



Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicentre, single-arm, phase 2 studies

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Summary

Background Rivaroxaban has been shown to be efficacious for treatment of venous thromboembolism in adults, and has a reduced risk of bleeding compared with standard anticoagulants. We aimed to develop paediatric rivaroxaban regimens for the treatment of venous thromboembolism in children and adolescents.

Methods In this phase 2 programme, we did three studies to evaluate rivaroxaban treatment in children younger than 6 months, aged 6 months to 5 years, and aged 6–17 years. Our studies used a multicentre, single-arm design at 54 sites in Australia, Europe, Israel, Japan, and north America. We included children with objectively confirmed venous thromboembolism previously treated with low-molecular weight heparin, fondaparinux, or a vitamin K antagonist for at least 2 months or, in children who had catheter-related venous thromboembolism for at least 6 weeks. We administered rivaroxaban orally in a bodyweight-adjusted 20 mg-equivalent dose, based on physiologically-based pharmacokinetic modelling predictions and EINSTEIN-Jr phase 1 data in young adults, in either a once-daily (tablets; for those aged 6–17 years), twice-daily (in suspension; for those aged 6 months to 11 years), or three times-daily (in suspension; for those younger than 6 months) dosing regimen for 30 days (or 7 days for those younger than 6 months). The primary aim was to define rivaroxaban treatment regimens that match the target adult exposure range. The principal safety outcome was major bleeding and clinically relevant non-major bleeding. Analyses were per-protocol. The predefined efficacy outcomes were symptomatic recurrent venous thromboembolism, asymptomatic deterioration on repeat imaging at the end of the study treatment period. These trials are registered at ClinicalTrials.gov, numbers NCT02564718, NCT02309411, and NCT02234843.

Findings Between Feb 11, 2013, and Dec 20, 2017, we enrolled 93 children (ten children younger than 6 months; 15 children aged 6 months to 1 year; 25 children aged 2–5 years; 32 children aged 6–11 years; and 11 children aged 12–17 years) into our study. 89 (96%) children completed study treatment (30 days of treatment, or 7 days in those younger than 6 months), and 93 (100%) children received at least one dose of study treatment and were evaluable for the primary endpoints. None of the children had a major bleed, and four (4%, 95% CI 1·2–10·6) of these children had a clinically relevant non-major bleed (three children aged 12–17 years with menorrhagia and one child aged 6–11 years with gingival bleeding). We found no symptomatic recurrent venous thromboembolism in any patients (0%, 0·0–3·9). 24 (32%) of 75 patients with repeat imaging had their thrombotic burden resolved, 43 (57%) patients improved, and eight (11%) patients were unchanged. No patient deteriorated. We confirmed therapeutic rivaroxaban exposures with once-daily dosing in children with bodyweights of at least 30 kg and with twice-daily dosing in children with bodyweights of at least 20 kg and less than 30 kg. Children with low bodyweights (<20 kg, particularly <12 kg) showed low exposures so, for future studies, rivaroxaban dosages were revised for these weight categories, to match the target adult exposure range. 61 (66%) of 93 children had adverse events during the study. Pyrexia was the most common adverse event (ten [11%] events), and anaemia and neutropenia or febrile neutropenia were the most frequent grade 3 or worse events (four [4%] events each). No children died or were discontinued from rivaroxaban because of adverse events.

Interpretation Treatment with bodyweight-adjusted rivaroxaban appears to be safe in children. The treatment regimens that we confirmed in children with bodyweights of at least 20 kg and the revised treatment regimens that we predicted in those with bodyweights less than 20 kg will be evaluated in the EINSTEIN-Jr phase 3 trial in children with acute venous thromboembolism.

Funding Bayer AG, Janssen Research and Development.

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Lancet Haematol 2019;
6: e500–09

Published Online
August 13, 2019
[http://dx.doi.org/10.1016/S2352-3026\(19\)30161-9](http://dx.doi.org/10.1016/S2352-3026(19)30161-9)

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Research in context

Evidence before this study

Treatment of venous thromboembolism in children is mainly based on evidence obtained in adults. Clinical experience with unfractionated heparin, low-molecular weight heparin, and vitamin K antagonist therapy indicates that higher doses (per kg of bodyweight) are required for the younger patients to achieve the anticoagulant effects established in adult patients with venous thromboembolism. For treatment of acute venous thromboembolism in adults, rivaroxaban, an oral, direct inhibitor of activated factor X, is given in a fixed-dose regimen. This regimen is as effective as conventional anticoagulant therapy, and it is associated with fewer major bleeding events and improved patient satisfaction. The availability of an oral anticoagulant treatment that does not require subcutaneous or intravenous injections or regular blood sampling for monitoring would be highly desirable in children. We searched PubMed for articles published in English until March 8, 2019, with the search terms "rivaroxaban", "treatment", "venous thromboembolism", and "pediatric". With this search, we found no randomised controlled studies. Kubitzka and colleagues evaluated a single administration of rivaroxaban in children aged 6 months to 18 years in a single-arm, phase 1 study, to establish bodyweight-adjusted regimens that had a similar exposure as had been observed in young adults treated with rivaroxaban in therapeutic dosages.

Added value of this study

Rivaroxaban treatment appears to be safe in children from birth to younger than 18 years. However, to match the target adult treatment exposure range, children required total daily rivaroxaban doses per kg bodyweight that increased substantially with decreasing bodyweights. By shortening the dosing interval from 24 h to 12 h in children with bodyweights of less than 30 kg, and further, to 8 h, in children with bodyweights of less than 12 kg, trough concentrations within the adult reference range were maintained and high peak concentrations avoided.

Implications of all the available evidence

The established paediatric rivaroxaban treatment regimens will be prospectively evaluated in the EINSTEIN-Jr phase 3 study, in which children of all ages with acute venous thromboembolism will be randomly assigned to receive the paediatric rivaroxaban regimens or standard anticoagulation therapy. The phase 3 trial aims to document the incidence of recurrent venous thromboembolism and major or clinically relevant non-major bleeding on a larger scale, and to confirm that the revised bodyweight-adjusted rivaroxaban regimens attained equivalent adult exposures.

Introduction

Paediatric clinical practice guidelines regarding anti-coagulant treatment for venous thromboembolism are mainly based on extrapolation of results from trials in adults, rather than on evidence specifically from randomised controlled trials in children. Anticoagulant treatment in children often requires parenteral administration of heparins and frequent blood sampling for laboratory monitoring.¹

Rivaroxaban is an oral, direct inhibitor of activated factor X (factor Xa). For treatment of acute venous thromboembolism in adults, rivaroxaban is given at a fixed dose of 15 mg twice daily for 21 days, followed by 20 mg once daily for a period of at least 3 months.²⁻⁴ This regimen is as effective as conventional anticoagulant therapy, and it is associated with fewer major bleeding events and improved patient satisfaction than standard anticoagulants.⁵⁻¹⁰ The availability of an oral anticoagulant treatment that does not require subcutaneous or intravenous injections, and regular blood sampling for monitoring is also desirable for children.

In collaboration with the European Medicines Agency and the US Food and Drug Administration,^{11,12} we developed a paediatric investigation plan to evaluate rivaroxaban for the treatment of acute venous thromboembolism in children. To manage the potential effects of the maturation of the haemostatic system in childhood, Attard and colleagues^{13,14} evaluated the in vitro

pharmacodynamic response to rivaroxaban in plasma from children and neonates. Willmann and colleagues¹⁵ developed a physiologically-based pharmacokinetic (PBPK) model, to inform the rivaroxaban dosing regimen for clinical studies in children. In the EINSTEIN-Jr phase 1 study,^{16,17} in which children received a single administration of rivaroxaban, we predicted bodyweight-adjusted regimens that gave a similar rivaroxaban exposure as that in young adults treated once daily with 20 mg rivaroxaban. These bodyweight-adjusted regimens were used in our studies, the EINSTEIN-Jr phase 2 programme.

In the EINSTEIN-Jr phase 2 studies, we aimed to confirm or adapt the predicted bodyweight-adjusted rivaroxaban regimens from the phase 1 study in children younger than 18 years with confirmed venous thromboembolism who had entered their final period of anticoagulation, based on long-term exposure data acquired during the study, and to document the efficacy and safety of these regimens.

Methods

Study design and participants

The EINSTEIN-Jr phase 2 programme consisted of three studies to evaluate rivaroxaban treatment in children younger than 6 months (ClinicalTrials.gov, number NCT02564718), aged 6 months to 5 years (NCT02309411), and aged 6-17 years (NCT02234843). Our

studies used a multicentre, single-arm design to evaluate the safety, efficacy, and pharmacokinetic and pharmacodynamic profiles of bodyweight-adjusted doses of rivaroxaban in children with venous thromboembolism. The studies were conducted at 54 sites in Australia, Europe, Israel, Japan, and north America (appendix p 8).

We considered children with objectively confirmed venous thromboembolism for enrolment if they had been treated with low-molecular weight heparin, fondaparinux, or a vitamin K antagonist (or more than one of these treatments) for at least 2 months or, in children with catheter-related venous thromboembolism, for at least 6 weeks. Children younger than 6 months were required to have a gestational age at birth of at least 37 weeks, a bodyweight of more than 2600 g, to have been feeding orally for at least 10 days, and to have completed at least 5 days of anticoagulant therapy. The main exclusion criteria were active bleeding or a high risk of bleeding contraindicating anticoagulant therapy and an estimated glomerular filtration rate of less than 30 mL/min per 1.73 m²; if younger than 6 months, children would also be excluded for a serum creatinine concentration more than 1.5 times higher than reference ranges, hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk, an alanine transaminase concentration more than five times higher than the upper limit of normal, or a total bilirubin concentration of more than twice the upper limit of normal with direct bilirubin representing more than 20% of the total bilirubin (appendix pp 3, 4).

Enrolment started with children aged 12–17 years when the pharmacokinetic data of rivaroxaban in the phase 1 study^{15–17} supported the use of the PBPK model for further dose and dosing regimen recommendations. After the data safety committee approved the pharmacokinetic, safety, and efficacy data, the steering committee was asked to enrol the next age cohort (6–11 years). This process was then repeated for the age groups 2–5 years, 6 months to 1 year, and younger than 6 months. When the confirmed or predicted rivaroxaban dose regimens were approved by the data safety and steering committee in an age group, that age group was also able to participate in the EINSTEIN-Jr phase 3 study,¹⁸ which was done almost in parallel with the phase 2 study.

The protocols were approved by the institutional review board of each participating centre and written permission from a parent or legal guardian and, when appropriate, child assent, was obtained. An independent data monitoring committee periodically reviewed study outcomes and provided recommendations to the steering committee.

Procedures

We began treating participants with rivaroxaban 4 h after discontinuation of unfractionated heparin, 6–12 h after discontinuation of low-molecular weight heparin (when it was administered in a twice-daily regimen),

and 12–24 h after discontinuation of fondaparinux or low-molecular weight heparin (when it was administered in a once-daily regimen). In children who had been receiving vitamin K antagonist therapy, we only started rivaroxaban treatment if the international normalised ratio was less than 2.5. We administered rivaroxaban orally in a bodyweight-adjusted 20 mg-equivalent dose, based on PBPK modelling predictions and EINSTEIN-Jr phase 1 data,^{15–17} in either a once-daily, twice-daily, or three times-daily dosing regimen (table 1). Because of the stepwise design of the EINSTEIN-Jr programme, ongoing dose optimisation, and because tablets (and not suspension) were available at the start of the study, we administered different daily doses for children with bodyweights of 20–40 kg who received tablets (those enrolled at the beginning of the study) rather than suspension (those enrolled later in the study). In children younger than 6 months, a cautious dosing approach was taken (designated part A) because of the absence of any phase 1 data and marked uncertainties in the PBPK predictions, and we subsequently escalated dosing on the basis of initial results (designated part B).

We administered rivaroxaban for 30 days, with hospital visits at days 1, 15, and 30. On these visits, we took blood

See Online for appendix

	Children aged 6–17 years*		Children aged 6 months to 5 years† (suspension, BID)	Children aged birth to 6 months‡		Rivaroxaban dose regimens recommended for phase 3§	
	Tablet, OD	Suspension, BID		Part A (suspension, BID)	Part B (suspension, TID)	Total daily dose	Regimen
2.6 to <3 kg	1.0	1.5	2.4	0.8 TID
3 to <4 kg	1.2	1.8	2.7	0.9 TID
4 to <5 kg	1.8	2.7	4.2	1.4 TID
5 to <6 kg	2.8	2.4	..	4.8	1.6 TID
6 to <7 kg	3.6	3.2	..	4.8	1.6 TID
7 to <8 kg	4.4	3.8	..	5.4	1.8 TID
8 to <9 kg	6.4	5.0	..	7.2	2.4 TID
9 to <10 kg	6.4	8.4	2.8 TID
10 to <12 kg	6.8	9.0	3.0 TID
12 to <20 kg	..	8.0	8.0	10.0	5.0 BID
20 to <30 kg	7.5	10.0	10.0	10.0	5.0 BID
30 to <40 kg	10.0	15.0	15.0	15.0	15.0 OD
40 to <50 kg	15.0	15.0	15.0	15.0	15.0 OD
≥50 kg	20.0	20.0	20.0	20.0 OD

Data are total daily doses of rivaroxaban in mg, as evaluated in phase 2 studies, stratified by bodyweight. Part A indicates the doses as derived from phase 1 and further amended during the ongoing dose optimisation (based on data already obtained in older children). Part B indicates the escalated doses and increase in administrations (from BID to TID) after initial results were analysed. Dosing regimen, including the dosing frequency, should be adjusted if the child's bodyweight changes. This suggested dosing schedule could be subject to changes based on the results of the EINSTEIN-Jr phase 3 study, and it should therefore not be used for treatment of children outside the framework of the study.

OD=once daily, BID=twice daily, TID=three times daily. ..=data not available. Registered at ClinicalTrials.gov, numbers *NCT01684423, †NCT02309411, ‡NCT02564718, and §NCT02234843.

Table 1: Bodyweight-adjusted rivaroxaban doses from the phase 2 programme, and recommended rivaroxaban dosing regimens to be used in the EINSTEIN-Jr phase 3 study

samples for pharmacokinetic and pharmacodynamic analyses, recorded safety events (bleeding, other adverse events), and checked the efficacy of the treatment (ie, any new thrombosis). Children younger than 6 months often receive short durations of anticoagulant therapy^{18,19} and, therefore, a treatment duration of 7 days was permitted, with hospital visits at days 1, 3, and 7. All children aged at least 12 years received rivaroxaban as tablet. Initially, children aged 6–11 years also received rivaroxaban as tablet, but when the study committees approved the adjusted rivaroxaban dose based on the ongoing dose optimisation, all subsequently recruited children received rivaroxaban as suspension. Rivaroxaban was administered with an age-appropriate volume of fluid for up to 2 h after eating a meal.

We took blood samples for pharmacokinetic analyses (rivaroxaban plasma concentrations) and pharmacodynamic analyses (prothrombin time, activated partial thromboplastin time [aPTT], and anti-factor Xa activity) with sparse sampling (ie, use of a restricted number of blood samples) for different age cohorts. In children aged 6–17 years, we took blood samples for pharmacokinetic and pharmacodynamic analyses in steady state whereas, in children younger than 6 years, we collected blood samples after the first administration of rivaroxaban and in steady state (appendix p 5). We measured these variables at central laboratories with methods described previously.^{16,17} Anti-factor Xa activity was determined with a photometric method in accordance with the recommendations of the manufacturer (Technoclone; Vienna, Austria) and rivaroxaban-specific calibrators and controls (Technoclone). The lower limit of quantification was 14·5 ng rivaroxaban per mL.

We did a repeat imaging test of the venous thrombosis at the end of the study treatment period (provided no additional ionising radiation or a general anaesthetic was required), and these images were compared with those at baseline. We classified these imaging results as normalised, improved (ie, the thrombus was still present but partly recanalised or involved fewer anatomical areas), no relevant change (ie, not recanalised and similar in extent), or deteriorated (ie, extended or new anatomical areas involved). A central independent adjudication committee who were masked to rivaroxaban treatment status (eg, dose, administration frequency) evaluated all index and suspected recurrent venous thromboembolism events, deaths, and suspected episodes of bleeding. The independent adjudication committee reviewed all repeat imaging tests performed at the end of the study treatment period. A 24-h medical emergency phone line was available for medical staff throughout the study.

All children who stopped study treatment earlier than scheduled were followed up until the end of the intended 30-day (or 7-day, if younger than 6 months) treatment period. Patients were instructed to report to the study centre if they had symptoms suggestive of recurrent

venous thromboembolism or bleeding. Objective testing was required for patients in whom a recurrence was suspected.

Adverse events were collected during the study treatment period and were coded according to the Medical Dictionary for Regulatory Activities, version 21.1. Events were categorised by primary system organ class, according to reported events that had been coded to preferred terms.

Outcomes

We were required to generate three separate protocols, implemented in the described stepwise manner, because of safety concerns in the children younger than 6 months. These protocols therefore varied in the stated primary outcomes. However, we had the same aims in all three protocols (as they were part of the same study): to assess safety, efficacy, and pharmacokinetic and pharmacodynamic activity.

The primary aim was to define rivaroxaban treatment regimens that match the target adult exposure range. The predefined safety outcomes were major and clinically relevant non-major bleeding.^{20,21} The predefined efficacy outcomes were symptomatic recurrent venous thromboembolism, asymptomatic deterioration on repeat imaging, and pharmacokinetic and pharmacodynamic findings at the end of the study treatment period.

Statistical analysis

Based on the initial high uncertainty regarding the safety of fixed-dose treatment with rivaroxaban in children, particularly younger children, we elected to run the EINSTEIN-Jr phase 2 programme with three separate protocols. We started with the evaluation of children aged 6–17 years, followed by those aged 6 months to 5 years, finishing with those younger than 6 months. Although data were analysed by age group because of our stepwise approach, we intended to report our data to the scientific community as a single programme. The programme did not have a formal sample size calculation. Children were evaluated by age cohort (12–17 years, 6–11 years, 6 months to 5 years, and younger than 6 months) with a stepwise approach. Clinical outcomes and pharmacokinetic data were shared regularly with the data safety committee. When the pharmacokinetic data supported the use of the PBPK model for further dose and dosing regimen recommendations, the steering committee independently decided to stop enrolment in the age cohort and open enrolment for the next age cohort.

Demographic and clinical characteristics and study outcomes are presented by formulation (rivaroxaban tablet or oral suspension) and age group. Our safety and pharmacokinetics and pharmacodynamics analyses included all children with valid informed consent who had received at least one dose of rivaroxaban. Pharmacokinetic and pharmacodynamic activity were evaluated

in all children who received treatment and had repeat imaging at the end of treatment.

Pharmacokinetic and pharmacodynamic activity outcomes were considered during the intended treatment period (30 days, or 7 days if the child was younger than 6 months), whereas safety outcomes were considered during the time from administration of the first dose of rivaroxaban to 48 h after the administration of the last dose.⁵⁻⁸ Two-sided 95% CIs were calculated with the Clopper–Pearson exact method.

The paediatric population pharmacokinetic model that was developed in the EINSTEIN-Jr phase 1 study¹⁶ was extended by integrating the plasma concentrations recorded in children younger than 6 months in the present study. An exploratory paediatric population pharmacokinetic model for younger children was used to evaluate these plasma concentration measurements. Based on these models, we derived the following pharmacokinetic parameters for rivaroxaban at steady

state for each individual: area under the plasma concentration–time curve from time 0 to 24 h (AUC[0–24]), the C_{max} , and the C_{trough} at the end of the dosing interval. These variables were plotted as a function of bodyweight and compared with the adult reference range (adults with venous thromboembolism younger than 45 years who had received 20 mg rivaroxaban once-daily, n=203).²²

The prothrombin time, aPTT, and anti-factor Xa activity findings were assessed as relative changes from baseline (prothrombin time, aPTT) and absolute values (anti-factor Xa activity), using samples obtained at the end of the dosing interval for baseline values, as baseline values. Individual prothrombin time and aPTT data were correlated with plasma concentrations and were compared with an adult reference population.

Calculations were performed with SAS version 9.2. These trials are registered at ClinicalTrials.gov, numbers NCT02564718, NCT02309411, and NCT02234843. These trials are closed to recruitment.

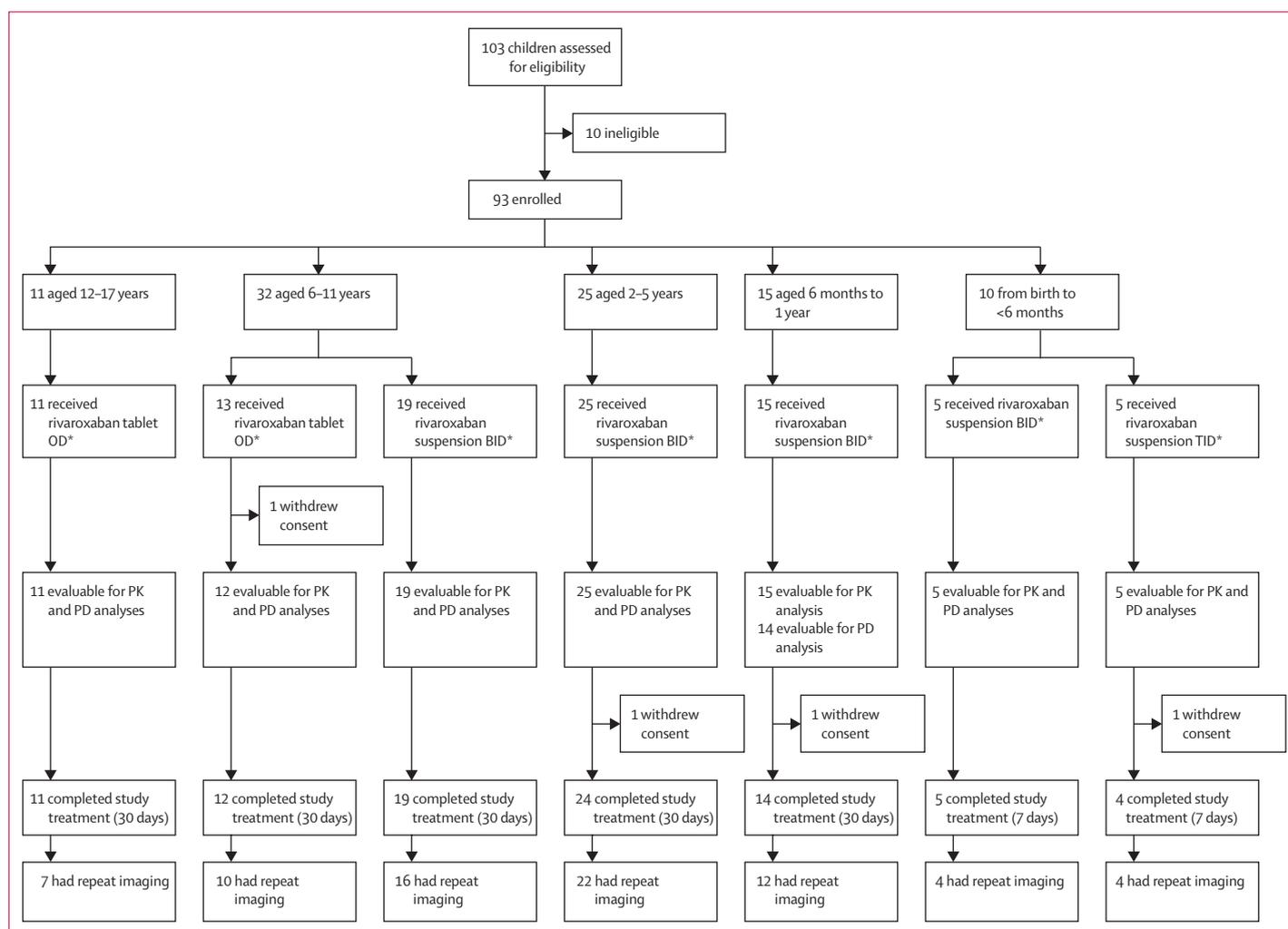


Figure 1: Trial profile

BID=twice daily. OD=once daily. PD=pharmacodynamic. PK=pharmacokinetic. TID=three times daily. *Evaluable for safety (n=93).

	Younger than 6 months, suspension (N=10)	6 months to 1 year, suspension (N=15)	2–5 years, suspension (N=25)	6–11 years, suspension (N=19)	6–11 years, tablet (N=13)	12–17 years, tablet (N=11)	Total (N=93)
Sex, n (%)							
Female	5 (50%)	9 (60%)	12 (48%)	6 (32%)	5 (38%)	8 (73%)	45 (48%)
Male	5 (50%)	6 (40%)	13 (52%)	13 (68%)	8 (62%)	3 (27%)	48 (52%)
Age, years							
Mean (SD)	0·1 (0·1)	1·4 (0·5)	4·2 (1·1)	8·0 (2·0)	9·2 (2·0)	16·1 (1·1)	6·4 (5·0)
Range	<0·1–0·5	0·6–2·0	2·1–5·8	6·1–12·0	6·7–11·9	14·5–17·3	<0·1–17·3
Weight, kg							
Mean (SD)	4·0 (1·6)	10·6 (2·4)	17·5 (5·4)	35·2 (11·9)	31·7 (9·9)	73·7 (44·6)	27·2 (25·9)
Range	2·8–8·2	5·8–14·1	12·5–39·6	18·4–58·2	21·8–55·9	20·0–194·2	2·8–194·2
Body-mass index, kg/m²							
Mean (SD)	..	17·8 (2·3)	16·3 (3·0)	19·2 (4·1)	17·8 (2·1)	26·0 (14·5)	18·8 (6·6)
Range	..	15·3–22·7	11·9–29·0	13·5–29·6	13·7–21·4	12·6–66·3	11·9–66·3
Race, n (%)							
White	8 (80%)	10 (67%)	23 (92%)	16 (84%)	11 (85%)	10 (91%)	78 (84%)
Black	1 (10%)	2 (13%)	1 (4%)	1 (5%)	1 (8%)	0	6 (6%)
Asian	0	1 (7%)	0	1 (5%)	0	1 (9%)	3 (3%)
Multiple or not reported	1 (10%)	2 (13%)	1 (4%)	1 (5%)	1 (8%)	0	6 (6%)
Index venous thromboembolism, n (%)							
Lower extremity, caval vein, lung, right atrium	7 (70%)	10 (67%)	6 (24%)	4 (21%)	1 (8%)	7 (64%)	35 (38%)
Upper extremity, subclavian vein, or both	0	0	4 (16%)	3 (16%)	4 (31%)	1 (9%)	12 (13%)
Cerebral vein and sinus, jugular vein or both	3 (30%)	5 (33%)	15 (60%)	12 (63%)	8 (62%)	3 (27%)	46 (49%)

..=not available.

Table 2: Baseline characteristics, by age group and method of administration

Role of the funding source

The funders of the study contributed to study design, data collection, data analysis, data interpretation, and writing of the report and were able to review and comment on the manuscript before publication. All authors had full access to all the data in the study, and the first author had final responsibility for the decision to submit for publication.

Results

Between Feb 11, 2013, and Dec 20, 2017, we enrolled 93 children (ten children younger than 6 months; 15 children aged 6 months to 1 year; 25 children aged 2–5 years; 32 children aged 6–11 years; and 11 children aged 12–17 years) into our study (figure 1). The demographic and clinical characteristics of the children are shown in table 2. Of the 93 children, 89 (96%) children completed study treatment and were evaluable for the safety and pharmacokinetic and pharmacodynamic endpoints. One (3%) child aged 6–11 years, one (4%) child aged 2–5 years, one (7%) child aged 6 months to 1 year, and one (10%) child younger than 6 months did not complete treatment (all because they withdrew consent). 92 (99%) children were evaluable for pharmacokinetic analyses (one [3%] child aged 6–11 years was excluded) and 91 (98%) children (one [3%] child aged 6–11 years and one [7%] child aged 6 months to 1 year were excluded) were evaluable for pharmacodynamic analyses. These two exclusions were because blood sampling was unsuccessful

(one of whom then withdrew consent). Repeat imaging at the end of the 30-day (or 7-day, if younger than 6 months) rivaroxaban treatment period was obtained in 75 (81%) children.

No major bleeding was reported in any patients. Clinically relevant non-major bleeding was reported in four (4%) children (95% CI 1·2–10·6), which presented as menorrhagia in three children aged 12–17 years and gingival bleeding in one child aged 6–11 years.

We found no symptomatic recurrent venous thromboembolism in any patients (0%; 95% CI 0–3·9). In those with repeat imaging, we found resolution of the venous thrombosis in 24 (32%) children, improvement in 43 (57%) children, and no relevant change in thrombosis burden in eight (11%) children (table 3). None of the children showed a deterioration on repeat imaging.

For children with a bodyweight of at least 30 kg, at steady state, all but one of the individual values for AUC(0–24), C_{max}, and C_{trough} were within the range of the adult reference population (figure 2). Children weighing less than 30 kg who received rivaroxaban once-daily as tablets had AUC(0–24) values lower than the adult median, with some values below the 5th percentile of the adult reference range. This effect on AUC(0–24) at steady state was not reported in children of the same bodyweight category who were treated with rivaroxaban oral suspension twice-daily, which can be explained by a higher daily rivaroxaban dose used in the twice-daily

regimen (table 1). In children with bodyweights of less than 20 kg, and particularly children with bodyweights of less than 12 kg, most individual AUC(0–24), C_{max} , and C_{trough} values were lower than the median or less than the adult reference range. Pharmacokinetic variable data did not cluster at the lower extreme of the range in the children with no relevant change on repeat imaging or at the higher extreme of the range in children with normalisation or improvement on repeat imaging or clinically relevant non-major bleeding (appendix p 6).

With few exceptions, individual prothrombin time and aPTT values were concordant with those of the adult reference population. The change in prothrombin time at the sampling timepoints during rivaroxaban treatment versus the prothrombin time at baseline were correlated with the plasma concentrations of rivaroxaban (appendix p 7). Results were comparable across all age categories and when rivaroxaban was administered as either once-daily tablets or oral suspension twice or three times daily. Few prothrombin time and aPTT values were greater than the 99% prediction intervals of the adult reference population. We found no age-related effects on pharmacodynamic response to rivaroxaban. We also noted a linear relationship between anti-factor Xa activity and rivaroxaban plasma concentrations (figure 3).

61 (66%) children had adverse events during the study (table 4). Pyrexia was the only adverse event that occurred in 10% of children or more. The most frequent grade 3 or worse adverse events were anaemia and neutropenia. No children were discontinued from rivaroxaban because of adverse events.

We confirmed rivaroxaban exposures after bodyweight-adjusted treatment with rivaroxaban once-daily in children with a bodyweight of at least 30 kg and twice-daily in children with a bodyweight of at least 20 kg but less than 30 kg (table 1). Children with a bodyweight of less than 20 kg, and particularly those with a bodyweight less than 12 kg, were found to have either a low or subtherapeutic exposure. Hence, rivaroxaban dosages to be used in future studies were revised for these weight categories to twice-daily administrations of rivaroxaban in those with a bodyweight of at least 12 kg but less than 20 kg and three times-daily administrations in those weighing less than 12 kg, to match the target adult exposure range while avoiding excessive concentrations at the end of the dosing interval (table 1).

Discussion

We found that, in children with a bodyweight of at least 30 kg, a once-daily rivaroxaban regimen had an exposure consistent with the adult reference range. In children with bodyweights of at least 20 kg but less than 30 kg, only the twice-daily rivaroxaban regimen offered an appropriate exposure. However, to achieve equivalent exposure, the daily dose of rivaroxaban should be increased in future studies in children with a bodyweight of less than 20 kg. Moreover, in children with bodyweight

	Younger than 6 months (N=8)	6 months to 1 year (N=12)	2–5 years (N=22)	6–11 years (N=26)	12–17 years (N=7)	Total (N=75)
Resolved	4 (50%)	5 (42%)	6 (27%)	6 (23%)	3 (43%)	24 (32%)
Improved	3 (38%)	4 (33%)	15 (68%)	17 (65%)	4 (57%)	43 (57%)
Unchanged	1 (13%)	3 (25%)	1 (5%)	3 (12%)	0	8 (11%)
Deteriorated	0	0	0	0	0	0

Data are n (%).

Table 3: Thrombotic burden between baseline imaging of the index event and repeat imaging at the end of the rivaroxaban treatment

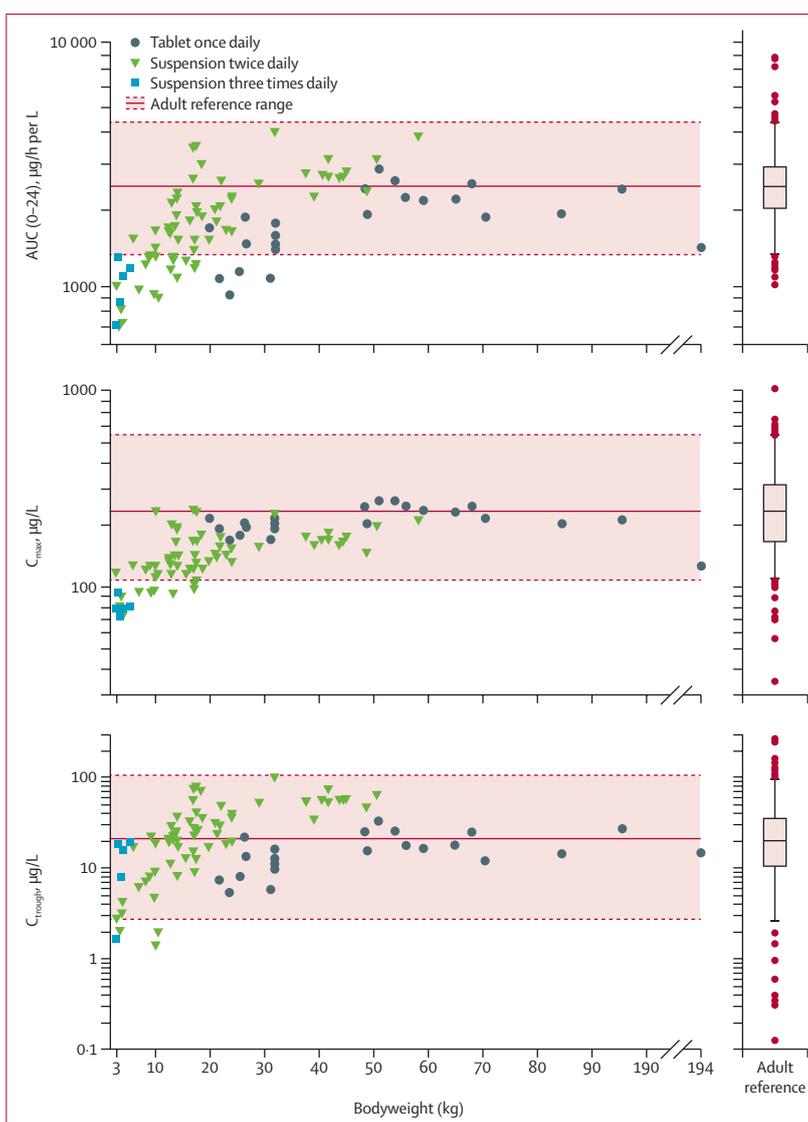


Figure 2: Pharmacokinetic results for children receiving bodyweight-adjusted rivaroxaban relative to adult patients with venous thromboembolism
Data are at steady state. Box and whisker plots (on the right of the graph) indicate the 5th, 25th, 50th, 75th, and 95th percentiles; open circles show individual values beyond the 5–95th percentile range of the adult venous thromboembolism patient population. AUC(0–24)=area under the plasma concentration–time curve from time 0 to 24 h.

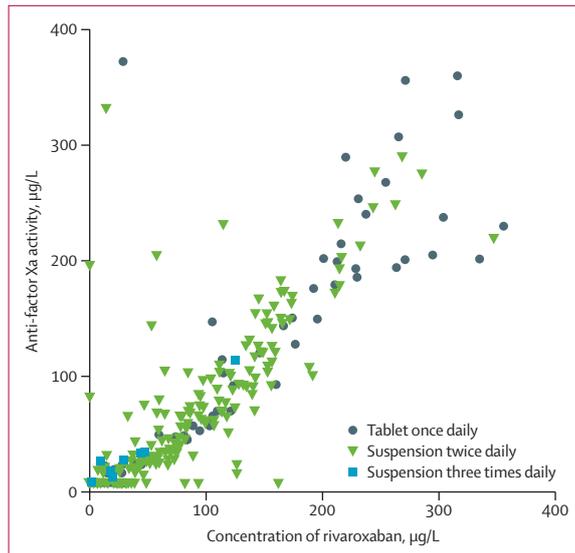


Figure 3: Factor Xa and rivaroxaban plasma concentrations

of less than 12 kg, a regimen of three administrations a day will be required. In our study, none of the children developed a recurrent venous thromboembolism or major bleeding, and most children showed either a normalisation or improvement of the index venous thromboembolism on repeat imaging at the end of the rivaroxaban treatment period, relative to the imaging tests obtained at presentation for the index event. However, all children received standard of care anticoagulation for the index event before the start of rivaroxaban and, therefore, the observed effects on thrombotic burden cannot be fully attributed to treatment with rivaroxaban.

Individual prothrombin time and aPTT values were within the adult reference range, and we confirmed linear correlations between change from baseline of these parameters and rivaroxaban plasma concentrations. We found no age-related effects on pharmacodynamic response to rivaroxaban, in concordance with results from previous in vitro experiments.^{13,14} We also observed a linear relationship between anti-factor Xa activity and plasma concentration of rivaroxaban.

Despite the absence of age-related differences in vitro, the required rivaroxaban daily doses per kg of bodyweight increased substantially with decreasing bodyweight, as was previously also reported for heparins and vitamin K antagonists.^{23,24} The exact mechanism for these differences is unknown and could relate to drug absorption, metabolism, or excretion. Further study of this observation is required. However, to achieve the required increase in daily dose of rivaroxaban while avoiding high peak concentrations and keeping trough concentrations within the adult reference range, a shortening of the dosing interval from 24 h to 12 h, and further to 8 h in the youngest children, was necessary.

	Grade 1-2	Grade 3	Grade 4
Any adverse event	48 (52%)	11 (12%)	2 (2%)
Acute lymphocytic leukaemia, recurrent	0	1 (1%)	0
Alanine aminotransferase (increased)	0	2 (2%)	0
Anaemia	0	4 (4%)	0
Asthma	0	1 (1%)	0
Atrial thrombosis*	0	1 (1%)	0
Bronchomalacia	0	1 (1%)	0
Cardiac arrest	0	0	1 (1%)
Febrile neutropenia	1 (1%)	0	1 (1%)
Gingival bleeding	0	1 (1%)	0
Influenza B virus (positive test)	0	1 (1%)	0
Neutropenia	2 (2%)	3 (3%)	0
Platelet count (decreased)	0	1 (1%)	0
Post-thrombotic syndrome	0	1 (1%)	0
Pyrexia	9 (10%)	1 (1%)	0
Thrombocytopenia	0	1 (1%)	0
Tracheomalacia	0	1 (1%)	0

Data are n (%) of events (as defined by the Medical Dictionary for Regulatory Activities). Data shown for all patients who received at least one dose of treatment (n=93). All grade 3 or worse events are shown, but grade 1-2 events are only shown if there were grade 3 or worse events. Grade 1-2 event would also have been shown had they occurred in at least 10% of children. No grade 5 events occurred. *The atrial thrombosis was discovered at the end of study treatment but was also retrospectively confirmed at baseline.

Table 4: Adverse events

Although the reported absence of major bleeding, recurrent venous thromboembolism, and deterioration on repeat imaging is reassuring, these findings do not provide proof of safety and efficacy of the established paediatric rivaroxaban dose regimens, predominantly because the number of children evaluated was relatively small, rivaroxaban was only administered after children had completed a period of weeks to months of anticoagulation with standard care, and daily rivaroxaban dosages were too low in those with bodyweights of less than 20 kg. It should be noted that, before the established paediatric rivaroxaban dose regimens can be implemented in clinical practice, additional randomised controlled evaluations in children with acute venous thromboembolism are required. In such studies, in which children will be treated with rivaroxaban soon after the onset of venous thromboembolism and for longer periods, both the efficacy and safety need to be documented. Additionally, the pharmacokinetic and pharmacodynamic profile of the established rivaroxaban regimens need to be confirmed for a longer treatment duration. In the EINSTEIN-Jr phase 3 study,^{18,19} several hundreds of children with differing manifestations of acute venous thromboembolism will be included. After initiation with parenteral anticoagulant therapy, children will be randomly assigned to continue treatment with either fixed doses of bodyweight-adjusted rivaroxaban,

with dosing regimens as determined in this study, or with standard of care, and they will be followed up to document the incidence of recurrent venous thromboembolism and bleeding. Extensive pharmacokinetic and pharmacodynamic data will be collected in the phase 3 study, to add further information about the optimal dosing for young children in subsequent clinical practice.

Our study has a few limitations. First, before starting rivaroxaban treatment, children were required to have completed anticoagulant treatment for at least 2 months or, in those with catheter-related venous thromboembolism, for at least 6 weeks. Children younger than 6 months were required to have completed at least 5 days of anticoagulant therapy. Since this treatment occurred before the study, we were unable to document treatment compliance and to assess its effects on the outcome of repeat imaging. Our decision to expose children to rivaroxaban at the time at which they had almost completed their regular anticoagulant treatment period was based on a safety-first approach because of the very little available data on rivaroxaban dosing in children and the high risk for recurrent venous thromboembolism and bleeding during the first weeks following presentation with acute venous thromboembolism. Second, we did not systematically collect data on individual risk factors for venous thromboembolism, and we are therefore unable to relate study outcomes to the presentation of venous thromboembolism. The importance of such risk factor profiles is recognised and, therefore, an extensive evaluation of risk factor profiles for venous thromboembolism in children is being completed in the large EINSTEIN-Jr phase 3 study. Finally, the studies evaluating children aged 6 years to younger than 18 years and 6 months to younger than 6 years initially had a randomised controlled design. However, because of slow recruitment and the need to collect enough pharmacokinetic and pharmacodynamic data in children of all ages, the studies were amended and continued as single-arm rivaroxaban studies.

In conclusion, treatment with bodyweight-adjusted rivaroxaban regimens appeared to be safe in children of all ages. Increased total daily doses are needed in children with bodyweights of less than 20 kg to achieve the exposures observed in young adults treated with 20 mg rivaroxaban once-daily, and a switch to twice-daily or three times-daily dosing regimens are required in children with bodyweights of at least 20 kg but less than 30 kg and less than 12 kg, to match the target exposure range while avoiding excessive peak plasma concentrations. The established paediatric rivaroxaban regimens will be prospectively evaluated in children with acute venous thromboembolism in EINSTEIN-Jr phase 3, to further document their clinical efficacy and safety.

Contributors

PM, AWAL, KT, CM, GY, ACM, UNG, GK, SK, SW, and DK designed the study design. AWAL, AFP, MB, and DK developed the statistical analysis

plan. AWAL, KT, SK, SW, TT, and DK were responsible for the daily conduct of the study. PM, IM, CM, AS, ES, RK, SH, PS, JR, GG, JH, PC, GY, ACM, UNG, GK, and JB-W recruited study participants. PM, AWAL, KT, CM, MHP, and DK wrote the manuscript with critical input from all co-authors, and all authors reviewed the revised manuscript and agreed to its submission.

Declaration of interests

AWAL, KT, SK, SW, AFP, MB, TT, and DK are employees of Bayer AG. IM, CM, RK, GY, GK, JB-W, and MHP report honoraria from Bayer AG. CM reports honoraria from Boehringer Ingelheim and Bristol-Myers Squibb. SH reports consultancy fees from Bristol-Myers Squibb. GY reports honoraria from Daiichi Sankyo and Portola Pharmaceuticals. GK reports honoraria from OPKO Biologics, Pfizer, CSL Behring, Alnylam Pharmaceuticals, Shire, and Roche. PM, AS, ES, PSa, PSi, JR, GG, JH, PC, ACM, and UNG declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this Article will be shared after de-identification (text, tables, figures, and appendices). The study protocol will also be made available. These data will become available beginning 1 year after Article publication, with no end date, to investigators whose proposed use of the data has been approved by researchers and who provide a methodologically sound proposal to achieve aims in the approved proposal. Proposals should be directed to the corresponding author (AWAL). To gain access, data requestors will need to sign a data access agreement.

Acknowledgments

This study was funded by Bayer AG and Janssen Research and Development.

References

- 1 Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th edn: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012; **141** (suppl 2): e737–801.
- 2 Buller HR, Lensing AWA, Prins MH, et al. A dose-ranging study evaluating once-daily oral administration of the factor Xa inhibitor rivaroxaban in the treatment of patients with acute symptomatic deep vein thrombosis: the EINSTEIN-DVT dose-ranging study. *Blood* 2008; **112**: 2242–47.
- 3 Agnelli G, Gallus A, Goldhaber SZ, et al. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59–7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59–7939 in Patients with Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation* 2007; **116**: 180–87.
- 4 Mueck W, Lensing AW, Agnelli G, et al. Rivaroxaban: population pharmacokinetic analyses in patients treated for acute deep vein thrombosis and exposure simulations in patients with atrial fibrillation treated for stroke prevention. *Clin Pharmacokinet* 2011; **50**: 675–86.
- 5 The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010; **363**: 2499–510.
- 6 The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med* 2012; **366**: 1287–97.
- 7 Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J* 2013; **11**: 21.
- 8 Weitz JI, Lensing AWA, Prins MH, et al. Extended treatment of venous thromboembolism. *N Engl J Med* 2017; **376**: 2491–92.
- 9 Bamber L, Wang MY, Prins MH, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. *Thromb Haemost* 2013; **110**: 732–41.
- 10 Prins MH, Bamber L, Cano SJ, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of pulmonary embolism; results from the EINSTEIN PE trial. *Thromb Res* 2015; **135**: 281–88.
- 11 Male C. Special situations III: medicines for children. In: Müller M, ed. *Clinical pharmacology: current topics and case studies*. Cham (Switzerland): Springer, 408–18.

- 12 Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. *Pediatrics* 2011; **128**: e1242–49.
- 13 Attard C, Monagle P, Kubitzka D, Ignjatovic V. The in vitro anticoagulant effect of rivaroxaban in children. *Thromb Res* 2012; **130**: 804–07.
- 14 Attard C, Monagle P, Kubitzka D, Ignjatovic V. The in-vitro anticoagulant effect of rivaroxaban in neonates. *Blood Coagul Fibrinolysis* 2014; **25**: 237–40.
- 15 Willmann S, Becker C, Burghaus R, et al. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. *Clin Pharmacokinet* 2014; **53**: 89–102.
- 16 Willmann S, Thelen K, Kubitzka D, et al. Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. *Thromb J* 2018; **16**: 32.
- 17 Kubitzka D, Willmann S, Becka M, et al. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban in children and adolescents: a phase I study. *Thromb J* 2018; **16**: 31.
- 18 Lensing AWA, Male C, Young G, et al. Rivaroxaban versus standard anticoagulation for acute venous thromboembolism in childhood. Design of the EINSTEIN-Jr phase III study. *Thromb J* 2018; **16**: 34.
- 19 Chan A, Lensing AW, Kubitzka D, et al. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. *Thromb J* 2018; **16**: 29.
- 20 Schulman S, Kearon C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005; **3**: 692–94.
- 21 Kaatz S, Ahmad D, Spyropoulos AC, Schulman S. Definition of clinically relevant non-major bleeding in studies of anticoagulants in atrial fibrillation and venous thromboembolic disease in non-surgical patients: communication from the SSC of the ISTH. *J Thromb Haemost* 2015; **13**: 2119–26.
- 22 Willmann S, Zhang L, Frede M, et al. Integrated population pharmacokinetic analysis of rivaroxaban across multiple patient populations. *CPT Pharmacometrics Syst Pharmacol* 2018; **5**: 309–20.
- 23 Malowany JI, Monagle P, Knoppert DC, et al. Enoxaparin for neonatal thrombosis: a call for a higher dose for neonates. *Thrombosis Res* 2008; **122**: 826–30.
- 24 Yee DL, O'Brien SH, Young G. Pharmacokinetics and pharmacodynamics of anticoagulants in paediatric patients. *Clin Pharmacokinet* 2013; **52**: 967–80.