >2 and ≤ 30 days after stop of study treatment, there were 2 children (both in the comparator group) with a primary efficacy outcome, i.e. recurrent VTE. Neither child had received local anticoagulant therapy in the days between stop of study treatment and occurrence of the recurrent VTE.

Secondary efficacy outcome (composite of recurrent VTE and asymptomatic deterioration)

During the main study treatment period, the secondary efficacy outcome (composite of recurrent VTE and asymptomatic deterioration) occurred in 5/335 children (1.5%; 95% CI 0.6-3.4%) in the rivaroxaban group and in 6/165 children (3.6%; 95% CI 1.6-7.6%) in the comparator group.

For the comparator, the event of asymptomatic deterioration on repeat imaging occurred in a subject aged 12-<18 years (weight group >/= 50 kg); for rivaroxaban, this event occurred in a subject aged 2-<6 years (weight group 10-<20 kg).

**Other outcomes involving efficacy**

**Table 12.** Incidences of other efficacy outcomes during the main treatment period (FAS, study 14372)

| | | Rivaroxaban N = 335 | | Comparator N = 165 | |
|---|---|---|---|---|---|
| | | Incidence | 95% CI | Incidence | 95% CI |
| **Composites** | Recurrent VTE + major bleeding | 4 (1.2%) | 0.4 - 3.0% | 7 (4.2%) | 2.0 - 8.4% |
| | Recurrent VTE + asymptomatic deterioration + no relevant change on repeat imaging | 21 (6.3%) | 4.0 - 9.2% | 19 (11.5%) | 7.3 - 17.4% |
| | Recurrent VTE + other clinically significant thrombosis | 5 (1.5%) | 0.6 - 3.4% | 6 (3.6%) | 1.6 - 7.6% |
| **Individual outcomes** | Major bleeding | 0 | | 2 (1.2%) | |
| | Recurrent VTE | 4 (1.2%) | | 5 (3.0%) | |
| | Asymptomatic deterioration | 1 (0.3%) | | 1 (0.6%) | |
| | No relevant change on repeat imaging | 16 (4.8%) | | 13 (7.9%) | |
| | Normalization without recurrent VTE | 128 (38.2%) | 33.0 - 43.5% | 43 (26.1%) | 19.8 - 33.0% |
| | Fatal or non-fatal pulmonary embolism | 1 (0.3%) | 0.0 - 1.6% | 1 (0.6%) | 0.0 - 3.1% |
| | Other clinically significant thrombosis | 1 (0.3%) | | 2 (1.2%) | |

FAS = full analysis set; VTE = venous thromboembolism
Note: Incidence = number of subjects having the event in the time window / number at risk
number at risk = number of subjects in reference population
*Upper extremity venous thrombosis includes axillary and subclavian vein thrombosis.

Thrombotic burden at repeat imaging

The thrombotic burden assessment was based on the comparison of the repeat imaging test at the end of the main treatment period with the imaging test of the index event and is reported only for children who did not have a recurrent VTE (**Table 18**). Imaging location and methods used are summarised in **Table 19**.

**Table 13.** Thrombotic burden assessment at repeated imaging at the end of the main treatment period including recurrent VTE (FAS, study 14372)

| Outcome | Rivaroxaban N=335 (100%) | Comparator N= 165 (100%) |
|---|---|---|
| Thrombotic burden assessment at repeated imaging including recurrent VTE | 335 (100.0%) | 165 (100.0%) |
| Normalized | 128 (38.2%) | 43 (26.1%) |
| Improved | 129 (38.5%) | 75 (45.5%) |
| Uncertain | 57 (17.0%) | 28 (17.0%) |
| No relevant change | 16 ( 4.8%) | 13 ( 7.9%) |
| Deterioration | 1 ( 0.3%) | 1 ( 0.6%) |
| Recurrent VTE | 4 ( 1.2%) | 5 ( 3.0%) |

VTE = venous thromboembolism; FAS = full analysis set

**Table 14.** Repeat imaging locations and methods (FAS, study 14372)

| Location Method | Rivaroxaban N=315 (100%) | Comparator N=152 (100%) |
|---|---|---|
| Lower extremity | 86 ( 27.3%) | 35 ( 23.0%) |
| Ultrasound | 84 ( 26.7%) | 35 ( 23.0%) |
| CT scan | 1 ( 0.3%) | 0 |
| Other | 1 ( 0.3%) | 0 |
| Vena cava | 2 ( 0.6%) | 0 |
| Ultrasound | 2 ( 0.6%) | 0 |
| Portal vein | 4 ( 1.3%) | 1 ( 0.7%) |
| Ultrasound | 3 ( 1.0%) | 1 ( 0.7%) |
| MRI | 1 ( 0.3%) | 0 |
| Renal vein | 4 ( 1.3%) | 0 |
| Ultrasound | 3 ( 1.0%) | 0 |
| CT scan | 1 ( 0.3%) | 0 |
| Heart, right | 2 ( 0.6%) | 1 ( 0.7%) |
| Ultrasound | 1 ( 0.3%) | 0 |
| MRI | 1 ( 0.3%) | 0 |
| Other | 0 | 1 ( 0.7%) |
| Lung | 43 ( 13.7%) | 23 ( 15.1%) |
| CT scan | 30 ( 9.5%) | 15 ( 9.9%) |
| Ultrasound* | 7 ( 2.2%) | 3 ( 2.0%) |
| Other | 5 ( 1.6%) | 5 ( 3.3%) |
| MRI | 1 ( 0.3%) | 0 |
| Upper extremity deep vein* | 11 ( 3.5%)* | 12 ( 7.9%)* |
| Ultrasound | 10 ( 3.2%)* | 11 ( 7.2%)* |
| MRI | 1 ( 0.3%) | 1 ( 0.7%) |
| Jugular vein | 9 ( 2.9%) | 2 ( 1.3%) |
| Ultrasound | 7 ( 2.2%) | 1 ( 0.7%) |
| MRI | 1 ( 0.3%) | 1 ( 0.7%) |
| CT scan | 1 ( 0.3%) | 0 |
| CVST | 66 ( 21.0%) | 42 ( 27.6%) |
| MRI | 52 ( 16.5%) | 31 ( 20.4%) |
| CT scan | 13 ( 4.1%) | 10 ( 6.6%) |
| Other* | 1 ( 0.3%) | 1 ( 0.7%) |

FAS = full analysis set; CT = computed tomography; MRI = magnetic resonance imaging
* Upper extremity venous thrombosis includes axillary and subclavian vein thrombosis.

Sensitivity analysis for the primary efficacy outcome

Sensitivity analyses were performed in order to evaluate the potential influence of dropouts on the incidence of the primary efficacy outcome (i.e. recurrent VTE) during the main treatment period. In these analyses which included only children who were assigned to 3 months of study treatment, children with premature termination before the end (defined as day 83) of the main treatment period were assumed as having a hazard of recurrent VTE 1.5 times (scenario 1) and twice (scenario 2) as high as the hazard calculated including all patients within each treatment group, assuming informative censoring. For this sensitivity analysis, an exponential distribution for the time-to-event outcome, i.e. constant incidence rates (hazard), was assumed and the analysis was performed for each treatment group separately (**Table 20**).

**Table 15.** Sensitivity analysis of the primary efficacy outcome (FAS, study 14372)

| Missing not at random assumption for the rivaroxaban groups | Comparison | Incidences (95% CrI) | Risk ratio (95% CrI) |
|---|---|---|---|
| IMHR=1.0 | Rivaroxaban vs. Comparator | 1.2% (0.3-2.7%) vs. 3.1% (1.1-6.4%) | 0.38 (0.089-1.46) |
| IMHR=1.5 | Rivaroxaban vs. Comparator | 1.2% (0.3-2.7%) vs. 3.1% (1.0-6.3%) | 0.38 (0.090-1.49) |
| IMHR=2.0 | Rivaroxaban vs. Comparator | 1.2% (0.3-2.7%) vs. 3.1% (1.0-6.3%) | 0.38 (0.093-1.49) |

CrI = credible interval; IMHR = informative missingness hazard ratio; FAS = full analysis set

The results of the sensitivity analysis show that even if one assumes that dropouts in the rivaroxaban group are more likely (1.5 and 2.0 times more likely applying the respective IMHR) to have a primary efficacy outcome than those in the comparator group, the point estimates of the comparisons between rivaroxaban and comparator are similar. Therefore, there is no impact on the conclusions based on the results of the primary efficacy analysis.

## Ancillary analyses

An exploratory analysis from study 14372 in patients with confirmed cerebral vein and sinus thrombosis (CVST) was performed.

In addition to the efficacy and safety outcomes described for study 14372 above, a modified Rankin Scale, modified for assessment in young children, was applied to describe the functional outcome at the end of the main study treatment period at 3 months. Due to the large age range (birth to 17 years), a dichotomized version of the score was applied: children with a modified Rankin Scale score of 0-2 were classified as having a favourable outcome, while children with a modified Rankin Scale score of 3-6 were classified as having a poor outcome. Classification of the dichotomized paediatric modified Rankin score was based on the local investigator's assessment 'Increased help for activities of daily living: requirement of (more) help with activities of daily living as before the CVST' (if yes, outcome is scored as poor, if not, as favourable). A premorbid mRS of 0-2 for all patients was assumed. The blinded central adjudication committee evaluated this scale for each individual child based on the local assessment.

## Results

**Table 16.** Incidence rates of efficacy outcomes at the end of the main treatment period for all children (FAS of CVST paediatric population, study 14372)

| Outcomes | Rivaroxaban | | Comparator | |
|---|---|---|---|---|
| | Incidence | 95% Conf. Int | Incidence | 95% Conf. Int |
| Primary Efficacy Outcome (all index events combined) | 0.0% ( 0/ 73) | 0.0% - 4.9% | 2.4% ( 1/ 41) | 0.1% - 12.4% |
| cerebral vein and venous sinus | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| CVST | 0.0% ( 0/ 73) | 0.0% - 4.9% | 2.4% ( 1/ 41) | 0.1% - 12.4% |
| cerebral vein and venous sinus | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| Composite of symptomatic recurrent VTE and asymptomatic deterioration in thrombotic burden on repeat imaging | 0.0% ( 0/ 73) | 0.0% - 4.9% | 4.9% ( 2/ 41) | 0.9% - 16.1% |
| Symptomatic recurrent VTE | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| Asymptomatic deterioration on repeat imaging | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| Composite of symptomatic recurrent VTE and major bleeding | 0.0% ( 0/ 73) | 0.0% - 4.9% | 4.9% ( 2/ 41) | 0.9% - 16.1% |
| Symptomatic recurrent VTE | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| Major bleeding | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| Composite of symptomatic recurrent VTE and asymptomatic deterioration and no change in repeat imaging | 6.8% ( 5/ 73) | 2.7% - 14.8% | 14.6% ( 6/ 41) | 6.6% - 28.5% |
| Symptomatic recurrent VTE | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| Asymptomatic deterioration on repeat imaging | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |
| No change on repeat imaging | 6.8% ( 5/ 73) | | 9.8% ( 4/ 41) | |
| Normalization on repeat imaging without confirmed symptomatic recurrent VTE | 24.7% ( 18/ 73) | 15.5% - 36.1% | 14.6% ( 6/ 41) | 6.6% - 28.5% |
| Fatal or non-fatal pulmonary embolism | 0.0% ( 0/ 73) | 0.0% - 4.9% | 0.0% ( 0/ 41) | 0.0% - 7.6% |
| Composite of symptomatic recurrent VTE and other clinically significant thrombosis | 0.0% ( 0/ 73) | 0.0% - 4.9% | 2.4% ( 1/ 41) | 0.1% - 12.4% |
| Symptomatic recurrent VTE | 0.0% ( 0/ 73) | | 2.4% ( 1/ 41) | |

Note: Incidence = # of events / # at risk, where:# of events = # of subjects having the event in the time window. # at risk = # of subjects in reference population.
Confidence Intervals calculated by applying the method of Blyth-Still-Casella.
*Upper extremity venous thrombosis includes axillary and subclavian vein thrombosis.
Subjects with more than one event component for a composite outcome are counted for all of the corresponding event components.

An end of treatment modified Rankin scale score of 0-2 was noted in 69/73 (95.5%) rivaroxaban treated subjects, and 38/41 (92.7%) comparator treated ones.

Thrombotic burden at repeat imaging

**Table 17.** Thrombotic burden assessment at repeated imaging at the end of the main treatment period including recurrent VTE (FAS of CVST population, study 14372)

| Outcomes | Rivaroxaban | Comparator |
|---|---|---|
| | Counts (%) | Counts (%) |
| Composite of symptomatic recurrent VTE and thrombotic burden assessment at repeated imaging | 73/ 73 (100.0%) | 41/ 41 (100.0%) |
| Normalized | 18/ 73 (24.7%) | 6/ 41 (14.6%) |
| Improved | 39/ 73 (53.4%) | 24/ 41 (58.5%) |
| Uncertain | 11/ 73 (15.1%) | 5/ 41 (12.2%) |
| No relevant change | 5/ 73 (6.8%) | 4/ 41 (9.8%) |
| Deterioration | 0/ 73 (0.0%) | 1/ 41 (2.4%) |
| Symptomatic recurrent VTE | 0/ 73 (0.0%) | 1/ 41 (2.4%) |

## Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application.

These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

**Table 18.** Summary of Efficacy for trial 14372

| | | | |
|---|---|---|---|
| **Title:** 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; the EINSTEIN Junior | | | |
| Study identifier | BAY 59-7939 / 14372<br>EudraCT 2014-000565-47<br>NCT02234843 | | |
| Design | Multicenter, open-label, active-controlled, randomized phase III study | | |
| | Duration of main phase:<br>Duration of Run-in phase:<br>Duration of Extension phase: | | 3 months (1 month in catheter-related-VTE in children < 2 years of age)<br>5-9 days (screening + initial parenteral anticoagulation)<br>3 blocks of 3 months each (if eligible) (2 blocks of 1 month each for catheter-related-VTE in children <2 years) |
| Hypothesis | No formal hypothesis | | |
| Treatments groups | Rivaroxaban (RIVA) | | Age and body weight-adjusted (OD, BID, or TID)<br>3 months (optional: 6, 9, 12 months) or 1 month (optional: 2, 3 months), in total 335 subjects |
| | Standard of care (SOC) | | As per standard of care (LMWH, fondaparinux, UFH, VKA)<br>3 months (optional: 6, 9, 12 months) or 1 month (optional: 2, 3 months), in total 165 subjects |
| Endpoints and definitions | Primary efficacy outcome | Primary efficacy outcome | Symptomatic recurrent VTE |
| | Secondary efficacy outcome | Secondary efficacy outcome | Composite of symptomatic recurrent VTE and asymptomatic deterioration at end of main treatment period |
| | | | |
| Database lock | 08 March 2019 (final release date of the clinical database) | | |
| **Results and Analysis** | | | |
| **Analysis description** | **Primary Analysis** | | |

| | | | | |
|---|---|---|---|---|
| Analysis population and time point description | Full analysis set (all randomised), main treatment period | | | |
| Descriptive statistics and estimate variability | Treatment group | RIVA | SOC | |
| | Number of subjects | 335 | 165 | |
| | Primary efficacy outcome | 1.2% (4/335) | 3.0% (5/165) | |
| | Variability | 95% CI: 0.4, 3.0% | 95% CI; 1.2, 6.6% | |
| | Secondary efficacy outcome | 1.5% (5/335) | 3.6% (6/165) | |
| | variability | 95% CI: 0.6, 3.4% | 95% CI: 1.6, 7.6% | |

## Analysis performed across trials (pooled analyses and meta-analysis)

Studies 11702 were 2 multi-center, randomized, open-label, assessor-blind, event-driven, non-inferiority studies for efficacy with a study treatment duration of 3, 6, or 12 months among adult subjects having DVT (one study) or PE with or without DVT (one study). The primary efficacy objective in these studies was to show that rivaroxaban was non-inferior to Enoxaparin and VKA (acenocoumarol or warfarin) in the treatment of patients with acute symptomatic DVT or PE in terms of preventing recurrent VTE.

An exploratory pooled analysis of studies 11702 and the paediatric study 14372, compared the incidences of selected efficacy events up to 3 months between treatment groups. The cumulative incidence of the primary endpoint and the corresponding Kaplan-Meier curves up to 3 months are presented in **Table 24** and **Figure 7** for the rivaroxaban treated patients and in **Table 25** and **Figure 8** for the comparator treated patients these trials.

**Table 19.** Cumulative rates of the primary efficacy outcome up to 3 months in the rivaroxaban (20 mg or equivalent) group (ITT populations, Einstein DVT and PE pooled and Einstein Junior)

| | Einstein DVT and PE pooled | | | | Einstein Junior Phase 3 | | | |
|---|---|---|---|---|---|---|---|---|
| Time Interval | N | Cum. # of Events | K-M Cum. Event Prob. (%) | K-M 95% CI (Lower-Upper limit) | N | Cum. # of Events | K-M Cum. Event Prob. (%) | K-M 95% CI (Lower-Upper limit) |
| Day 0 | 4150 | 0 | | | 335 | 0 | | |
| Day 1 - 7 | 4087 | 27 | 0.7 | 0.4 - 1.0 | 330 | 2 | 0.6 | 0.2 - 2.4 |
| Day 8 - 14 | 4054 | 38 | 0.9 | 0.7 - 1.3 | 330 | 2 | 0.6 | 0.2 - 2.4 |
| Day 15 - 21 | 4038 | 39 | 0.9 | 0.7 - 1.3 | 330 | 2 | 0.6 | 0.2 - 2.4 |
| Day 22 - 28 | 4021 | 46 | 1.1 | 0.8 - 1.5 | 324 | 4 | 1.2 | 0.5 - 3.2 |
| Day 29 - 60 | 3969 | 65 | 1.6 | 1.2 - 2.0 | 296 | 4 | 1.2 | 0.5 - 3.2 |
| Day 61 - 98 | 0 | 69 | 1.7 | 1.3 - 2.1 | 0 | 4 | 1.2 | 0.5 - 3.2 |

Notes: K-M Cum. Event Prob. (%) = Kaplan-Meier estimates of the cumulative probability for an event, calculated as 100 * (1 minus the Kaplan-Meier estimates of the survival function).
Kaplan-Meier confidence limits are calculated using the log-log transformation for estimating the standard error.
Time intervals display number of subjects (N) left at risk, cumulative event numbers, cumulative probabilities and confidence limits at end of interval.
CI = Confidence Interval, K-M = Kaplan-Meier., cum. = cumulative

**Figure 7.** Kaplan-Meir curve of the primary efficacy outcome up to 3 months in the rivaroxaban (20 mg or equivalent) group (ITT populations, Einstein DVT and PE pooled and Einstein Junior)

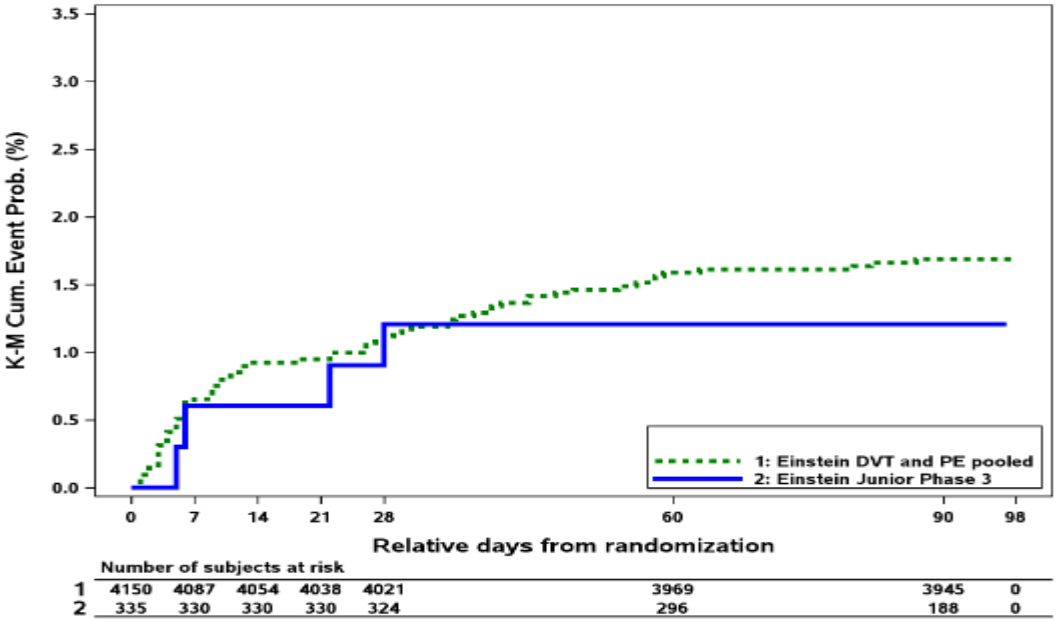
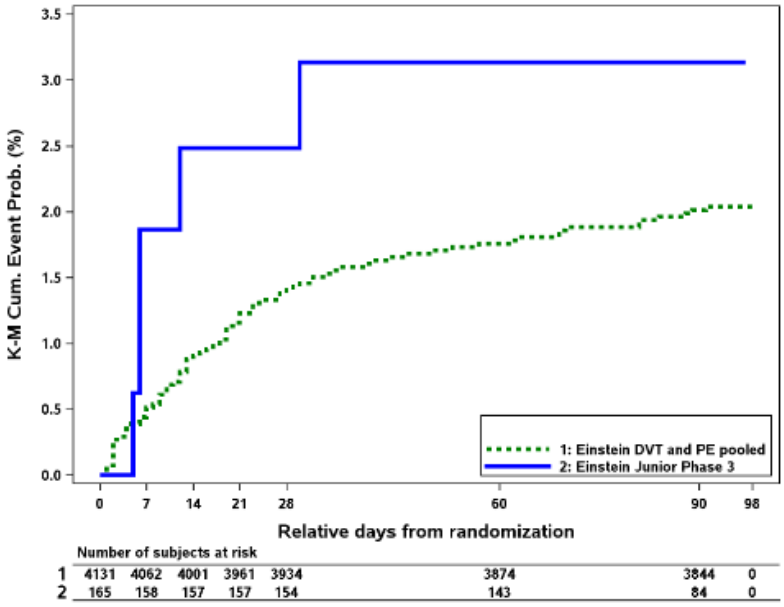



**Table 20.** Cumulative rates of the primary efficacy outcome up to 3 months in the anti-coagulants, comparator group (ITT populations, Einstein DVT and PE pooled and Einstein Junior)

| | Einstein DVT and PE pooled | | | | Einstein Junior Phase 3 | | | |
|---|---|---|---|---|---|---|---|---|
| Time Interval | N | Cum. # of Events | K-M Cum. Event Prob. (%) | K-M 95% CI (Lower-Upper limit) | N | Cum. # of Events | K-M Cum. Event Prob. (%) | K-M 95% CI (Lower-Upper limit) |
| Day 0 | 4131 | 0 | | | 165 | 0 | | |
| Day 1 - 7 | 4062 | 21 | 0.5 | 0.3 - 0.8 | 158 | 3 | 1.9 | 0.6 - 5.7 |
| Day 8 - 14 | 4001 | 37 | 0.9 | 0.7 - 1.2 | 157 | 4 | 2.5 | 0.9 - 6.5 |
| Day 15 - 21 | 3961 | 50 | 1.2 | 0.9 - 1.6 | 157 | 4 | 2.5 | 0.9 - 6.5 |
| Day 22 - 28 | 3934 | 57 | 1.4 | 1.1 - 1.8 | 154 | 4 | 2.5 | 0.9 - 6.5 |
| Day 29 - 60 | 3874 | 71 | 1.8 | 1.4 - 2.2 | 143 | 5 | 3.1 | 1.3 - 7.4 |
| Day 61 - 98 | 0 | 82 | 2.0 | 1.6 - 2.5 | 0 | 5 | 3.1 | 1.3 - 7.4 |

Notes: K-M Cum. Event Prob. (%) = Kaplan-Meier estimates of the cumulative probability for an event, calculated as 100 * (1 minus the Kaplan-Meier estimates of the survival function).
Kaplan-Meier confidence limits are calculated using the log-log transformation for estimating the standard error.
Time intervals display number of subjects (N) left at risk, cumulative event numbers, cumulative probabilities and confidence limits at end of interval.
CI = Confidence Interval, K-M = Kaplan-Meier., cum. = cumulative

**Figure 8.** Kapalan-Meier curve of the primary efficacy outcome up to 3 months in the rivaroxaban (20 mg or equivalent) group (ITT populations, Einstein DVT and PE pooled and Einstein Junior)




## Clinical studies in special populations

**Patients with renal impairment**

Subjects with more than moderately impaired kidney dysfunction were excluded from the study.

There were very few subjects with moderate kidney dysfunction (30 to < 50 mL/min/1.73m2); 2 in each treatment group (for children above 1 year of age; eGFR cannot be calculated for children below 1 year of age). There were 23 subjects with mild kidney dysfunction (50 to < 80 mL/min/1.73m2), 17 rivaroxaban treated and 6 in comparator group. A primary efficacy outcome event was not recorded for any of these patients.

## *Supportive studies*

**Study 17618:**

Phase 1/2. Multicenter, open-label 7 days study of oral bodyweight adjusted rivaroxaban in suspension given b.i.d. or t.i.d. Primary objective: PK/PD profile. Secondary objectives: major/CRNM bleeding; recurrent VTE, asymptomatic deterioration

Initially, children from birth to <6 months with catheter-related venous or arterial thrombosis with at least 2 weeks of anticoagulant therapy were recruited. With an amendment, children from birth to <6 months with venous or arterial thrombosis with at least 5 days of anticoagulant therapy were recruited.

**Results:**

10 children were valid for full analysis set (FAS). None of the 10 children had a confirmed symptomatic recurrent VTE during the treatment period or during the 30-day post study treatment period. Repeat imaging was available in 9/10 (90%) children in FAS. Of the 9 children who had repeat imaging, the thrombus burden was normalized in 5 (55.6%) children, improved in 3 (33.3%) children and unchanged in 1 (11.1%) child. None of the children had asymptomatic deterioration of the thrombus burden.

**Study 14373:**

Phase 2. Multicenter, single-arm 30 days study of oral age- and bodyweight-adjusted rivaroxaban in suspension or tablets. Primary objective: major/CRNM bleeding. Secondary objective: recurrent VTE; asymptomatic deterioration of thrombotic burden on repeat imaging; PK/PD profile of 30 days oral rivaroxaban treatment.

Children aged 6-18 years with at least 2 months of anticoagulant treatment for a VTE (at least 6 weeks for catheter-related thrombosis) were included. 64 children formed the Full Analysis Set. 63 treated subjects received treatment and formed the Safety Analysis Set: 11 children aged 12-18 years received rivaroxaban o.d. as tablets. 13 children aged 12-18 years received comparator. 13 children aged 6-12 years received rivaroxaban o.d. as tablets. 19 children aged 6-12 years were administered rivaroxaban b.i.d. as oral suspension. 7 children aged 6-12 years received comparator (comparator cohort removed during the course of the study).

**Results**

None of the 63 children treated with study medication had a confirmed symptomatic recurrent VTE during the treatment period and during the 30-day post treatment period. Repeat imaging was available in only 43 children (repeat imaging was introduced via an amendment during the course of the study). None of these had an asymptomatic deterioration of the thrombus burden upon repeat imaging. In the 33 children treated with rivaroxaban who had repeat imaging, the thrombus burden was normalized (9/33; 27.3%), improved (21/33; 63.6%) or unchanged (3/33; 9.1%). In the 10 children treated with comparator who had repeat imaging, the thrombosis burden was normalized (3/10; 30%), improved (4/10; 40%) and not evaluable (3/10; 30%). The distribution of adjudication outcomes was similar across age cohorts, formulations and treatment arms.

**Study 14374:**

Phase 2. Multicenter, single-arm 30 days study of oral age- and bodyweight-adjusted rivaroxaban in suspension. Primary objective: major/CRNM bleeding. Secondary objectives: recurrent VTE; asymptomatic deterioration of thrombotic burden on repeat imaging; PK/PD profile of 30 days oral rivaroxaban treatment.

Children aged 6 months to <6 years with at least 2 months of anticoagulant treatment for a VTE (at least 6 weeks for catheter-related thrombosis) were included. 46 children were valid for FAS and SAF: 25 children aged 2-6 years and 15 children aged 6 months-2 years received diluted rivaroxaban ready-to-use suspension b.i.d. 6 children aged 2-6 years received anticoagulation comparator (comparator cohort removed during the course of the study).

**Results**

None of the 46 children treated with study medication had a confirmed symptomatic recurrent VTE during the treatment period or during the 30-day post treatment period. Repeat imaging was available in 38/46 (82.6%) children. Of the 33 children in rivaroxaban groups, who had repeat imaging, the thrombus burden was

normalized in 10/33 (30.3%) children, improved in 19/33 (57%) children, and unchanged in 4/33 (12.1%) children. Of the 5 children in comparator group, who had repeat imaging, the thrombus burden was normalized in 1/5 (20%) child, improved in 3/5 (60%) children, and unchanged in 1/5 (20%) child.

## 2.5.2. Discussion on clinical efficacy

### *Design and conduct of clinical studies*

The pivotal study 14372 was an open-label, active-controlled, randomised phase III study to assess efficacy and safety of age- and body weight-adjusted rivaroxaban as compared to standard of care in children from birth to <18 years with acute VTE after at least 5 days of initial parenteral anticoagulant therapy. To reflect this the CHMP considered that the indication should be amended and specify the time period on parenteral anticoagulant therapy before rivaroxaban treatment can be initiated  Enrolment was staggered by age, starting with children aged 12 to <18 years; each subsequent age cohort was opened via a protocol amendment once the bodyweight-adjusted dose regimen had been determined in Phase 2 for the respective age groups. The study design is overall deemed adequate, and in line with the PIP and the scientific advice that the MAH received, in which the open-label design and was endorsed and the limitations were recognised with regards to feasibility of performing an adequately powered study in children providing statistically significant results, due to the rarity of VTE in the paediatric population.

As discussed in the Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease, there are some important differences between younger children and adults regarding clinical factors for VTE, course and response to VTE treatment. Therefore, relying entirely on an extrapolation of efficacy and safety data from adults based on similar exposure and PD data to support the paediatric indication would not be sufficient, and efficacy and safety data from children would still be required. Existing data in an indication already approved in adults (e.g.: treatment and secondary prevention of DVT/PE) could however, complement the results of the paediatric studies and further support the use in children based on the totality of the data without requesting a study powered to test a formal statistical hypothesis in children.

The inclusion criteria allowed for a broad range of VTE subtypes, encompassing several VTE locations that have not been studied in adults; although this is reasonable, given the differences in VTE locations among children as compared to adults, this also suggests a heterogeneity in the study population in terms of VTE subtype . The children included were required to be expecting treatment with anticoagulant therapy for at least three months (one month for catheter-related thromboses in children <2 years); the rationale for expecting such length of therapy was at the discretion of the investigator. A large proportion of children with subacute or chronic CVC-VTE were included (44% of the CVC-VTE population), despite the aim of the study being at acute paediatric VTE, and a large proportion of children with CVC-VTE had asymptomatic VTE (40%). The exclusion criteria were considered reasonable, excluding in particular children at high risk of bleeding, children with more than moderately reduced renal function and children with hepatic impairment.

Children with severe bleeding disorders were included, such as haemophilia with inhibitors. However, there were only 5 children (out of the 500 randomised children in the study) with underlying inherited or acquired bleeding disorders; their contribution to the overall data is considered negligible.

There is no centrally approved anticoagulant product in the EU for treatment or secondary prevention of VTE in children. In large, the recommended choices and posologies for the comparator group are in line with widely recognised ACCP guidelines from 2012. VKA-treated patients were monitored to an INR 2-3. Most subjects in the comparator group were treated with LMWH with or without UFH; according to the MAH, it was assumed that monitoring of anti-FXa-activity in line with the ACCP guidelines would be performed, however, no data on actual monitoring and results thereof have been provided. In addition, the compliance for the comparator group could not be robustly assessed, as in 72/162 children, locally dispensed comparator treatment was used and thus could not be returned for compliance check.

The outcomes are deemed clinically relevant, with the primary efficacy outcome being symptomatic recurrent VTE, similar to the pivotal DVT/LE studies in adults. The composite secondary endpoint consists of the primary endpoint combined with asymptomatic deterioration at repeat imaging; the latter is considered clinically relevant as it could relate to an increased risk of complications and affect treatment decisions. As noted in the Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease, thrombotic burden definitions available in adults have not been validated in children, which prevents for inclusion as part of the primary efficacy endpoint in confirmatory trials; however, deterioration in thrombotic burden has been associated with poor long term outcomes and post-thrombotic syndrome in both adult and paediatric thrombosis. All primary and secondary efficacy outcome events were adjudicated by a blinded adjudication committee.

Neither VTE-related death or all-cause mortality were included in the primary or secondary efficacy outcomes, which is considered a draw-back of the study design; only fatal pulmonary embolism was included as an 'other efficacy outcome'. Since no claim vs comparator were prespecified, and the actual deaths reported during the study (see Clinical safety section of this report) were deemed to be unrelated to either study treatment or VTE, omission of these endpoints is not considered of major importance.

The study aimed at assessing incidences of the primary efficacy outcomes; no claims with regards to rivaroxaban versus comparator were prespecified. Primarily, incidence proportions were calculated for the efficacy outcomes by treatment group at the end of the main treatment period for the combined data over all children and by classification of index event. In exploratory analyses statistical models were fitted in order to compare outcomes between rivaroxaban and standard of care.

### *Efficacy data and additional analyses*

The incidence of the primary efficacy outcome event was low in both treatment groups, with numerically fewer events in the rivaroxaban group (4/329 = 1.2%; 95% CI 0.4-3.0%) in rivaroxaban group, and 5/162 = 3.1%; 95% CI 1.2-6.7%) in the comparator group during the main study treatment period of 3 months (1 month for children < 2 years with catheter-related thrombosis). Asymptomatic deterioration on repeat imaging, which constituted the other part of the composite secondary efficacy outcome, occurred in only one child in each treatment group during main treatment period.

The assessment of thrombotic burden at repeated imaging showed normalisation or improvement in more than two thirds of subjects, with a higher proportion of subjects achieving normalisation in the rivaroxaban group. The incidences for the primary efficacy outcome during the main treatment period are slightly lower than what has been described for paediatric recurrent VTE during anticoagulation; in the REVIVE trial (Massicotte P et al 2003), recurrent VTE occurred in 5.6% and 10% of patients during three months of treatment with reviparin-sodium and UFH/oral anticoagulation respectively, however, absolute number of participants was low (36 and 40 in each treatment group). During the extended treatment period, only three

primary efficacy events occurred in total (1 in the rivaroxaban group at day 223 and 2 in the comparator group, at day 98 and 211); all events occurred in adolescents and affected the same location as the index event in two of three subjects. All subjects had a non-CVC-VTE index event. A large discrepancy between suspected and adjudicated primary efficacy outcome events is noted: during the main and extended treatment periods, recurrent VTE was adjudicated in 8.3% of 60 suspected cases in the rivaroxaban group and in 21.9% of 32 suspected cases in the comparator group, respectively, and was thus refuted in the vast majority of cases. This discrepancy is considered explained primarily by the fact that also events that were locally considered to be refuted were to be reported.

135 subjects with CVST, non-CVC-VTE or CVC-VTE >/= 2 years were included in the first extension period (3-6 months) in the rivaroxaban group (63 subjects in comparator group) and 53 subjects with CVST, non-CVC-VTE or CVC-VTE >/= 2 years were included in the second extension period (6-9 months) in the rivaroxaban group (24 subjects in the comparator group). However, exposure beyond 3 months was very limited in the youngest children, with only two subjects <2 years of age in the rivaroxaban group and one subject in the comparator group.

The four primary efficacy events during main treatment in the rivaroxaban group occurred in adolescents (which was the most populous age group) and were non-CVC-related VTE occurring at same site as index event. In both treatment groups, the recurrent VTEs occurred early, with no primary efficacy events after day 30.

### *Additional expert consultation*

The Scientific Advisory Group on Cardiovascular Issues (SAG-CVS) was asked to provide their view on the following issues:

1. **The MAH is proposing an indication including children of all ages. However, the experience of using rivaroxaban in children younger than 2 years is limited and safety in this age group is currently questioned.**
    a. **Please discuss the adequacy of extrapolating efficacy and safety data from adults to the youngest children based on the known age-related development of haemostasis.**
    b. **Please discuss the acceptability of the increased incidence of bleedings in this age group compare to standard of care (for treatment emergent bleedings in age group birth to < 0.5 years, incidence 5/15 children (33.3%) in the rivaroxaban group and 0/8 (0%) in the comparator SOC group; for age group 0.5-2 years, incidence 8/21 (38.1%) in the rivaroxaban group and 3/9 (33.3%) in comparator group.**
    c. **Should particular precautions be applied in the youngest children if rivaroxaban is approved in all age groups?**

    The experts advised that the optimal target International Normalised Ratios (INRs) for anti-coagulation in the paediatric population are not precisely known due to the lack of randomised data in these patients. This uncertainty therefore limits any extrapolation between adult and paediatric patients. The Group noted that the results from the submitted randomised trial in very young patients were limited, but larger than any other randomized studies. This is due to the rarity of the condition in this population but also the difficulties to enrol such patients in randomised trials.

Despite these limitations, the Group considered that the use of rivaroxaban in all paediatric patients is sufficiently supported by the results from the trial, as a similar efficacy and safety profile to what has been previously shown in adult patients was observed. With regards to the small increased incidence of bleedings in the rivaroxaban treated patients, the experts advised that the nature of these events, for which no sequalae was reported, did not raise concern for the use of rivaroxaban also in the very young patients or the need for specific precautions in this age group. One expert suggested PK monitoring in some very specific paediatric groups to establish anti-coagulation ranges in e.g. small bowel disease. The Group stressed the difficulties associated with SOC in terms of administration and monitoring and considered that the benefits of having an oral preparation available in clinical in practice outweighs the small increased risk of bleeding. In this context the group noted the benefits of making rivaroxaban also available to the youngest age group.

Due to the small number of patients included in the trial, the experts emphasized the need for a post-authorisation study to better characterise the safety profile of rivaroxaban in the paediatric population as the only way of further characterising the use of rivaroxaban in the very young children.

2. **The proposed paediatric target population includes some types of VTE for which extrapolation of efficacy and safety from adults is not possible, and thus the evidence relies more heavily on the observed paediatric data from the phase III study. This is of particular concern for cerebral vein and sinus thrombosis (CVST) and catheter-related thrombosis (CVC-VTE).**

    a. **Concerning CVST, please discuss the importance and acceptability of the relatively high risks of bleedings as indicated from the pivotal clinical study (incidence of major bleeding + clinically relevant non-major bleeding 6.8% in the rivaroxaban group and 2.3 % in comparator SOC group; incidence of any bleedings 35.1% in the rivaroxaban group vs 30.2% in comparator group) considering that this is a condition which is known to be associated with intracerebral haemorrhage. Are there subpopulations (age, disease states, underlying disease conditions) or instances of CVST where the risk of bleeding may be too high? Is the proposed treatment duration (at least 3 months) adequate? Is there a need for particular precautions/monitoring? Based on what is known about paediatric CVST, please discuss the adequacy of extrapolating data on efficacy and safety of treatment with rivaroxaban in older children with CVST to children < 2 years of age, for whom there is very little data in the phase III study (no data at all for children < 0.5 years of age)?**

    b. **As reflected in the literature the overall benefits of anticoagulation are generally less clear for CVC-VTE than for other paediatric VTE-subtypes. Considering this, please discuss the acceptability of the documented bleeding rates (treatment-emergent bleedings 31.0% in the rivaroxaban group vs 21.6% in the comparator SOC group). Also discuss the relevance of the duration of anticoagulation proposed in the current rivaroxaban SmPC (at least 1 month). Are there particular subpopulations or instances of CVC-VTE where the risk of bleeding is considered too high? Please discuss the relevance of data on efficacy and safety in subjects with chronic or sub-acute CVC-VTE (44% of the CVC-VTE population in study 14372) for the proposed target indication.**

The Group noted the imbalance in the incidence of bleedings between rivaroxaban and Standard of Care (SOC) treated patients with CVST and CVC-VTE. The Group advised that these findings are in line with

what has been observed in adult patients and are to be expected following treatment with an inhibitor of Factor Xa. Importantly, no intracranial bleeding was reported in patients treated with rivaroxaban. The Group, however, advised caution in patients with inflammatory intracranial conditions including meningitis, encephalitis and intracranial abscesses and recommended a contraindication for these conditions. The Group did not identify a need for any particular precautions in patients with CVST and CVC-VTE.

Regarding duration of treatment, the Group noted that in paediatric patients this has not been well defined and is largely extrapolated from adult data. The Group advised that duration of treatment in these patients as proposed by the MAH are in line with current treatment guidelines which recommend a 3-month course of anticoagulation for paediatric patients with provoked VTE and a shorter, 6-week course, of anticoagulation in certain instances such as CVC-VTE.

## 2.5.3. Conclusions on the clinical efficacy

The efficacy data provided are considered sufficient to support the use of rivaroxaban for the treatment and secondary prevention of VTE in children.

## *2.6. Clinical safety*

### *Patient exposure*

Paediatric safety data are available from 6 studies summarised in **Table 26**.

**Table 21.** Overview of rivaroxaban paediatric development program: relevant studies for Safety

| Study ID | Report ID | Treatment | | Number of children treated | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Formulation | Duration | Total | Age groups (years) | | | | |
| | | | | N | 12 to <18 | 6 to <12 | 2 to <6 | 0.5 to <2 | <0.5 |
| **Phase 1** | | | | | | | | | |
| 12892 | PH-38444 | Suspension/ tablet | single dose | 59 | 0 (suspension)<br>9 (tablet) | 16 (suspension)<br>8 (tablet) | 16 (suspension) | 10 (suspension) | - |
| 17992 | PH-38996 | Suspension | single dose | 47 | - | 16 (suspension) | 13 (suspension) | 16 (suspension) | 2 |
| **Phase 1/2** | | | | | | | | | |
| 17618 | PH-39733 | Suspension | 7 days | 10 | - | - | - | - | 10 |
| **Phase 2** | | | | | | | | | |
| 14373 | PH-38995 | Suspension/ tablet | 30 days | 43+20[a] | 11 (tablet)<br>13 (comparator) | 13 (tablet)<br>19 (suspension)<br>7 (comparator) | - | - | - |
| 14374 | PH-39333 | Suspension | 30 days | 40+6[a] | - | - | 25 (suspension)<br>6 (comparator) | 15 (suspension) | - |
| **Phase 3** | | | | | | | | | |
| 14372 | PH-40166 | Suspension/ tablet | ≥ 3 months[b] | 329+162[a] | 74 (suspension)<br>106 (tablet)<br>89 (comparator) | 49 (suspension)<br>18 (tablet)<br>34 (comparator) | 45 (suspension)<br>1 (tablet)<br>22 (comparator) | 21 (suspension)<br>9 (comparator) | 15 (suspension)<br>8 (comparator) |
| **Total** | | | | 528+188[a] | 200+102[a] | 139+41[a] | 100+28[a] | 62+9[a] | 27+8[a] |

ID = identification number; CVC-VTE = central venous catheter venous thromboembolism, catheter-related venous thromboembolism

[a] Comparator (standard of care)

[b] ≥ 1 month for children under 2 years old with CVC-VTE

However, the MAH considered that for most age cohorts, pooling did not increase the sample size substantially (beyond the Phase 3 study). In addition, pool-ability of the Phase 2 and Phase 3 data was limited due to the different rivaroxaban dosing schedules, and duration and timing of study treatment. Therefore, pivotal safety data for this application were from the large phase III study 14372. Information from the other paediatric studies was provided as supportive data.

In the phase III study 14372, patients aged birth to < 18 years, received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to receive either rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). Rivaroxaban was administered as either tablets or as granules for oral suspension. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC VTE up to 3 months) in total. Cumulative treatment durations are provided in **Tables 27** and **28** for children aged ≥2 years and < 2 years with CVC VTE respectively.

**Table 22.** Study 14372 - Cumulative treatment duration for children with non-CVC-VTE, CVST, or CVC-VTE aged ≥ 2 years (SAF)

| Treatment duration | Rivaroxaban N=304 (100%) | Comparator N=151 (100%) |
|---|---|---|
| Cumulative interval | | |
| At least 1 month | 294 (96.7%) | 144 (95.4%) |
| At least 2 months | 290 (95.4%) | 143 (94.7%) |
| At least 3 months | 199 (65.5%) | 92 (60.9%) |
| At least 6 months | 80 (26.3%) | 37 (24.5%) |
| At least 9 months | 40 (13.2%) | 20 (13.2%) |
| At least 12 months | 9 (3.0%) | 6 (4.0%) |

CVC-VTE = central venous catheter venous thromboembolism, catheter-related venous thromboembolism; CVST = cerebral vein and/or sinus thrombosis; SAF = safety analysis set
Treatment duration does not include gaps in study drug.

**Table 23.** Study 14372 - Cumulative treatment duration for children with CVC-VTE aged < 2 years (SAF)

| Treatment duration | Rivaroxaban N=25 (100%) | Comparator N=11 (100%) |
|---|---|---|
| Cumulative interval | | |
| At least 1 week | 24 (96.0%) | 11 (100.0%) |
| At least 2 weeks | 23 (92.0%) | 11 (100.0%) |
| At least 3 weeks | 23 (92.0%) | 11 (100.0%) |
| At least 1 month | 19 (76.0%) | 7 (63.6%) |
| At least 2 months | 12 (48.0%) | 6 (54.5%) |
| At least 3 months | 5 (20.0%) | 3 (27.3%) |

CVC-VTE = central venous catheter venous thromboembolism, catheter-related venous thromboembolism; SAF = safety analysis set

Mean treatment duration during the main treatment period for children with CVST, non-CVC-VTE, or aged ≥2 years with CVC-VTE treated with rivaroxaban was 88.0 days and for children treated with comparator 86.7 days. For children aged <2 years with CVC-VTE treated with rivaroxaban, mean treatment duration during main period was 29.8 days and in children treated with comparator 29.5 days. The overall mean study treatment duration was for children with CVST, non-CVC-VTE, or CVC-VTE aged ≥ 2 years 149.0 days in the rivaroxaban group and 146.3 days in the comparator group. For children with CVC-VTE <2 years, the overall mean study treatment duration was 60.9 days for rivaroxaban and 62.7 days for the comparator.

For children 12->18 years, the majority had a non-CVC VTE as the index event while for subjects 6<12 and 2->6 years, CVST was most common. For subjects from birth to <2 years, CVC-VTE was the most common index event. A majority of VTE cases were provoked, 90.4% (rivaroxaban) and 81.8% (comparator). The most frequent persistent risk factors were major organ disease (18.8% rivaroxaban vs 12.1% comparator) and active cancer (11.9% rivaroxaban vs 9.7% comparator). A total of 95.1% of the children received at least one concomitant medication. Please refer also to clinical efficacy assessment for a presentation of demographic data.

## *Adverse events*

Overview of adverse events in phase III study 14372

A summary of TEAEs in SAF during the main treatment period is found in **Table 29**.

**Table 24.** Study 14372 - Overall summary of number of children with TEAEs during the main treatment period i.e. up to the end of the main treatment period (SAF)

| | Rivaroxaban N=329 (100%) | Comparator N=162 (100%) |
|---|---|---|
| Number (%) of subjects with TEAEs | | |
| **Any AE** | **274 ( 83.3%)** | **122 ( 75.3%)** |
| Maximum intensity for any AE | | |
| MILD | 130 ( 39.5%) | 55 ( 34.0%) |
| MODERATE | 102 ( 31.0%) | 44 ( 27.2%) |
| SEVERE | 42 ( 12.8%) | 23 ( 14.2%) |
| **Any study drug-related AE** | **90 ( 27.4%)** | **27 ( 16.7%)** |
| Maximum intensity for study drug-related AE | | |
| MILD | 64 ( 19.5%) | 18 ( 11.1%) |
| MODERATE | 22 ( 6.7%) | 7 ( 4.3%) |
| SEVERE | 4 ( 1.2%) | 2 ( 1.2%) |
| **Any AE related to procedure required by the protocol** | **12 ( 3.6%)** | **15 ( 9.3%)** |
| **Any AE leading to discontinuation of study drug** | **11 ( 3.3%)** | **3 ( 1.9%)** |
| **Any SAE** | **71 ( 21.6%)** | **32 ( 19.8%)** |
| Any study drug-related SAE | 7 ( 2.1%) | 2 ( 1.2%) |
| Any SAE related to procedures required by the protocol | 0 | 0 |
| Any SAE leading to discontinuation of study drug | 7 ( 2.1%) | 1 ( 0.6%) |
| **AE with outcome death** | **1 ( 0.3%)** | **0** |

Note: Treatment-emergent is defined as event that occurred after randomization until last intake of study drug plus 2 days
SAF = safety analysis set; AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event

After the main treatment phase, at least one TEAE occurred in 130 (26.5%) of the 491 children: 91 (27.7%) in the rivaroxaban group and 39 (24.1%) in the comparator group. SAEs were reported for 13/329 (4.0%) children in the rivaroxaban group, and 6/162 (3.7%) children in the comparator group.

In total, 421/491 children (85.7%) had at least one AE (i.e. also taking into account AEs that were not TEAEs): 88.1% in the rivaroxaban group and 80.9% in the comparator group. In the rivaroxaban group, AEs were reported as recovered/resolved, recovering/resolving, not recovered/resolved in 50.5%, 10.9%, and 25.4% of children, as compared to 37.0%, 8.6% and 27.2% of children in the comparator group. The worst outcome was reported as "fatal" for two children in the rivaroxaban group. At least one SAE occurred in 122 (24.8%) children: 25.5% in the rivaroxaban group and 23.5% in the comparator group. SAEs were reported as recovered/resolved, recovering/resolving, not recovered/resolved in 21.9%, 1.2%, and 1.8% or children, respectively, in the rivaroxaban group, and in 18.5%, 1.2%, and 2.5% of children in the comparator group. As stated above, the worst outcome was reported as "fatal" for two children in the rivaroxaban group (see section below: 4.4 Serious adverse events and deaths).

Common Adverse events

The most common TEAEs occurring with an incidence of ≥ 10% were (SAF, main treatment period):

- Rivaroxaban: headache (17%), epistaxis (11.2%), vomiting (10.6%), pyrexia (10.3%)
- Comparator: headache (14.8%), epistaxis (11.1%)

## *Serious adverse event/deaths/other significant events*

Incidences by MedDRA terms were described for the following AEs defined as AEs of special interest: (1) Liver-related AEs or concurrent elevations of ALT >5x ULN and total bilirubin >2x ULN, (2) Thrombocytopenia or treatment-emergent platelet count< 50 109/L and (3) Treatment-emergent drug-related allergic skin reactions, allergic systemic reactions.

One case in the rivaroxaban group was reported with a liver-related AESI (0.3%), and 1 case in each treatment group was observed with thrombocytopenia (0.3% rivaroxaban vs 0.6% comparator), for suspected/confirmed allergic skin/systemic reactions, there were 24 (7.3%) in the rivaroxaban group and 13 (8.0%) in the comparator group (SAF, main treatment period), see also below under the heading "Laboratory findings".

ALT > 5x ULN (upper limit of normal) with TB > 2x ULN was reported for 2/329 children (0.6%) in the rivaroxaban group during the main treatment period. One event was related to cardiogenic shock prior to heart transplant; it was not considered as treatment emergent as the child had discontinued study medication more than 2 days before the event. For the other event, ALT and TB had already increased prior to study drug medication.

Bleeding events

*Definitions of bleedings and principal safety outcome (major + CRNM bleedings)*

The principal safety outcome in study 14372 was the composite of treatment-emergent overt major bleeding and CRNM bleeding, as defined in **Table 30**.

**Table 25.** Definition of bleeding events in study 14372

| | |
|---|---|
| **Major bleeding** | • Overt bleeding *and any of the following* |
| | • Associated with a fall in Hb of 2 g/dL or more, or |
| | • Leading to a transfusion of the equivalent of ≥ 2 units of packed red blood cells or whole blood in adults, or |
| | • Occurring in a critical site (e.g. intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal) or |
| | • Contributing to death |
| **Clinically relevant non-major bleeding** | • Overt bleeding not meeting the criteria for major bleeding, *but associated with any of the following*: |
| | • Medical intervention, or |
| | • Unscheduled contact (visit or telephone call) with a physician, or |
| | • Discomfort for the child such as pain, or |
| | • (temporary) cessation of study treatment, or |
| | • Impairment of activities of daily life (such as loss of school days or hospitalization) |
| **Trivial bleeding** | • All other overt bleeding episodes not meeting the criteria for clinically relevant non-major bleeding |

Hb = hemoglobin

Treatment-emergent was defined as occurring after randomization until the last intake of study drug plus 2 days. Bleeding events with onset on the day of randomization are considered only if the investigator stated that the event was related to the study drug.

*Principal safety outcome during main treatment period*

Clinically relevant bleeding occurred in 10 children (3%; all CRNM bleeding) in the rivaroxaban group and in 3 children (1.9%; 2 major bleeding, 1 CRNM bleeding) in the comparator group. No major bleeding was seen under rivaroxaban treatment. The principal safety outcome by index event and age group during the main treatment period is shown in **Table 31**.

**Table 26.** Study 14372 - Incidence of treatment-emergent principal safety outcome during the main treatment period by index event and age group (SAF)

| Index event | Rivaroxaban | | Comparator | |
|---|---|---|---|---|
| | Incidence | 95% CI | Incidence | 95% CI |
| **All index events** | **3.0% ( 10/ 329)** | **1.6% - 5.5%** | **1.9% ( 3/ 162)** | **0.5% - 5.3%** |
| CVST | 6.8% ( 5/ 74) | 2.7% - 14.6% | 2.3% ( 1/43) | 0.1% - 11.8% |
| CVC-VTE | 3.4% ( 3/ 87) | 0.9% - 9.1% | 0.0% ( 0/37) | 0.0% - 8.3% |
| Non-CVC-VTE | 1.2% ( 2/168) | 0.2% - 4.2% | 2.4% ( 2/82) | 0.4% - 7.9% |
| **Age: 12 - < 18 years** | | | | |
| **All index events** | **1.7% (3/ 180)** | **0.5% - 4.7%** | **2.2% (2/ 89)** | **0.4% - 7.3%** |
| CVST | 12.5% (2/ 16) | 2.3% - 35.4% | 0.0% (0/ 9) | 0.0% - 29.9% |
| CVC-VTE | 0.0% (0/ 28) | 0.0% - 10.7% | 0.0% (0/ 11) | 0.0% - 25.0% |
| Non-CVC-VTE | 0.7% (1/ 136) | 0.0% - 3.7% | 2.9% (2/ 69) | 0.5% - 9.3% |
| **Age: 6 - < 12 years** | | | | |
| **All index events** | **3.0% (2/ 67)** | **0.5% - 9.6%** | **0.0% (0/ 34)** | **0.0% - 9.0%** |
| CVST | 6.5% (2/ 31) | 1.2% - 20.0% | 0.0% (0/ 17) | 0.0% - 18.4% |
| CVC-VTE | 0.0% (0/ 16) | 0.0% - 19.8% | 0.0% (0/ 8) | 0.0% - 34.9% |
| Non-CVC-VTE | 0.0% (0/ 20) | 0.0% - 15.4% | 0.0% (0/ 9) | 0.0% - 29.9% |
| **Age: 2 - < 6 years** | | | | |
| **All index events** | **6.5% (3/ 46)** | **1.8% - 17.7%** | **0.0% (0/ 22)** | **0.0% - 13.9%** |
| CVST | 4.3% (1/ 23) | 0.2% - 19.8% | 0.0% (0/ 12) | 0.0% - 23.6% |
| CVC-VTE | 11.1% (2/ 18) | 2.0% - 32.5% | 0.0% (0/ 7) | 0.0% - 37.7% |
| Non-CVC-VTE | 0.0% (0/ 5) | 0.0% - 50.0% | 0.0% (0/ 3) | 0.0% - 63.2% |
| **Age: Birth - < 2 years** | | | | |
| **All index events** | **5.6% (2/ 36)** | **1.0% - 18.6%** | **5.9% (1/ 17)** | **0.3% - 27.8%** |
| CVST | 0.0% (0/ 4) | 0.0% - 52.7% | 20.0% (1/ 5) | 1.0% - 65.7% |
| CVC-VTE | 4.0% (1/ 25) | 0.2% - 18.5% | 0.0% (0/ 11) | 0.0% - 25.0% |
| non-CVC-VTE | 14.3% (1/ 7) | 0.7% - 55.4% | 0.0% (0/ 1) | 0.0% - 95.0% |
| **Age: 0.5 - < 2 years** | | | | |
| **All index events** | **4.8% ( 1/ 21)** | **0.2% - 21.8%** | **11.1% ( 1/ 9)** | **0.6% - 44.3%** |
| CVST | 0.0% ( 0/ 4) | 0.0% - 52.7% | 25.0% ( 1/ 4) | 1.3% - 75.1% |
| CVC-VTE | 0.0% ( 0/ 15) | 0.0% - 21.3% | 0.0% ( 0/ 4) | 0.0% - 52.7% |
| Non-CVC-VTE | 50.0% ( 1/ 2) | 2.5% - 97.5% | 0.0% ( 0/ 1) | 0.0% - 95.0% |
| **Age: Birth - < 0.5 years** | | | | |
| **All index events** | **6.7% ( 1/ 15)** | **0.3% - 30.2%** | **0.0% ( 0/ 8)** | **0.0% - 34.9%** |
| CVST | ( 0/ 0) | | 0.0% ( 0/ 1) | 0.0% - 95.0% |
| CVC-VTE | 10.0% ( 1/ 10) | 0.5% - 44.4% | 0.0% ( 0/ 7) | 0.0% - 37.7% |
| Non-CVC-VTE | 0.0% ( 0/ 5) | 0.0% - 50.0% | ( 0/ 0) | |

Note: Treatment-emergent is defined as event that occurred after randomization until last intake of study drug plus 2 days. Incidence = number of subjects having the event in the time window / number at risk. Number at risk = number of subjects in reference population.

Confidence intervals calculated by applying the method of Blyth-Still-Casella.

CI = confidence interval; CVC-VTE = central venous catheter-related venous thromboembolism; CVST = cerebral vein and/or sinus thrombosis; SAF = safety analysis set

Principal safety outcomes in the rivaroxaban group occurred in individual children in all bodyweight groups except 'weight 20 to < 30 kg'. In the comparator group, 2/77 children with a bodyweight of ≥ 50 kg and 1/7 children with a body weight of 5 to < 10 kg had a principal safety outcome.

4.0% (5/125) of children taking rivaroxaban tablets and 2.5% (5/204) taking the rivaroxaban suspension reported a principal safety outcome vs 1.9% (3/162) of children taking the comparator.

*Principal safety outcome during extended treatment period*

During extended treatment period 1, there was 1 principal safety outcome (CRNM) in the rivaroxaban group, the event occurred in the age group 12-<18 years. During extended treatment period 2, there were 2 principal safety outcomes (CRNM) in the rivaroxaban group and 1 in the comparator group. The event in the comparator group and one of the events in the rivaroxaban group occurred in the age group 12-<18 years while the other event in the rivaroxaban group occurred in the age group <2 years. During extended

treatment period 3, no primary safety outcomes were reported. No major bleedings were recorded during treatment extension.

Thus, overall, the incidence of the principal safety outcome in the SAF were during the main and extended treatment periods in total 4.0% (13/329) and 2.5% (4/162).

*Principal safety outcome during follow-up period*

Two incidences of principal safety outcome were reported in the rivaroxaban group during follow-up period. One of the children was receiving anticoagulant therapy at the time of the event.

*All confirmed treatment-emergent bleedings during main treatment period*

The number of children with treatment-emergent bleeding by age groups during the main treatment period is displayed in **Table 32**.

**Table 27.** Study 14372 – Number of children with confirmed treatment-emergent bleeding during the main treatment period by age group, category and site (SAF)

| Age group<br>Bleeding category<br>Bleeding site | Rivaroxaban<br>N=329 | Comparator<br>N=162 |
|---|---|---|
| **Age: 12 to < 18 years** | **N=180 (100%)** | **N=89 (100%)** |
| Any confirmed | 76 ( 42.2%) | 27 ( 30.3%) |
| **Major bleeding** | **0** | **1 ( 1.1%)** |
| Respiratory tract | 0 | 1 ( 1.1%) |
| **Clinically relevant non-major bleeding** | **3 ( 1.7%)** | **1 ( 1.1%)** |
| Gastrointestinal tract | 2 ( 1.1%) | 0 |
| Genital | 1 ( 0.6%) | 0 |
| Nasal | 0 | 1 ( 1.1%) |
| **Trivial bleeding** | **74 ( 41.1%)** | **27 ( 30.3%)** |
| Genital* | 24 ( 13.3%) | 7 ( 7.9%) |
| Injection site* | 1 ( 0.6%) | 10 ( 11.2%) |
| Nasal* | 26 ( 14.4%) | 12 ( 13.5%) |
| Skin* | 25 ( 13.9%) | 8 ( 9.0%) |
| **Age: 6 - < 12 years** | **N=67 (100%)** | **N=34 (100%)** |
| Any confirmed | 20 ( 29.9%) | 9 ( 26.5%) |
| **Clinically relevant non-major bleeding** | **2 ( 3.0%)** | **0** |
| Nasal | 1 ( 1.5%) | 0 |
| Urinary tract | 1 ( 1.5%) | 0 |
| **Trivial bleeding** | **20 ( 29.9%)** | **9 ( 26.5%)** |
| Injection site* | 2 ( 3.0%) | 4 ( 11.8%) |
| Skin* | 7 ( 10.4%) | 3 ( 8.8%) |
| **Age: 2 - < 6 years** | **N=46 (100%)** | **N=22 (100%)** |
| Any confirmed | 10 ( 21.7%) | 6 ( 27.3%) |
| **Clinically relevant non-major bleeding** | **3 ( 6.5%)** | **0** |
| Gastrointestinal tract | 1 ( 2.2%) | 0 |
| Injection site | 1 ( 2.2%) | 0 |
| Nasal | 1 ( 2.2%) | 0 |
| **Trivial bleeding** | **8 ( 17.4%)** | **6 ( 27.3%)** |
| Skin* | 3 ( 6.5%) | 3 ( 13.6%) |
| **Age: 0.5 - < 2 years** | **N=21 (100%)** | **N=9 ( 100.0%)** |
| Any confirmed | 8 ( 38.1%) | 3 ( 33.3%) |
| **Major bleeding** | **0** | **1 ( 11.1%)** |
| Intracranial | 0 | 1 ( 11.1%) |
| **Clinically relevant non-major bleeding** | **1 ( 4.8%)** | **0** |
| Oral cavity | 1 ( 4.8%) | 0 |
| **Trivial bleeding** | **7 ( 33.3%)** | **2 ( 22.2%)** |
| Injection site* | 0 | 1 ( 11.1%) |
| Nasal* | 3 ( 14.3%) | 1 ( 11.1%) |
| **Age: Birth to < 0.5 years** | **N=15 (100%)** | **N=8 (100%)** |
| Any confirmed | 5 ( 33.3%) | 0 |
| **Clinically relevant non-major bleeding** | **1 ( 6.7%)** | **0** |
| Gastrointestinal tract | 1 ( 6.7%) | 0 |
| **Trivial bleeding** | **4 ( 26.7%)** | **0** |
| Gastrointestinal tract* | 2 ( 13.3%) | 0 |

* only events with at least ≥10% in any treatment group are reported
Note: Although a subject may have had 2 or more events, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator.
'Oral cavity' includes oral cavity and gingival only.
Treatment-emergent is defined as an event that occurred after randomization until last intake of study drug plus 2 days
SAF = safety analysis set

The incidence of confirmed treatment-emergent bleedings up to the end of main treatment period by weight group (safety analysis set) was also presented. In the lightest children i.e children included in the weight group<5 kg, the incidence was 5/13 (38.5%) in the rivaroxaban group vs 0/7 (0% in the comparator). In the group 5-<10 kg, the incidences were 40.0% vs 42.9%, in 10 - <20 kg 26.4% vs 26.1%, in 20 - <30 kg 26.2% vs 15.8%, in 30 - <40 kg 36.4% vs 23.1%, in 40 - <50 kg 26.9% vs 31.3% and in >= 50 kg 43.0% vs 32.5%.

Children with non-CVC-VTE had the highest incidence of treatment-emergent bleeding events (39.3% in the rivaroxaban group vs 29.3% in the comparator group) followed by children with CVST (35.1% rivaroxaban vs 30.2% comparator), and by children with CVC-VTE (31.0% rivaroxaban vs 21.6% comparator).

Analysis of incidence of all confirmed treatment-emergent bleedings up to the end of main treatment period by formulation, showed that 32.4% that received the rivaroxaban suspension, 42.4% that received rivaroxaban tablets and 27.8% that received the comparator had such event.

*All confirmed treatment-emergent bleedings during the overall duration of treatment*

Incidence of all confirmed treatment-emergent bleedings, for the overall duration of treatment (SAF) were also presented; 130/329 (39.5%) in the rivaroxaban group and 49/162 (30.3%) had such event. In the group birth<0.5 years, there were 6/15 (40%) with any confirmed bleeding in the rivaroxaban group and 0/8 (0%) in the comparator group.

*Composite of symptomatic recurrent VTE and major bleeding at the end of the main treatment period*

The incidence (95% CI) of the composite of symptomatic recurrent VTE and major bleeding (in FAS) was 1.2% (0.4-3.0%) in the rivaroxaban group and 4.2 % (2.0-8.4%) in the Comparator group.

Other safety outcomes: Menstrual bleedings and vascular events

Approximately one half to two thirds of the girls in the rivaroxaban group, and one third to two thirds of the children in the comparator group who had menstrual bleeding, had menstrual bleeding that was "more than usual" in intensity.

There were no myocardial infarctions, cerebrovascular accidents, non-CNS systemic reported.

***AEs in the other paediatric studies: phase I-II studies***

In none of the five phase I-II studies, deaths or major bleedings were reported for rivaroxaban treated subjects but CRNM bleedings and more trivial bleedings were reported. As presented above, the new granules for oral suspension formulation was not used in all these studies.

Two of the studies; 17992 (Phase 1) and 17618 (Phase 1/2) included subjects that were <0.5 years of age, in none of these studies any CRNM bleedings were reported. In total, these studies included 12 subjects that were <0.5 years of age (2+10 subjects).

In study 17992 (in which subjects received rivaroxaban granules for oral suspension formulation) it is stated that 2 children were included in Group C that enrolled Children with an age ≥ 2 months and no confirmed bleedings or TEAEs was recorded in this group.

In study 17618, 10 children from birth to <6 months were included (subjects received diluted "ready-to-use" suspension, n=4 and granules for oral suspension n=6). There was a non-TESAE of cardiac arrest. The cardiac arrest was occurred in infant patient with congenital hypoplastic left heart syndrome who completed the 7-day treatment course of rivaroxaban and was hospitalized with severe cardiac dysfunction and cardiac arrest nearly 4 weeks (27 days) after completion of rivaroxaban treatment. The event was considered unrelated to rivaroxaban. No death, major bleeding or other bleeding events occurred.

## Serious adverse events and deaths

The overall incidence of any TESAE across the two treatment groups was 21.6% in the rivaroxaban and 19.8% in the comparator group

The most commonly affected SOCs in the rivaroxaban group were 'blood and lymphatic system disorders' and 'gastrointestinal disorders'(3.0% each vs 1.9% each in the comparator group), whereas 'infections and infestations' and 'nervous system disorders' were more common in the comparator group (6.2% and 5.6%, respectively, vs 4.9% and 2.7% with rivaroxaban). In most cases, the events were reported as recovering/resolved or recovering/resolving.

The most common TESAEs with ≥ 4% incidence by age group are provided in **Table 33**.

**Table 28.** Study 14372 - Number of children with common (≥ 4%) TESAEs by age group during the main treatment period (SAF)

| **Primary system organ class**<br>**Preferred term** (MedDRA version 21.1) | **Rivaroxaban** | **Comparator** |
|---|---|---|
| **Age group: Birth -<0.5 years** | **N=15 (100%) [1]** | **N=8 (100%) [2]** |
| **Cardiac disorders** | | |
| Atrial tachycardia | 0 | 1 ( 12.5%) |
| Pericardial effusion | 1 ( 6.7%) | 0 |
| **Infections and infestations** | | |
| Bronchiolitis | 1 ( 6.7%) | 0 |
| Gastroenteritis rotavirus | 1 ( 6.7%) | 0 |
| Meningitis bacterial | 1 ( 6.7%) | 0 |
| Peritonitis | 0 | 1 ( 12.5%) |
| Urinary tract infection | 1 ( 6.7%) | 0 |
| Wound infection | 1 ( 6.7%) | 0 |
| **Investigations** | | |
| Oxygen saturation decreased | 0 | 1 ( 12.5%) |
| **Metabolism and nutrition disorders** | | |
| Fluid overload | 1 ( 6.7%) | 0 |
| Metabolic acidosis | 1 ( 6.7%) | 0 |
| **Nervous system disorders** | | |
| Cerebral infarction | 0 | 1 ( 12.5%) |
| Seizure | 0 | 1 ( 12.5%) |
| **Surgical and medical procedures** | | |
| Colostomy | 0 | 1 ( 12.5%) |
| **Age group: 0.5 -<2 years** | **N=21 (100%) [1]** | **N=9 (100%) [2]** |
| **Blood and lymphatic system disorders** | | |
| Febrile neutropenia | 1 ( 4.8%) | 0 |
| **Injury, poisoning and procedural complications** | | |
| Accidental overdose | 0 | 1 ( 11.1%) |
| Accidental underdose | 1 ( 4.8%) | 0 |
| Procedural haemorrhage | 1 ( 4.8%) | 0 |
| Subdural haemorrhage | 0 | 1 ( 11.1%) |
| **Nervous system disorders** | | |
| Epilepsy | 1 ( 4.8%) | 0 |
| **Surgical and medical procedures** | | |
| Sclerotherapy | 0 | 1 ( 11.1%) |
| **Age group: <2 years** | **N=36 (100%) [1]** | **N=17 (100%) [2]** |
| **Cardiac disorders** | | |
| Atrial tachycardia | 0 | 1 ( 5.9%) |
| **Infections and infestations** | | |
| Peritonitis | 0 | 1 ( 5.9%) |
| **Injury, poisoning and procedural complications** | | |
| Accidental overdose | 0 | 1 ( 5.9%) |
| Subdural haemorrhage | 0 | 1 ( 5.9%) |
| **Investigations** | | |
| Oxygen saturation decreased | 0 | 1 ( 5.9%) |
| **Nervous system disorders** | | |
| Cerebral infarction | 0 | 1 ( 5.9%) |
| Seizure | 0 | 1 ( 5.9%) |
| **Surgical and medical procedures** | | |
| Colostomy | 0 | 1 ( 5.9%) |
| Sclerotherapy | 0 | 1 ( 5.9%) |

The overall incidence of any drug-related TESAE was 2.1% in the rivaroxaban group and 1.2% in the comparator group (summarised in **Table 34**).

**Table 29**. Study 14372 - Number of children with study drug-related TESAEs by primary system organ class and preferred term during the main treatment period (SAF)

| **Primary system organ class**<br>**Preferred term** (MedDRA version 21.1) | **Rivaroxaban N=329 (100%)** | **Comparator N=162 (100%)** |
|---|---|---|
| Number (%) of subjects with at least one TEAE | 7 ( 2.1%) | 2 ( 1.2%) |
| **Eye disorders** | | |
| Retinal haemorrhage | 1 ( 0.3%) | 0 |
| **Gastrointestinal disorders** | | |
| Enterocolitis haemorrhagic | 1 ( 0.3%) | 0 |
| Gastric haemorrhage | 1 ( 0.3%) | 0 |
| **Injury, poisoning and procedural complications** | | |
| Procedural haemorrhage | 1 ( 0.3%) | 0 |
| Subdural haemorrhage | 0 | 1 ( 0.6%) |
| **Investigations** | | |
| Oxygen saturation decreased | 0 | 1 ( 0.6%) |
| **Renal and urinary disorders** | | |
| Urinary bladder haemorrhage | 1 ( 0.3%) | 0 |
| Urinary retention | 1 ( 0.3%) | 0 |
| **Vascular disorders** | | |
| Haemorrhage | 1 ( 0.3%) | 0 |

Note: Treatment-emergent is defined as event that occurred after randomization until last intake of study drug plus 2 days
A subject is counted only once within each preferred term or any primary system organ class.
MedDRA = Medical Dictionary for Regulatory Activities; SAF = safety analysis set; TEAE = treatment-emergent adverse event

There were two fatal events in the phase III study, both of which were assessed as unrelated to the study drug by the investigator.

## Laboratory findings

For the phase 3 study; laboratory parameters for Hb, platelets, ALT, creatinine, bilirubin/direct bilirubin were collected at screening and, with the exception of serum creatinine, at Visit 4; Day 90 (Visit 2; Day 30 for children with CVC-VTE aged < 2 years).

Treatment-emergent high or low laboratory abnormalities by laboratory category and treatment (safety analysis set) are presented in **Tables 35** and **36** respectively.

**Table 30.** Study 14372-Number of subjects with treatment-emergent high laboratory abnormalities by laboratory category and treatment (safety analysis set)

| Laboratory variable | Rivaroxaban (N=329) Num/Den(%) | Comparator (N=162) Num/Den(%) | TOTAL (N=491) Num/Den(%) |
|---|---|---|---|
| GENERAL CHEMISTRY | | | |
| Direct Bilirubin (mg/dL) in Serum | 6/191 ( 3.1%) | 4/ 88 ( 4.5%) | 10/279 ( 3.6%) |
| Bilirubin (mg/dL) in Serum | 9/274 ( 3.3%) | 8/117 ( 6.8%) | 17/391 ( 4.3%) |
| Creatinine (mg/dL) in Serum - Enzymatic Colorimetric Assay | 0/ 9 ( 0.0%) | 0/ 3 ( 0.0%) | 0/ 12 ( 0.0%) |
| Creatinine (mg/dL) in Serum - Jaffe Method | 0/ 3 ( 0.0%) | 0/ 3 ( 0.0%) | 0/ 6 ( 0.0%) |
| Alanine Aminotransferase (U/L) in Serum | 16/193 ( 8.3%) | 12/ 88 ( 13.6%) | 28/281 ( 10.0%) |
| HEMATOLOGY | | | |
| Hemoglobin (g/dL) in Blood | 19/275 ( 6.9%) | 5/124 ( 4.0%) | 24/399 ( 6.0%) |
| Platelets (GIGA/L) in Blood | 7/217 ( 3.2%) | 9/108 ( 8.3%) | 16/325 ( 4.9%) |

The denominator (Den) represents the number of subjects at baseline with a normal or lower than normal laboratory assessment who also had at least one valid laboratory value after start of treatment. Subjects with missing or high abnormal values at baseline are not included in the denominator.
The numerator (Num) represents the number of subjects with at least one high laboratory assessment after start of treatment who had a normal or lower than normal laboratory assessment at baseline.
Laboratory assessments measured within 2 days of treatment end are included.

**Table 31.** Study 14372-Number of subjects with treatment-emergent low laboratory abnormalities by laboratory category and treatment (safety analysis set)

| Laboratory variable | Rivaroxaban (N=329) Num/Den(%) | Comparator (N=162) Num/Den(%) | TOTAL (N=491) Num/Den(%) |
|---|---|---|---|
| GENERAL CHEMISTRY | | | |
| Direct Bilirubin (mg/dL) in Serum | 0/208 ( 0.0%) | 0/ 99 ( 0.0%) | 0/307 ( 0.0%) |
| Bilirubin (mg/dL) in Serum | 4/272 ( 1.5%) | 3/123 ( 2.4%) | 7/395 ( 1.8%) |
| Creatinine (mg/dL) in Serum - Enzymatic Colorimetric Assay | 0/ 8 ( 0.0%) | 0/ 3 ( 0.0%) | 0/ 11 ( 0.0%) |
| Creatinine (mg/dL) in Serum - Jaffe Method | 0/ 1 ( 0.0%) | 0/ 1 ( 0.0%) | 0/ 2 ( 0.0%) |
| Alanine Aminotransferase (U/L) in Serum | 5/281 ( 1.8%) | 2/123 ( 1.6%) | 7/404 ( 1.7%) |
| HEMATOLOGY | | | |
| Hemoglobin (g/dL) in Blood | 19/158 ( 12.0%) | 6/ 71 ( 8.5%) | 25/229 ( 10.9%) |
| Platelets (GIGA/L) in Blood | 16/269 ( 5.9%) | 6/125 ( 4.8%) | 22/394 ( 5.6%) |

The denominator (Den) represents the number of subjects at baseline with a normal or higher than normal laboratory assessment who also had at least one valid laboratory value after start of treatment. Subjects with missing or low abnormal values at baseline are not included in the denominator.
The numerator (Num) represents the number of subjects with at least one low laboratory assessment after start of treatment who had a normal or higher than normal laboratory assessment at baseline. Laboratory assessments measured within 2 days of treatment end are included.

During the main treatment period of the phase III study, a platelet count below 50x109/L was reported for 12/329 children (3.6%) in the rivaroxaban group, and for 3/162 children (1.9%) in the comparator group. All but 2 events were related to chemotherapy. Only one of those 2 cases was reported in the rivaroxaban group, and had started before use of rivaroxaban and could be explained by another concomitant medication.

No clinically relevant laboratory findings were found in the phase 1 and 2 studies.

### *Safety in special populations*

Out of 2 children with moderate kidney dysfunction, 1 had a principal safety outcome. No child in the comparator group and no child with mild kidney dysfunction had a principal safety outcome.

No clinical data is available in children with hepatic impairment since based on exclusion criterion 3, children presenting with hepatic disease associated with either coagulopathy leading to a clinically relevant bleeding risk, or ALT >5x ULN or TB >2x ULN with direct bilirubin >20% of the total were excluded.

## Safety related to drug-drug interactions and other interactions

Based on the physicochemical properties of rivaroxaban and based on PK data obtained in adults, in all studies children received rivaroxaban tablet or oral suspension during or closely after feeding or meal intake and with a typical serving of drink to ensure reliable rivaroxaban dosing in children. In line with data obtained in adults, a decrease in relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses also in children, even when taken with food. No further analyses on drug-food interactions in children were conducted.

Based on the data obtained in adults, concomitant use of strong inhibitors of both cytochrome P450 isoenzyme 3A4 (CYP3A4) and P-glycoprotein (P-gp), as well as concomitant use of strong inducers of CYP3A4 were excluded per protocol in all paediatric studies. In the integrated rivaroxaban popPK model for adult

patients, weak, moderate and strong CYP3A4 inhibitors, P-gp inhibitors and CYP3A4 inducers were identified as covariates. Therefore, the influence of these five classes of medications, when taken concomitantly and via administration routes which may result in relevant systemic exposure, on rivaroxaban clearance in children was explored. Overall, results did not indicate a new drug-drug interaction potential not already known from adults.

As an anticoagulant, rivaroxaban has the potential to interact with other drugs that influence the coagulation system. The potential for pharmacodynamic drug-drug interactions (LMWH, anti-platelet agents, NSAIDs, VKA) was studied in adults. No dedicated pharmacodynamic interaction studies were performed in children. As only a very limited number of bleeding events were observed in the paediatric studies, no meaningful sub-analysis could be performed to evaluate the potential pharmacodynamic interaction in children. It is however, expected that co-administration of antiplatelet or anti-inflammatory agents or anticoagulants will result in similar effects as those observed in adults.

## Discontinuation due to adverse events

**Table 37** summarises the incidence of TEAEs that led to discontinuation of study drug during the main treatment period of the phase III study by SOC and MedDRA PT.

**Table 32**. Study 14372-Number of children with TEAEs resulting in discontinuation of study drug due to adverse events during the main treatment period (SAF)

| **Primary system organ class**<br>**Preferred term** (MedDRA version 21.1) | **Rivaroxaban**<br>**N=329 (100%)** | **Comparator**<br>**N=162 (100%)** |
|---|---|---|
| **Number (%) of subjects with at least one such an AE** | **11 ( 3.3%)** | **3 ( 1.9%)** |
| **Blood and lymphatic system disorders** | | |
| Thrombocytopenia | 1 ( 0.3%) | 0 |
| **Cardiac disorders** | | |
| Low cardiac output syndrome | 1 ( 0.3%) | 0 |
| **Gastrointestinal disorders** | | |
| Large intestinal haemorrhage | 1 ( 0.3%) | 0 |
| Vomiting | 2 ( 0.6%) | 0 |
| **General disorders and administration site conditions** | | |
| Injection site haematoma | 0 | 1 ( 0.6%) |
| **Hepatobiliary disorders** | | |
| Hepatic function abnormal | 1 ( 0.3%) | 0 |
| **Injury, poisoning and procedural complications** | | |
| Procedural haemorrhage | 1 ( 0.3%) | 0 |
| Subcutaneous haematoma | 0 | 1 ( 0.6%) |
| Subdural haemorrhage | 0 | 1 ( 0.6%) |
| **Musculoskeletal and connective tissue disorders** | | |
| Pain in extremity | 1 ( 0.3%) | 0 |
| **Nervous system disorders** | | |
| Epilepsy | 1 ( 0.3%) | 0 |
| Headache | 1 ( 0.3%) | 0 |
| **Renal and urinary disorders** | | |
| Haematuria | 1 ( 0.3%) | 0 |
| Urinary bladder haemorrhage | 1 ( 0.3%) | 0 |
| Urinary retention | 1 ( 0.3%) | 0 |
| **Reproductive system and breast disorders** | | |
| Menorrhagia | 0 | 1 ( 0.6%) |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Pulmonary haemorrhage | 1 ( 0.3%) | 0 |
| **Vascular disorders** | | |
| Haemorrhage | 1 ( 0.3%) | 0 |

Note: Treatment-emergent is defined as event that occurred after randomization until last intake of study drug plus 2 days
A subject is counted only once within each preferred term or any primary system organ class
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SAF = safety analysis set; TEAE = treatment-emergent adverse event

A total of 4 (1.2%) of the 329 children in the rivaroxaban group who continued study medication after the main study treatment period discontinued study drug at least once due to an AE: the preferred terms reported were anaemia and haemorrhagic ovarian cyst, nephropathy, rash, and mastoidectomy. No discontinuations due to AEs were reported for the 162 children in the comparator group who continued study medication after the main study treatment period.

## Post marketing experience

Cases of rivaroxaban exposure in children outside the sponsor's paediatric clinical development program have been routinely reviewed in XARELTO PSURs /PBRERs and relates to exposure via parent, accidental use by children, medication errors, overdose and occasional intentional use for medical purpose.

Between the start of rivaroxaban marketing in 2008 and 15 JUN 2019 (data lock point for this analysis), the sponsor's global safety database accumulated 292 post marketing cases involving rivaroxaban use in children aged less than 18 year.

In 5 of the 292 cases, events of overdose (with 2 cases specifically reporting the event of intentional overdose) were reported: 1 non-serious case with an accidental overdose and 4 serious cases including 2 serious events of overdose, 1 serious event of intentional overdose and 1 non-serious event of intentional overdose. Altogether, in 37 (12.7%) of the 292 cases events of accidental exposure to product were reported, with 34 cases more specifically reporting the event of accidental exposure to product by child, and 1 of these overlapping with the non-serious event of accidental overdose. No fatalities were reported. 12 of the 41 cases reporting events of overdose and accidental exposure to product were assessed as serious and 29 were assessed as non-serious. Most of the cases were only reporting information on circumstances of exposure (medication error, overdose, etc.) without reference to any harm to patient's health. In 31 of the 41 cases the outcome of the reported events was reported as unknown or no information on the outcome of the events were reported. Only in 1 case the outcome of the event of accidental exposure to the product was reported as not recovered / not resolved at the time of the reporting. However, no symptoms were reported at the time of reporting. In 1 case in which rivaroxaban film-coated tablet was used for deep vein thrombosis, the outcome of the event of overdose was reported as recovered/ resolved with sequelae. In 8 of the 41 cases with reported events of overdose and accidental exposure to product, the outcome of the events was reported as recovered/resolved or recovering/resolving.

Bleeding was reported in 32/115 serious cases of children who were exposed to rivaroxaban outside the sponsor's paediatric clinical development program and in 40/292 cases overall, and comprised of 4 cases of gastrointestinal bleeding events, 9 cases of epistaxis, 8 cases of menorrhagia, 2 cases of vaginal haemorrhage, 1 case of menometrorrhagia, 1 case of penile haemorrhage, and 1 case each of periorbital haematoma and retinal haemorrhage.

Overall, no particular risk was identified in these case reviews resulting from rivaroxaban exposure in children aged less than 18 years.

## 2.6.1. Discussion on clinical safety

***Nature of safety data and extent of exposure***

Paediatric safety data in support for this application are derived from 6 studies: two phase 1 studies (single-dose, tablets/diluted/undiluted ready-to-use oral suspension in the first study, granules for oral suspension formulation in the second), one phase 1/2 study (7-day, diluted "ready-to-use" suspension and granules for oral suspension), two phase 2 studies (30 days, tablets and diluted ready-to-use oral suspension in the first, diluted ready-to-use suspension in the second) and one phase 3 study (>3 months, tablets or as granules for oral suspension). Safety analysis set (SAF) included all randomized children who received at least one dose of study medication: n= 528 patients. In the phase III, Study 14372, a total of 491 children; 329 rivaroxaban, 162 comparator, were included in the SAF; analysis of the SAF was performed according "as treated" and MAH's safety evaluation focused on "treatment-emergent" AEs i.e. TEAEs (events occurring after randomization until the last intake of study medication plus 2 days) that happened during the main treatment period.

As dosing of rivaroxaban cannot be reliably determined in children less than 6 months of age who at birth had less than 37 weeks of gestation, or have a body weight of less than 2.6 kg, or have had less than 10 days of oral feeding use in such patients is not recommended. .

The safety results from the Phase 1, 2 and 3 clinical studies were pooled as pre-specified. However, the MAH focused mainly on the pivotal phase III for the safety evaluation. This is accepted although, the safety outcome of the other paediatric studies are considered as supportive data, especially for age cohorts for which the phase III study only provided a limited number of subjects. In the age group <0.5 years, there were only 15 included rivaroxaban-treated children in the phase III study but an additional 12 more rivaroxaban-treated children in the other studies.

A total of 304 (90.7%) of the 335 children randomized to rivaroxaban and 148 (89.7%) of the 165 children randomized to the comparator group completed study treatment in accordance with the per protocol treatment window for the main treatment period, defined as 30 days ± 7 days for children with CVC-VTE < 2 years and 90 ± 7 days for the remaining children. 3/26 (11.5%) in the rivaroxaban group < 2 years of age with CVC-VTE were treated for a shorter period than 23 days (0/11 in comparator group).

The phase III study included 117 subjects (including 80 in the rivaroxaban group) exposed at least 6 months and 15 subjects (including 9 in the rivaroxaban group) exposed at least 12 months. This is in line with the scientific advice that the MAH had received for the data required to support a secondary prevention indication for which the CHMP considered that an extension of the study (up to 6 months) would be preferred in conjunction with the supportive information available from the adult population. For children < 2 years of age, there were only two subjects in the rivaroxaban group and one subject in the comparator group receiving treatment for more than 3 months. Moreover, extrapolation from adults in this population is limited due to developmental haemostasis in the young children,

The proposed posology section states that treatment can be extended up to 12 months when clinically necessary (except for patients <2 years, or in cases of CVC-VTE). In addition, prescribers are advised that the benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis vs the potential bleeding risk.

The experts from the SAG meeting also advised caution for use of rivaroxaban in patients with CVST and inflammatory intracranial conditions including meningitis, encephalitis and intracranial abscesses. Based on the data from study 14372, the CHMP did consider a contraindication in these patients necessary. None of the children in the rivaroxaban group who had a concomitant CVST and CNS infection had a treatment-emergent major or clinically relevant non-major bleeding event. Nevertheless, the amount of data is limited (13

children in the rivaroxaban group) and there was one major bleeding in the comparator group in a child with concomitant CVST and CNS infection, suggesting that special caution could be warranted in this setting. Therefore, a warning has been included in the SmPC that the risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban in such patients.

***Adverse events***

Treatment-emergent adverse events, serious treatment-emergent adverse events and treatment-emergent adverse event leading to discontinuation of study drug were all higher in the rivaroxaban group as compared to in the comparator group in the phase III study 14372.

The incidence of the principal safety outcome during the main treatment period (major bleeding + clinically relevant non-major bleeding) was also numerically higher in the rivaroxaban group (10 children, 3%; all CRNM bleeding) compared to the comparator group (3 children, 1.9%; 2 major bleeding, 1 CRNM bleeding) and there were additional events recorded during the extended treatment periods and during follow-up.

The proportion of children with any confirmed treatment-emergent bleeding during the main treatment period was 36.2% in the rivaroxaban group compared to 27.8% in the comparator group. In the clinical studies, mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genitourinary including abnormal vaginal or increased menstrual bleeding) and anaemia were seen more frequent during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding and quantify the clinical relevance of overt bleeding, as judged to be appropriate.

With regards to safety in the different age strata, it is noted that in the youngest strata, i.e. birth to <0.5 years, 5/15 children (33.3%) in the rivaroxaban group had any confirmed treatment-emergent bleeding during the main treatment period by age group as compared to 0/8 (0%) of the comparator group. Considering the overall treatment period, there was one additional subject with a bleeding in the rivaroxaban group and none in the comparator group and in addition there were two post-treatment bleedings in the rivaroxaban group compared to none in the comparator group. This observation was mirrored in the outcome of the incidence of confirmed treatment-emergent bleedings by weight group. For children < 2 years of age, 15/36 (41.7%) children in the rivaroxaban group had a treatment-emergent bleed during the entire study period, 3 of which were CRNM bleeding. Thirteen of these occurred during the main treatment period (2 of which were CRNM bleeding). For the comparator in the same age group, there were 3/17 (17.6%) subjects with a treatment-emergent bleeding during the entire study period, 1 of which was a major bleeding. All bleeding episodes occurred during the main treatment period. Repeat bleeding events for children < 2 years of age was noted only in the rivaroxaban group; there were in total 20 treatment-emergent bleeding events during the main treatment period, 6 of which were CRNM. No child in the comparator group had a repeat bleed. The relevance of these findings is underlined by the fact that they concern an age group for which extrapolation from adults is less straight forward than for the elderly children. In order to better characterise the risk of bleeding in the young paediatric population the MAH will conduct a post-authorisation safety study will investigate the safety of rivaroxaban granules for oral suspension in at least 50 very young (< 2 years of age) VTE patients from start of rivaroxaban treatment until 1 month (30 days) after stop of treatment and children with VTE treated with other anticoagulants.

Thrombocytopenia which is known to be adverse reaction in the adult population was also observed in the paediatric clinical trials and this is reflected in the SmPC which states that *"Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical trials"*. Increases in alanine aminotransferase and bilirubin were also observed and are adequately reflected in the PIL**.**

Accidental over- and underdose was overall more frequent in the rivaroxaban group than in the comparator group in the phase III study. Although the incidences were relatively low also in the rivaroxaban group, these events can be expected to occur more frequently post-approval as compared to the controlled study-setting. For this reason, medication errors in relation to the reconstitution of the oral suspension and dosing with the new pharmaceutical form 1 mg/mL granules for oral suspension has been included in the RMP as an important potential risk. Additional risk minimisation measures in the form of educational material for the prescribers, an educational video showing how to prepare and administer the oral suspension and a patient alert card together with the information included in the SmPC and PIL are considered sufficient to minimise this risk.

***Safety in special populations and related to interactions***

The analysis of the impact of kidney function on rivaroxaban exposure did not reveal any influence of renal function on the rivaroxaban PK/PD in children, which might be explained by the fact that the majority of patients in the paediatric studies had normal kidney function. Rivaroxaban is not recommended in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m2 or in children younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data are available.

No clinical data is available in children with hepatic impairment. According to the MAH, overall results did not indicate a new drug-drug interaction potential not already known from adults (see also section on clinical pharmacology).

## Additional expert consultations

See discussion on clinical efficacy.

## 2.6.2. Conclusions on the clinical safety

This application for a paediatric indication and new formulation is supported by data by paediatric studies as and to some extent from extrapolation of adult data. Overall, the observed safety data from the paediatric studies indicate a safety profile that is in line with the safety profile in the approved adult VTE indication and reflect the underlying conditions of the studied population. The limited information in the youngest children will be supplemented by a planned post-authorisation safety study. Although an imbalance with regards to treatment-emergent bleedings for rivaroxaban as compared to standard of care was observed in the pivotal study 14372, this risk is considered to be adequately managed by the proposed routine and additional risk minimisation measures.

## *2.7. Risk Management Plan*

## *Safety concerns*

| Summary of safety concerns | |
|---|---|
| Important identified risks | • Haemorrhage |
| Important potential risks | • Embryo-fetal toxicity<br>• Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension |
| Missing information | • Patients with severe renal impairment (CrCl < 30 mL/min)<br>• Patients receiving concomitant systemic inhibitors of CYP 3A4 or P-gp other than azole antimycotics (e.g. ketoconazole) and HIV-protease inhibitors (e.g. ritonavir)<br>• Remedial pro-coagulant therapy for excessive haemorrhage<br>• Pregnant or breast-feeding women<br>• Patients with atrial fibrillation (AF) and a prosthetic heart valve<br>• Long-term therapy with rivaroxaban in treatment of DVT, PE, SPAF and ACS in real-life setting<br>• Patients with significant liver diseases (severe hepatic impairment/Child Pugh C) |

## *Pharmacovigilance plan*

**Table 33:** On-going and planned additional Pharmacovigilance Activities in relation to the new paediatric indication

| Study Status | Summary of objectives | Safety concerns/efficacy issue addressed | Milestones | Due dates |
|---|---|---|---|---|
| **Children from birth to less than 2 years diagnosed with VTE and treated with rivaroxaban (SN XXXXX)** | | | | |
| **Category 3** - Required additional pharmacovigilance activities | | | | |
| | To investigate the safety of rivaroxaban granules for oral suspension in 50 very young (< 2 years of age) VTE patients. | Important identified risk:<br>• Haemorrhage<br>Important potential risk:<br>• Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for | Start of data collection<br>End of data collection<br>Final report of study results | Estimated Q4 2021<br>Estimated Q4 2024<br>Estimated Q4 2025 |

| |
|---|
| oral suspension |

### *Risk minimisation measures*

Risk minimisation measures introduced in the RMP for the new paediatric line extension and indication

| | |
|---|---|
| Important potential risk:<br>Medication errors in relation to the reconstitution of the oral suspension and dosing with the pharmaceutical form 1 mg/mL granules for oral suspension | **Routine risk minimisation measures:**<br>SmPC (Xarelto 1 mg/mL granules for oral suspension)<br>Section 4.2 (Posology and method of administration)<br>Section 4.4 (Special warnings and precautions for use)<br>Section 6.5 (Nature and contents of container)<br>**Additional risk minimisation measures:**<br>Educational material for prescribers<br>Patient alert cards<br>Video |

### *Conclusion*

The CHMP and PRAC considered that the risk management plan version 12.4 is acceptable.

## *2.8. Pharmacovigilance*

### *Pharmacovigilance system*

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

### *Periodic Safety Update Reports submission requirements*

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *2.9. Product information*

### 2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet for Xarelto 1 mg/mL granules for oral suspension  submitted by the MAH show that the package leaflet meets the criteria for

readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

No full user consultation with target patient groups on the package leaflet has been performed for Xarelto 15 and 20 mg film-coated tablets on the basis of a bridging report making reference to Xarelto 1 mg/mL granules for oral suspension. The bridging report submitted by the MAH has been found acceptable.

### 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Xarelto (rivaroxaban) is included in the additional monitoring list as it has a PASS imposed either at the time of authorisation or afterwards.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

# 3. Benefit-Risk Balance

## *3.1. Therapeutic Context*

As described in the Paediatric Addendum on the guidelines on clinical investigation of medicinal products for the treatment and prophylaxis of venous thromboembolic disease, venous thrombosis in children is rare, with an incidence at about 100 times lower than in adults. An annual incidence of VTE of between 53-57 per 100 000 has been reported among hospitalized children and between 1.4-4.9 per 100 000 in the community overall. The distribution of events is bimodal with the majority occurring in neonates/infants and in adolescents. Idiopathic paediatric venous thromboses are very uncommon; more than 90 per cent of children who experience a VTE have been described to have a serious underlying disease including malignancy, congenital heart disease and nephrotic syndrome; a hereditary pro-thrombotic condition; or a precipitating factor such as surgery, infection, trauma or an indwelling catheter such as central venous catheter (CVC). In adolescents, hormonal contraception is a common triggering factor for VTE.

Location of VTE differs, with neonates and young children more often experiencing upper venous system VTE (most frequently CVC-related VTE) as compared to adolescents and adults.

The coagulation system differs in particular in neonates and infants aged < 6 months, as compared to older children and adults. At birth, the plasma levels of vitamin K-dependent coagulation factors (II, VII, IX, X) are only half of the adult values, and increase during the first 6-12 months of life but remain at about 15% lower levels as compared to adults. Both quantitative and qualitative differences of the coagulation system have been described in the youngest children, and their response to anticoagulant therapy is known to be different compared to older children and adults.

The aim of anticoagulant VTE therapy is generally to prevent disease progression (including prevention of occurrence of severe manifestations such as pulmonary embolism), prevent VTE recurrence and the development of sequelae such as post thrombotic syndrome.

### 3.1.1. Available therapies and unmet medical need

The ACCP management guidelines (Monagle et al 2012) generally recommends for the initial treatment of VTE in children adjusted-dose unfractionated heparin (UFH), bodyweight-adjusted low-molecular-weight heparin (LMWH) or fondaparinux. For subsequent treatment, either INR-titrated vitamin K antagonist (VKA) or bodyweight-adjusted LMWH is recommended. Suggested treatment durations are 3 months for children with provoked VTE in whom the risk factor has resolved and extended anticoagulant therapy (for secondary prevention of recurrent VTE) in children who have ongoing risk factors. For children with idiopathic VTE, the suggested treatment duration has a minimum of 3 months and a maximum of 6 to 12 months. Children with recurrent unprovoked VTE are usually treated indefinitely.

In the ACCP guidelines, it is further stated that it is suggested that central venous access devices or umbilical venous catheters associated with confirmed thrombosis is to be removed after 3 to 5 days of therapeutic anticoagulation rather than left in situ. Either initial anticoagulation or supportive care with radiologic monitoring for extension of thrombosis is suggested as well as start of anticoagulation if extension occurs in previously untreated patients. Anticoagulation should be with either LMWH or UFH followed by LMWH with a total duration of anticoagulation of between 6 weeks and 3 months. As discussed in these guidelines, clear evidence that all thromboses in neonates or children require treatment, particularly for asymptomatic thrombosis, is lacking and further studies are required so that adequate risk-benefit assessments of treatment options can be determined.

According to the ACCP guidelines, for children with CSVT without significant intracranial haemorrhage, anticoagulation is suggested, initially with UFH or LMWH and subsequently with LMWH, for a total therapy duration between 6 weeks and 3 months. For children with CSVT with significant haemorrhage, either anticoagulation or supportive care with radiologic monitoring of the thrombosis at 5 to 7 days and anticoagulation if thrombus extension is noted is recommended. However, according to the AHA guidelines (Roach et al 2008), there is currently a consensus that older children without haemorrhage should be anticoagulated (International Paediatric Stroke Study consensus) but few neonates with CVST have been treated with anticoagulants, and such treatment is not recommended in neonates except perhaps in selected patients with clinical deterioration or with radiological evidence of clot propagation

There is no centrally approved anticoagulant product in the EU for treatment or secondary prevention of VTE in children. There is an unmet need for a new treatment-option with well documented efficacy and safety in children. In the paediatric setting, an alternative that requires less monitoring than existing standard of care would also be a benefit.

### 3.1.2. Main clinical studies

The focus of the application is the phase III trial, study 14372, in which patients aged birth to < 18 years with acute VTE, received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to then receive either rivaroxaban (age- and bodyweight-adjusted) or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). Rivaroxaban was administered as either tablets or as granules for oral suspension (in a body weight-adjusted 20 mg equivalent dose). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC VTE up to 3 months) in total. The treatment period was followed by an observational period of 30 days.

In total 500 patients were randomized (335 to rivaroxaban, 165 to comparator) and 491 (329 rivaroxaban and 162 comparator) started treatment. Requirement for 90 days anticoagulation (30 days in children aged younger than 2 years with CVC-VTE) were included in the inclusion criteria.

The most common index events in the phase III study were lower extremity VTE (rivaroxaban 33.4% and comparator 32%), CVST (rivaroxaban 22.1% and comparator 26.1%), and pulmonary embolism (rivaroxaban 14.6% and comparator 18.8%). CVC-VTE was found in 25.4% children (26.9% in rivaroxaban group and 22.4% in comparator group), primarily among the youngest children. A large proportion of subjects with CVC-VTE (44%) had subacute or chronic VTE.

There were 15 rivaroxaban-treated children in the age group <0.5 years included in the phase III study in the Safety Analysis set (SAF; all randomized children who received at least one dose of study medication included, there were 16 in the FAS that included all randomized subjects).

## *3.2. Favourable effects*

The primary efficacy outcome of recurrent VTE occurred in 1.2% (4/335 subjects) randomised to rivaroxaban; 95% CI 0.4-3.0%, and in 3% (5/165 subjects) randomised to comparator; 95% CI 1.2-6.6% during the main treatment period of 3 months (1 month for CVC-VTE in children < 2 years of age). All recurrent VTEs in the rivaroxaban group occurring during the main treatment period occurred in children aged between 12 and 18 years, which was also the largest age group in the study (4/184; 2.2%;95% CI 0.7 - 5.3%). In the comparator group, recurrent VTE occurred in 3 of the 92 children aged between 12 and 18 years (3.3%; 95% CI 0.9 - 8.6%), in 1 of the 34 children aged between 6 and 12 years (2.9%; 95 CI 0.2% - 15.1%) and in 1 of the 22 children aged between 2 and 6 years (4.5%; 95% CI 0.2 - 20.7%). In both treatment groups, early recurrence predominated; there were no primary efficacy events after day 30.

During the extended treatment period, only three primary efficacy events occurred in total (1 in the rivaroxaban group at day 223 and 2 in the comparator group, at day 98 and 211); all events occurred in adolescents. All subjects had a non-CVC-VTE index event. Only subjects with CVST, non-CVC-VTE or CVC-VTE >/= 2 years were treated for more than three months: 135 subjects were included in the first extension period (3-6 months) in the rivaroxaban group (63 subjects in comparator group), 53 subjects were included in the second extension period (6-9 months) in the rivaroxaban group (24 subjects in the comparator group), and 31 subjects were included in the third extension period (9-12 months) in the rivaroxaban group (17 subjects in the comparator group).

The incidences of recurrent VTE are largely in line with the pivotal VTE studies (deep vein thrombosis and pulmonary embolism only) in adults.

There were no primary efficacy events after stop of study treatment in subjects randomized to rivaroxaban, thus, no rebound effect of rivaroxaban is apparent. There were two primary efficacy events in the comparator group after stop of study treatment, both occurring in children with persistent risk factors for VTE.

The secondary efficacy outcome was a composite of the primary efficacy outcome (recurrent VTE) and asymptomatic deterioration on repeat imaging, and occurred in 5/335 (1.5%, 95% CI 0.3-3.4%) of rivaroxaban treated subjects and 6/165 (3.6%, 95% CI 1.6-7.6%). The majority of secondary efficacy events were recurrent VTE (primary efficacy outcome); only 1 subject in each treatment group had asymptomatic deterioration during the main treatment period.

## 3.3. Uncertainties and limitations about favourable effects

The study was not powered to test a formal hypothesis; thus, no type I error/multiplicity considerations have been made, which needs to be considered in the interpretation of outcomes. Although there were no formal claims with regards to comparator treatment, it is noted that there was no robust assessment of compliance for 72/162 children in the comparator group. Therefore, the data included in the SmPC pertaining to study 14372 are to be descriptive only.

The concept of developmental haemostasis precludes full extrapolation of efficacy data in adults to the youngest children. Even though the number of children below the age of 2 included in the pivotal study was limited, the data on favourable effects in all age groups are deemed conclusive enough to support adequate efficacy for treatment and secondary prevention of VTE in children of any age as also confirmed by the experts in the SAG meeting. Therefore, the Applicant´s proposal to include children of all age groups in the indication is accepted.

## 3.4. Unfavourable effects

During the main treatment period, any treatment-emergent adverse event (TEAE) occurred in 83.3% of subjects in the rivaroxaban group and 75.3% in the comparator group while the frequency of serious TEAE occurred in 21.6% vs 19.8% and TEAE leading to discontinuation of study drug in 3.3% vs 1.9%.

The principal safety outcome (a composite of major bleeding and clinically relevant non-major bleeding; CRNM) occurred in 10/329 children in the rivaroxaban group ( 3%; all CRNM bleeding) and 3/162 children compared in the comparator group ( 1.9%; 2 major bleeding, 1 CRNM bleeding) during the main treatment period. Overall, considering both the main and extended treatment periods the incidence of the principal safety outcome in the SAF was in total 13/329 (4.0%) vs 4/162 (2.5%). In addition, two incidences of principal safety outcome were reported in the rivaroxaban group during follow-up period.

The proportion of children with any confirmed treatment-emergent bleeding during the main treatment period was 36.2% in the rivaroxaban group and 27.8% in the comparator group. In the rivaroxaban group, these bleedings included mucosal bleedings such as gastrointestinal bleedings, epistaxis, bleedings from mouth and genitourinary bleedings (including increased menstrual bleedings). There were no intracranial bleedings in the rivaroxaban group (but one subdural haemorrhage in the comparator group). Incidence of all confirmed treatment-emergent bleedings, for the overall duration of treatment (SAF) was 39.5% in the rivaroxaban group and 30.2 % had such event in the comparator group.

In the youngest age strata, i.e. birth to <0.5 years, 5/15 children (33.3%) in the rivaroxaban group had confirmed treatment-emergent bleeding (out of which 1 was a CRNM) during the main treatment period as compared to 0/8 (0%) of the comparator group.

Taking into account the entire treatment period, there was 1 additional subject with a bleeding in the rivaroxaban group (thus 40% of the rivaroxaban-treated subjects had a bleeding during the overall treatment period) and 0 in the comparator group. In addition, there were 2 post-treatment bleedings in the rivaroxaban group compared to none in the comparator group. For children < 2 years of age, 15/36 (41.7%) children in the rivaroxaban group had a treatment-emergent bleed during the entire study period, 3 of which were CRNM bleeding. Thirteen of these occurred during the main treatment period (2 of which were CRNM bleeding). For the comparator in the same age group, there were 3/17 (17.6%) subjects with a treatment-emergent

bleeding during the entire study period, 1 of which was a major bleeding. All bleeding episodes occurred during the main treatment period. Repeat bleeding events for children < 2 years of age was noted only in the rivaroxaban group; there were in total 20 treatment-emergent bleeding events during the main treatment period, 6 of which were CRNM. No child in the comparator group had a repeat bleed.

In children with CVST as index event, the incidence of the principal safety outcome (major bleedings + CRNMs) was in the rivaroxaban group 5/74 (6.8%) and in the comparator group 1/43 (2.3%) during the main treatment period. The incidence of any confirmed bleeding was 35.1% rivaroxaban vs 30.2% comparator.

In children with CVC-VTE, the incidence of the principal safety outcome was 3/87= 3.4% in the rivaroxaban group vs 0/37 in the comparator group during the main treatment period. The incidence of treatment-emergent bleedings was 31.0% in rivaroxaban-group vs 21.6% in comparator.

## *3.5. Uncertainties and limitations about unfavourable effects*

The concept of developmental haemostasis precludes full extrapolation of safety data in adults to the youngest children. Nevertheless, the data on unfavourable effects in all age groups are deemed conclusive enough to support adequate safety for treatment and secondary prevention of VTE in children of any age. The number of children in each age group in study 14372, and the bleeding data including all bleeding events are reflected in the product information.

## *3.6. Effects Table*

**Table 34:** Effects Table for Xarelto for treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years following after at least 5 days of initial parenteral anticoagulation treatment

| Effect | Short Description | Unit | Rivaroxaban (n=335) | SoC | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| **Favourable Effects** | | | | | | |
| Recurrent VTE | Symptomatic adjudicated recurrent VTE | N (%) | 4 (1.2%) | 5 (3.0%) | | Study 14372[(1)] |
| Asymptomatic Deterioration | Radiologically confirmed asymptomatic deterioration | N (%) | 1 (0.3%) | 1 (0.6%) | | |
| **Unfavourable Effects** | | | | | | |

| Effect | Short Description | Unit | Rivaroxaban (n=335) | SoC | Uncertainties/ Strength of evidence | References |
|---|---|---|---|---|---|---|
| Principal safety outcome | A composite of treatment-emergent overt major bleeding and CNRM | N (%) | 10(3.0) | 3(1.9) | Treatment emergent bleeding was reported in 123 (37.3%) of rivaroxaban and 47 (29%) of SOC treated patients | Study 14372 |

Abbreviations: VTE: Venous thromboembolism, CNRM: clinically relevant non-major bleeding, SOC: Standard of Care
Notes:[1]Full analysis set during main treatment period of study 14372

## *3.7. Benefit-risk assessment and discussion*

### 3.7.1. Importance of favourable and unfavourable effects

***Importance of favourable effects***

Overall, the efficacy demonstrated for the paediatric rivaroxaban group is deemed well in line with what is expected for an anticoagulant for treatment and secondary prevention of VTE, supported by a low number of recurrent VTEs during main treatment period as well as during extended treatment periods. Efficacy is further supported by the repeat imaging with improved or normalised thrombotic burden in a majority of subjects. The magnitude of the effect as presented is deemed well in line with what is known in adults and in previous paediatric VTE studies.

***Importance of unfavourable effects***

For the overall paediatric population, treatment with rivaroxaban appears to carry an increased risk for bleedings compared to standard of care. This a known risk from the use of rivaroxaban in the adult population and is associated with its anticoagulant properties. Even though no major bleedings were reported with rivaroxaban, detailed information on this risk and necessary precautions on how to minimise is included in the product information. Additional risk minimisation measures already in place for adult patients are also expected to contribute to effective management of this risk in the paediatric population.

Furthermore, as advised by the SAG post-authorisation safety data on the use of rivaroxaban in the youngest children will be collected through a planned PASS. This study will focus on children < 2 years of age and addressing the risk of bleeding as well as the risk of medication errors with the new paediatric formulation.

### 3.7.2. Balance of benefits and risks

There is an unmet need for a new treatment-option with well documented efficacy and safety in children with VTE. Overall, the efficacy data in this application are considered to support a clinically adequate efficacy of rivaroxaban for treatment and secondary prevention of VTE in children and it is possible that this new

treatment option will decrease the need for parenteral therapy and monitoring. Taken together, this is considered to outweigh the observed risks of bleeding in this patient group.

With respect to safety, it is acknowledged that the incidence of treatment related bleedings (albeit not major bleedings) are higher in the groups treated with rivaroxaban compared to standard of care. However, as also confirmed by the experts at the SAG meeting, this risk can be handled in clinical practice.

Therefore, the benefits associated with rivaroxaban uses are considered to outweigh the observed risks of bleeding in children of all ages. The granules for oral suspension can be used in in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment. In children and adolescents aged less than 18 years and weighing from 30 kg to 50 kg the 15 mg film-coated tablets can also be used and in children and adolescents aged less than 18 years and weighing more than 50 kg the 20mg film-coated tablets can be used.

### *3.8. Conclusions*

The overall B/R of Xarelto in the sought indications is considered positive.

# 4. Recommendations

### *Outcome*

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Xarelto 1 mg/mL granules for oral suspension is favourable in the following indication:

Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years after at least 5 days of initial parenteral anticoagulation treatment.

The CHMP therefore recommends the extension of the marketing authorisation for Xarelto subject to the following conditions:

### *Conditions or restrictions regarding supply and use*

Medicinal product subject to medical prescription.

### *Conditions and requirements of the marketing authorisation*

**Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

## *Conditions or restrictions with regard to the safe and effective use of the medicinal product*

**Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**Additional risk minimisation measures**

The MAH shall provide an educational pack prior to launch, targeting all physicians who are expected to prescribe/use Xarelto. The educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk. The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards [Text included in Annex III]
- Patient Alert Cards (Xarelto granules for oral suspension) [Text included in Annex III]

The MAH must agree the content and format of the Prescriber Guide together with a communication plan, with the national competent authority in each Member State prior to distribution of the educational pack in their territory. The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be counselled about:
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance

- The need for intake of the 15 mg and 20 mg tablets with food
- Necessity to carry the Patient Alert Card that is included in each pack, with them at all times
- The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.

- That all parents/caregivers of pediatric patients and all paediatric patients administered Xarelto granules for oral suspension should be counselled about:
  - reconstitution and dosing of the oral suspension

The MAH shall also provide a Patient Alert Card in each medicine pack, the text of which is included in Annex III.

To ensure correct reconstitution and handling of Xarelto granules for oral suspension, a training video for healthcare providers and caregivers will be made available by the MAH electronically on company webpages (as per local country requirements). The MAH shall send notifications to potential prescribers in line with the communication plan agreed with the national competent authority detailing the location of the training video, the necessity of training and the documentation of training.

**Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due dates |
|---|---|
| A post-authorisation study programme that addresses the safety of rivaroxaban in the secondary prevention of Acute Coronary Syndrome (ACS) outside the clinical trial setting, especially with regard to incidence, severity, management and outcome of bleeding events in all population and particularly in patients at increased risk of bleeding consisting of the following remaining studies:<br>• Drug Utilisation and Outcome Studies in the UK, Germany, The Netherlands and Sweden<br>• Specialist Cohort Event Monitoring (SCEM) ACS Study<br>With the submission of the last final study report from the programme, the MAH should provide an overview and discussion of the results from all studies of the programme in view of ACS patients. | • Interim analyses reports provided annually beginning Q4 2015 until completion of the study programme.<br>• Final Study Reports submitted by Q4 2020 |

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan, P/0126/2019, and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In addition, CHMP recommends the variations to the terms of the marketing authorisation concerning the following changes:

| **Variations requested** | | **Type** | **Annexes affected** |
|---|---|---|---|
| C.I.6.a | C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | Type II | I, IIIA and IIIB |

Extension of indication to include treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in term neonates, infants and toddlers, children, and adolescents aged less than 18 years following initiation of standard anticoagulation treatment for Xarelto 15 and 20 mg tablets.
As a consequence, sections 4.2,4.4,4.5, 4.8, 4.9, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated accordingly.

In addition, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC is updated for all other dose strengths (2.5/10/ and 15/20 mg initiation packs) of Xarelto and corresponding sections of the Package Leaflet. Section 4.4 has been updated with regards to sodium content according to Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668).

The RMP version 12.4 has also been submitted.