Author/s:
Young, G;Lensing, AWA;Monagle, P;Male, C;Thelen, K;Willmann, S;Palumbo, JS;Kumar, R;Nurmeev, I;Hege, K;Bajolle, F;Connor, P;Hooimeijer, HL;Torres, M;Chan, AKC;Kenet, G;Holzhauer, S;Santamaría, A;Amedro, P;Beyer-Westendorf, J;Martinelli, I;Massicotte, MP;Smith, WT;Berkowitz, SD;Schmidt, S;Price, V;Prins, MH;Kubitza, D

Title:
Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation

Date:
2020-07-01

Citation:
Young, G., Lensing, A. W. A., Monagle, P., Male, C., Thelen, K., Willmann, S., Palumbo, J. S., Kumar, R., Nurmeev, I., Hege, K., Bajolle, F., Connor, P., Hooimeijer, H. L., Torres, M., Chan, A. K. C., Kenet, G., Holzhauer, S., Santamaría, A., Amedro, P. ,... Kubitza, D. (2020). Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr phase 3 dose-exposure-response evaluation. Journal of Thrombosis and Haemostasis, 18 (7), pp.1672-1685. https://doi.org/10.1111/jth.14813.

DR GUY YOUNG (Orcid ID : 0000-0001-6013-1254)

DR ANTHONY K CHAN (Orcid ID : 0000-0003-1551-3995)

DR IDA MARTINELLI (Orcid ID : 0000-0001-9218-3622)

DR SCOTT DARRELL BERKOWITZ (Orcid ID : 0000-0002-9428-4408)

Article type : Original Article

Rivaroxaban for treatment of pediatric venous thromboembolism. An Einstein-Jr Phase 3 dose-exposure-response evaluation

Guy Young,[1] Anthonie W.A. Lensing,[2] Paul Monagle,[3] Christoph Male,[4] Kirstin Thelen,[2] Stefan Willmann,[2] Joseph S. Palumbo,[5] Riten Kumar,[6] Ildar Nurmeev,[7] Kerry Hege,[8] Fanny Bajolle,[9] Philip Connor,[10] Hélène L. Hooimeijer,[11] Marcela Torres,[12] Anthony K.C. Chan,[13] Gili Kenet,[14] Susanne Holzhauer,[15] Amparo Santamaría,[16] Pascal Amedro,[17] Jan Beyer-Westendorf,[18] Ida Martinelli,[19] M. Patricia Massicotte,[20] William T. Smith,[21] Scott D. Berkowitz,[21] Stephan Schmidt,[22] Victoria Price,[23] Martin H. Prins,[24] Dagmar Kubitza,[2] for the EINSTEIN-Jr. Phase 3 Investigators*

1. Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, USA;
2. Bayer AG, Wuppertal, Germany;
3. Department of Clinical Haematology, Royal Children's Hospital, Haematology Research Murdoch Children's Research Institute, Department of Paediatrics, University of Melbourne, Australia.
4. Department of Paediatrics, Medical University of Vienna, Vienna, Austria;

5. Cancer and Blood Diseases Institute, Cincinnati Children's Hospital Medical Center; Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, OH, USA;
6. Nationwide Children's Hospital, The Ohio State University, Columbus, OH, USA;
7. Kazan State Medical University, Russia;
8. Riley Hospital For Children at IU Health, Indianapolis, IN, USA;
9. M3C-Necker Enfants malades, Université Paris Descartes, Sorbonne Paris Cité, Paris, France;
10. The Noah's Ark Children's Hospital for Wales, Cardiff, United Kingdom;
11. Department of Hematology and Oncology, University Medical Center Groningen, Beatrix Children's Hospital, Groningen, the Netherlands;
12. Department of Hematology and Oncology, Cook Children's Medical Center, Fort Worth, TX, USA;
13. McMaster Children's Hospital, Hamilton, ON, Canada;
14. Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, and the Israeli National Hemophilia Center and Thrombosis Unit, and The Amalia Biron Thrombosis Research Institute, Sheba Medical Center, Tel Hashomer, Israel;
15. Charité University Medicine, Department of Pediatric Hematology and Oncology, Berlin, Germany;
16. Hemostasis and Thrombosis Unit, Department of Hematology, University Hospital Vall d´Hebron, Barcelona, Spain;
17. Paediatric and Congenital Cardiology Department, M3C Regional Reference Centre, Montpellier University Hospital, PhyMedExp, INSERM, CNRS, Montpellier, France;
18. Department of Medicine I, Division of Haematology and Haemostaseology, University Hospital "Carl Gustav Carus" Dresden, and King's Thrombosis Service, Department of Haematology, King's College London, United Kingdom;
19. Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico, A. Bianchi Bonomi Hemophilia and Thrombosis Center, Milano, Italy;
20. Department of Paediatrics, University of Alberta, Edmonton, AB, Canada;
21. Bayer U.S., LLC, Whippany, NJ, USA;
22. Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, University of Florida, Orlando, USA,
23. Division of Pediatric Hematology/Oncology, Dept Pediatrics, Dalhousie University, IWK Health Centre, Halifax, Canada;
24. Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Center, Maastricht, The Netherlands

* A list of the EINSTEIN-Jr. investigators and collaborators is provided in the appendix.

Address reprint requests to Dr. Guy Young, Children's Hospital Los Angeles, University of Southern California Keck School of Medicine, Los Angeles, USA, or at GYoung@chla.usc.edu

Summary: 250

Article: 2798

Keywords: anticoagulation; bodyweight-adjusted dosing; pediatric patients; rivaroxaban; suspension; pharmacokinetics; venous thromboembolism.

Essentials

- Pediatric rivaroxaban treatment regimens with tablet or newly-developed oral suspension formulation had an exposure within the adult range
- Low or high values of pharmacokinetic parameters were not linked to efficacy, bleeding, or adverse event outcomes
- Bodyweight-adjusted pediatric rivaroxaban regimens are validated and provide for appropriate treatment of children with VTE

Abstract

Background Recently, the randomized EINSTEIN-Jr. study showed similar efficacy and safety for rivaroxaban and standard anticoagulation for treatment of pediatric venous thromboembolism (VTE). The rivaroxaban dosing strategy was established based on phase 1 and 2 data in children and through pharmacokinetic (PK) modeling.

Methods Rivaroxaban treatment with tablets or the newly-developed granules-for-oral suspension formulation was bodyweight-adjusted and administered once-daily, twice-daily or thrice-daily for children with bodyweights of ≥30, ≥12-<30, and <12kg, respectively. Previously, these regimens were confirmed for children weighing ≥20kg but only predicted in those <20kg. Based on sparse blood sampling, the daily area under the plasma concentration–time curve [$AUC_{(0-24)ss}$] and trough [$C_{trough,ss}$] and

maximum [$C_{max,ss}$] steady-state plasma concentrations were derived using population PK modeling. Exposure-response graphs were generated to evaluate the potential relationship of individual PK parameters with recurrent VTE, repeat imaging outcomes, and bleeding or adverse events. A taste-and-texture questionnaire was collected for suspension-recipients.

Results Of the 335 children (aged 0-17 years) allocated to rivaroxaban, 316 (94.3%) were evaluable for PK analyses. Rivaroxaban exposures were within the adult exposure range. No clustering was observed for any of the PK parameters with efficacy, bleeding, or adverse event outcomes. Results were similar for the tablet and suspension formulation. Acceptability and palatability of the suspension were favorable.

Discussion Based on this analysis and the recently documented similar efficacy and safety of rivaroxaban compared with standard anticoagulation, we conclude that bodyweight-adjusted pediatric rivaroxaban regimens with either tablets or suspension are validated and provide for appropriate treatment of children with VTE.

Funding

Bayer AG and Janssen Research & Development, LLC

Introduction

Randomized trials to evaluate anticoagulant therapy for venous thromboembolism (VTE) have almost exclusively targeted the adult population,[1,2] with only a single small randomized trial in children reported in 2003.[3] Regulatory initiatives in the United States and Europe to stimulate the development of high quality, adequately studied, ethically researched medicines for children,[4,5] have recently led to the development of the direct oral anticoagulant rivaroxaban for the treatment of VTE in children.[6]

The EINSTEIN-Jr. phase 3 trial compared the efficacy and safety of bodyweight-adjusted rivaroxaban regimens with those of standard anticoagulation in 500 children with acute VTE.[6] The incidence of recurrent VTE was low for rivaroxaban (1.2%;

4/335) and standard therapy (3.0%; 5/165), whereas no major bleeding events were observed with rivaroxaban. The absolute incidences of study outcomes and relative treatment effects observed in children who received rivaroxaban were similar to those in the large rivaroxaban VTE studies in adults.[7-10]

The rivaroxaban treatment regimens used in EINSTEIN-Jr. were based on the results of a phase 1 and 2 program in which children of all ages were administered rivaroxaban to target an exposure similar to that observed in young adults with VTE treated with rivaroxaban 20 mg once-daily.[11-14] In children with a bodyweight of 20 kg or more, the observed exposures were within the adult reference range.[14] However, in children with a bodyweight below 20 kg, exposures were too low and, therefore, the rivaroxaban treatment regimens for these children were adjusted based on pharmacokinetic (PK) modelling.[14]

To confirm that the revised bodyweight-adjusted rivaroxaban regimens used in the EINSTEIN-Jr. study attained adult exposures, blood samples were taken for PK analyses, applying a sparse sampling approach. In addition, values of the derived PK parameters were related to recurrent VTE, repeat imaging results, bleeding events, and adverse events.

Methods

Study design

EINSTEIN-Jr. (clinicaltrials.gov: NCT02234843) is a randomized, open-label, multi-center trial that compared the efficacy and safety of rivaroxaban with those of standard anticoagulants for treatment of VTE and evaluated the PK of rivaroxaban.[15] Clinical efficacy and safety results have previously been published.[6] The study was conducted at 107 sites in Australia, Europe, Israel, Japan, China, South America, and North America. The main study treatment period was 3 months, with the exception of children with catheter-related VTE younger than two years, for whom it was 1 month.[16] Randomization occurred in a 2 (rivaroxaban) to 1 (standard anticoagulation) ratio. The protocol was approved by the institutional review board of each participating center and written permission from a parent or legal guardian and, when appropriate, child assent, was obtained. The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization

Guidelines for Good Clinical Practice. A central, independent adjudication committee whose members were unaware of allocation of study treatment evaluated all index and suspected recurrent VTE events, deaths, and suspected episodes of bleeding. In addition, the committee reviewed all repeat imaging tests performed at the end of the study treatment period.

Patients

Children with objectively confirmed VTE were considered if they had initiated treatment with unfractionated heparin, low molecular weight (LMWH) heparin or fondaparinux. Children younger than 0.5 year were required to have a gestational age at birth of at least 37 weeks, a bodyweight above 2600 grams, and to have had oral feeding for at least 10 days.[15] The main exclusion criteria were 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, active bleeding or high risk of bleeding contraindicating anticoagulant therapy, an estimated glomerular filtration rate <30 mL/min/1.73 m^2 if younger than 1 year, serum creatinine >97.5th percentile, hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk, or ALT >5x upper limit of normal (ULN) or total bilirubin >2x ULN with direct bilirubin >20% of the total.[6,15]

Enrolment started with children aged 12 to 17 years once the PK data of rivaroxaban in the phase 2 study became available to support further dose and dosing regimen recommendations.[13,14] Thereafter, children aged 6-11, 2-5, 0.5-1 years, were enrolled, respectively, using a similar stepwise approach. Finally, we evaluated children younger than 0.5 year following the demonstration of safety in older children.

Rivaroxaban treatment regimens

Children were required to have completed at least 5 days of initial heparinization prior to start of treatment with rivaroxaban. Rivaroxaban was administered in a bodyweight-adjusted 20 mg-equivalent dose based on phase 1 and 2 data and comprehensive PK modeling predictions in either a once-daily, twice-daily or thrice-daily regimen in children with a bodyweight ≥30kg, ≥12-<30 kg, or <12 kg, respectively (table 1).[14] In children weighing <12kg, the lower range of the adult exposure range was targeted to avoid excessive concentrations at the end of the dosing interval.

Rivaroxaban was administered as immediate release film-coated tablets in dose strengths of 5, 10, 15 or 20 mg, or as a newly developed fruit-flavored suspension for oral use. The suspension was provided as granules in a bottle that had to be filled with water to achieve a concentration of 1 mg/mL and was administered using a standardized dosing device. Both rivaroxaban formulations were administered with an age-appropriate serving of fluid during or shortly after a meal. Initially, rivaroxaban was administered as tablets, but once recruitment of children younger than 6 years was allowed, all newly randomized children, including those older than 6 years, received the suspension.

Follow-up and outcomes

All children who stopped study treatment earlier than scheduled were followed until the end of the intended 3-month (or 1-month, if younger than 2 years and the VTE was catheter-related) treatment period. Patients were instructed to report to the study center if they had symptoms suggestive of bleeding or recurrent VTE. Bleeding events were classified as major, clinically relevant non-major, or trivial bleeding, respectively.[17,18] Objective testing was required for children in whom a recurrent VTE was suspected. In children without recurrence, repeat imaging of the venous thrombosis was performed at the end of the study treatment period (provided no additional ionizing radiation or general anesthetic was required) and was compared with baseline images. Results were classified as normalized, improved, uncertain, no relevant change, or deteriorated.[6,15] Adverse events were coded according to the Medical Dictionary for Regulatory Activities, version 21.1, and categorized by primary system organ class according to reported events coded to preferred terms.

Pharmacokinetic Assessments

Blood samples for PK were taken within specified time windows (table 2) and assessed at a central laboratory. Plasma concentrations of rivaroxaban were measured employing high-pressure liquid chromatography and tandem mass spectrometric detection with a calibration range from 0.500 to 500 µg/L. Quality control samples in the concentration range from 1.50 to 375 µg/L were determined with an accuracy of 100.0% to 100.8% and a precision of 4.7% to 7.2%.

A comprehensive pediatric population PK model, developed based on a previous pediatric model version and PK data pooled from all prior rivaroxaban pediatric

studies,[13,14,19] was used to evaluate rivaroxaban PK. The following main PK parameters were derived at steady-state ($_{SS}$) for each individual: area under the plasma concentration–time curve from time 0 to 24 hours [$AUC(0\text{-}24)_{ss}$] as a measure for daily exposure, maximum plasma concentration [$C_{max,ss}$], and concentration at the end of the dosing interval [$C_{trough,ss}$]. Individual results were plotted as a function of bodyweight and compared with the adult reference range (obtained in 203 adults with VTE younger than 45 years who had received 20 mg rivaroxaban once-daily).[19] In addition, exposure-response graphs were created to display the relationship of PK parameters with individual outcomes associated with poor efficacy (i.e., symptomatic recurrent VTE, or asymptomatic deterioration or no relevant change on repeat imaging), or bleeding events, or adverse events.

Taste-and-texture questionnaire

Acceptability and palatability of the rivaroxaban granules-for-oral-suspension formulation was assessed at the day 30 visit in children aged 4-17 years, using a hedonic scale of facial expressions (comfortable, indifference, or uncomfortable) and questions (like it, do not like it, or do not know). Children were also asked if they agreed with specific descriptors of taste and texture.

Statistical Analysis

Demographics and clinical characteristics are presented by formulation (rivaroxaban tablet or suspension) and age group. Efficacy outcomes were considered during the main study treatment period, whereas safety outcomes and adverse events were considered for the same period but during the time from administration of the first dose of rivaroxaban to 48 hours after the administration of the last dose. For this analysis, recurrent VTE, results of repeat imaging, bleeding and adverse events were considered in the population of children who were valid for PK analyses. Calculations were performed using SAS 9.2 (SAS Institute Inc., Cary, NC, USA). This trial is registered with ClinicalTrials.gov, number NCT02234843.

Role of the funding source

The study was supported by Bayer AG and Janssen Research & Development, LLC. The funders contributed to study design, data collection, data analysis, data interpretation, writing of the report, and had the possibility to review and comment the manuscript before publication. Data were collected by the authors and their research

teams. All authors had access to all study data and the first author had responsibility for the final version of the manuscript that was submitted.

Results

Between November 14, 2014 and September 28, 2018, a total of 335 children were allocated to receive rivaroxaban. Of these, 19 (5.7%) children were excluded from this analysis because they did not receive rivaroxaban (n=6), withdrew informed consent (n=6), or an adequate blood sample could not be obtained (n=7). The demographic and clinical characteristics of the 316 (94.3%) children in the five age groups (birth-<0.5 year, n=13; 0.5-1 year, n=21; 2-5 years, n=44; 6-11 years, n=65; and 12-17 years, n=173) are shown in table 3. A total of 121 (38.3%) children received the rivaroxaban tablet formulation and 195 (61.7%) the suspension formulation.

Clinical outcomes

Symptomatic recurrent VTE occurred in 2 children (0.6%) during rivaroxaban treatment. Repeat imaging outcomes in the asymptomatic children were classified as normalized 124 (39.2%), improved in 125 (39.6%), no relevant change in 16 (5.1%), and deteriorated in 1 (0.3%). In 48 children (15.2%) the result of repeat imaging was uncertain. No major bleeding events occurred with rivaroxaban treatment, whereas clinically relevant non-major bleeding and trivial bleeding were observed in 10 (3.2%) and 111 (35.1%) children, respectively. A total of 488 adverse events were identified.

Dose-exposure relationship

Geometric mean values for the half-life of rivaroxaban decreased with decreasing age from 4.2 h in children aged 12 years or older to approximately 3 h in children aged 2 to11 and 1.9 and 1.6 h in children aged 0.5 to 1 year and less than 0.5 year, respectively. As expected, relative oral bioavailability decreased with increasing dose per bodyweight. Individual values for $AUC(0\text{-}24)_{ss}$, $C_{max,ss}$ and $C_{trough,ss}$ were within the adult reference range, irrespective of rivaroxaban formulation, age, bodyweight, and treatment regimens. The vast majority of the individual values were within the 5^{th} to 95^{th} percentile of the adult exposure range (figure 1). As intended, in children with bodyweight below 12 kg, values for $AUC(0\text{-}24)_{ss}$ scattered below the median of the adult exposure range with decreasing bodyweights. In children with bodyweight below 7 kg, some $AUC(0\text{-}24)_{ss}$ values even fell below the 5^{th} percentile of the adult

exposure range but were still in the range of individual adult values below the 5th percentile. Values for $C_{max,ss}$ were within the adult exposure range and inversely correlated with the number of daily rivaroxaban administrations: compared with once-daily administration, the $C_{max,ss}$ was lower with twice-daily and lowest with thrice-daily administration. Values for $C_{trough,ss}$ were also well within the adult exposure range and showed a trend towards slightly higher values for twice-daily and thrice-daily administrations as compared with once-daily administration. Results were comparable for the tablet and suspension formulation (table 4). No influence of weak, moderate and strong CYP3A4 inhibitors, P-gp inhibitors and CYP3A4 inducers on rivaroxaban clearance was identified.

Exposure-response relationship

Figures 2, 3 and 4 show the individual results for $AUC(0\text{-}24)_{ss}$, $C_{max,ss}$ and $C_{trough,ss}$ in relation to recurrent VTE, results of repeat imaging, bleeding events, and (treatment-related) adverse events, respectively. Values of these PK parameters did not cluster at the lower part of the exposure range in children with recurrent VTE, asymptomatic deterioration or no relevant change on repeat imaging. There was also no evidence of PK parameters clustering at the higher end of the range in children with normalization or improvement on repeat imaging, or bleeding. No clustering at the lower or higher end of the exposure range was observed with adverse events.

Acceptability and palatability of the rivaroxaban suspension

The taste-and-texture questionnaire was completed by 130 out of 168 children (77.4%) who were administered the suspension formulation. The majority of children responded with expressions of comfort or indifference regarding the appearance (93.9%), smell (93.1%), and taste (86.8%), respectively). The majority also liked the taste (83.1%) and would like to take the suspension again (79.1%). The most frequent affirmative responses for descriptors of taste and texture of the suspension were for ‘sweet’ (50.0%) and ‘creamy’ (40.0%).

Discussion

In children with acute VTE, bodyweight-adjusted pediatric rivaroxaban regimens, as derived based on extensive phase 1 and 2 evaluations and PK modelling,[13,14] achieved an exposure match with the targeted adult exposure range, while avoiding

high plasma concentrations at peak and at the end of the dosing intervals. The observed trend towards decreasing oral bioavailability of rivaroxaban with increasing dose per bodyweight is in line with the dose-dependency of the relative oral bioavailability observed in adults.[19] Exposure-response evaluations did not reveal clustering of any of the main PK parameters with efficacy outcomes, bleeding events, or adverse events (figures 2-4), suggesting a wide therapeutic window of the pediatric rivaroxaban treatment regimens. Results were similar for the tablet and the newly-developed suspension formulation. Based on this dose-exposure-response analysis and the recently reported similar efficacy and safety of rivaroxaban compared with standard anticoagulation,[6] we conclude that the bodyweight-adjusted rivaroxaban regimens with either tablets or the new suspension formulation are validated and provide an alternative treatment option for VTE in children.

The availability of an anticoagulant treatment regimen which is administered orally and does not require routine laboratory monitoring and dose titration is a major step forward for the treatment of VTE in children. In the comparator group of the EINSTEIN-Jr. phase 3 study,[6] only one-third of children transitioned from initial subcutaneous heparin treatment to oral treatment with a vitamin K antagonist, necessitating the majority of neonates, infants, and young children to be exposed to subcutaneous injections on a twice-daily basis for a period of weeks to months. In addition, the rapid onset of action of rivaroxaban,[7] in combination with the a priori bodyweight-defined therapeutic dose, translates into a minimization of exposure at sub-therapeutic or supra-therapeutic concentrations.

Liquid formulations of anticoagulants for use in children are not commercially available, and, therefore, the introduction of the rivaroxaban granules-for-oral suspension is a milestone in itself. The availability of such a formulation will be instrumental to abolish the common practice of manipulation of adult dosage forms of anticoagulants to achieve the recommended pediatric dose,[20-22] thereby preventing issues with stability, and dosing errors associated with such manipulation. Although not evaluated in the present study, it can be assumed that patient-reported satisfaction and quality of life would also be improved with the pediatric rivaroxaban treatment regimens compared with long-term parenteral low-molecular-weight heparin with or without subsequent laboratory-adjusted vitamin K antagonist therapy. Indeed, studies have shown that hospitalized children report needle procedures as

one of the most feared and painful experiences which may result in needle phobia and increased avoidance behavior and attempts to eliminate any possible exposure to needles.[23,24]

Although the pediatric rivaroxaban treatment regimens matched the adult exposure reference range (figure 1) and no relationship was found between low or high plasma concentrations and efficacy or safety outcomes (figures 2-4), occasional laboratory measurement and dose titration may be useful in certain children. Children who may qualify for measurement include those with potentially impaired absorption due to gastrointestinal disease, severe renal impairment, complicated morbidities, and multiple drug use. In addition, judicious laboratory measurement may be indicated to determine drug levels in case of suspected therapeutic failure, bleeding, poor adherence, or planned invasive procedures. In a separate publication, the pharmacodynamic assessment of children treated with rivaroxaban will be reported in detail and possibilities for therapeutic drug monitoring will be discussed.

Our study has the following limitations. First, a conventionally designed study using rich blood sampling to determine concentrations for a full PK parameter calculation using standard PK methods was not possible in children due to limitations on blood sample volumes taken in any single 24-h period and across other time periods. However, we adopted a sparse sampling approach using population-based PK modelling that allowed for a reduction in the number of samples required from each child within an age group by increasing the overall population size. Second, PK measurements were collected at predefined moments and were correlated with recurrent VTE, bleeding or adverse events that occurred throughout the duration of the study. PK measurements immediately before these events occurred were not available.

In summary, treatment of children with bodyweight-adjusted rivaroxaban regimens resulted in exposures similar to that previously observed in young adults treated with rivaroxaban 20 mg once daily. Observed values of rivaroxaban exposure were not related to the occurrence of efficacy, safety outcomes, or adverse events. Based on this analysis and in conjunction with the documented similar efficacy and safety of rivaroxaban compared with standard anticoagulation, we conclude that the bodyweight-adjusted pediatric rivaroxaban regimens with either tablets or the newly

developed suspension are validated and provide an alternative treatment option for VTE in children.

Acknowledgements

The authors thank the children who participated in this study and their supportive families, as well as the investigators, subinvestigators, and coordinators at each of the study sites. This work was funded by Bayer AG and Janssen Research & Development. LLC.

Author Contribution

G.Y., A.W.A.L., P.M., C.M., A.K.C.C., G.K., M.P.M., D.K. designed the study, led the study, analyzed the data, and wrote the manuscript; K.T., S.W. performed the pharmacokinetic analyses and modelling, developed the analysis plan, and edited the manuscript; J.S.P., R.K., I.N., K.H., F.B., P.C., H.L.H., M.T., S.H., A.S., P.A., J. B-W., I.M. were study principal investigators, analyzed data, and edited the manuscript; W.T.S., S.D.B. led the study, and edited the manuscript; M.H.P. was member of the adjudication committee, analyzed data, and edited the manuscript; S.S., V.P. were members of the data safety monitoring board, and edited the manuscript. All authors contributed to the writing of the manuscript, approved the final version, and agree to be accountable for all aspects of the report.

Conflict of interest

G.Y. has received honoraria from Bayer AG, Daiichi-Sankyo, and Portola; C.M. has received honoraria from Bayer AG, Boehringer Ingelheim, and Bristol-Myers Squibb; R.K. receiving personal fees from Bayer, Genentech, and Kedrion; P.C. receiving personal fees from Onyx Health Limited; A.K.C.C. receiving personal fees from Bayer and fees, paid to his institution, from Bayer, Pfizer, Daiichi Sankyo, and Bristol-Myers-Squibb; G.K. receiving personal fees from Bayer, Boehringer Ingelheim, and Daiichi-Sankyo and fees, paid to her institution from Pfizer; S.H. receiving personal fees from Pfizer and fees, paid to her institution, from Bayer, Pfizer, and Daiichi Sankyo; A.S. receiving personal fees from Bayer, Pfizer, Daiichi Sankyo and Boehringer Ingelheim; P.A. receiving personal fees and fees, paid to his institution, from Abbvie and Bayer, and fees paid to his institution from Actelion, Novartis, and Daiichi Sankyo; J.B-W.

receiving personal fees and fees, paid to his institution, from Bayer, Daiichi Sankyo, DOASENSE and Portola and fees, paid to his institution, from Pfizer; I.M. receiving fees from Sanofi and Bayer; M.P.M. receiving personal fees from Bayer; S.S., V.P., and M.H.P. receiving personal fees from Bayer AG; A.W.A.L., K.T., S.W., W.T.S., S.D.B., and D.K. being employees of Bayer AG; the remaining authors declare no competing financial interests.

References

1. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic therapy for VTE disease: CHEST guideline and expert panel report. Chest 2016;149:315-52.
2. Monagle P, Chan AK, Goldenberg NA, Ichord RN, Journeycake JM, Nowak-Göttl U, Vesely SK. Antithrombotic therapy in neonates and children: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e737S-801S.
3. Massicotte P, Julian JA, Gent M, Shields K, Marzinotto V, Szechtman B, Andrew M; REVIVE Study Group. An open-label randomized controlled trial of low molecular weight heparin compared to heparin and coumadin for the treatment of venous thromboembolic events in children: the REVIVE trial. Thromb Res 2003;109:85-92. 32.
4. European Medicines Agency, Rivaroxaban Paediatric Investigation Plan, 2017. http://www.ema.europa.eu/docs/en_GB/document_library/PIP_decision/WC500232013.pdf (last accessed 2019-04).
5. FDA list of pediatric written requests issued: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050002.htm (last accessed 2019-04).
6. Male C, Lensing AWA, Palumbo J, et al. Randomised controlled trial of rivaroxaban compared to standard anticoagulants for the treatment of acute venous thromboembolism in children. Lancet Haematology 2019 https://doi.org/10.1016/S2352-3026(19)30219-4.

7. 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.
8. The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-2510.
9. The EINSTEIN–PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-1297.
10. 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;11:21-21.
11. Willmann S, Thelen K, Kubitza D, Lensing AWA, Frede M, Coboeken K, Stampfuss J, Burghaus R, Mück W, Lippert J: Pharmacokinetics of rivaroxaban in children using physiologically based and population pharmacokinetic modelling: an EINSTEIN-Jr phase I study. Thromb J 2018;16:32.
12. Willmann S, Becker C, Burghaus R, Coboeken K, Edginton A, Lippert J, Siegmund HU, Thelen K, Mück W. Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. Clin Pharmacokinet 2014;53:89-102.
13. Kubitza D, Willmann S, Becka M, et al. Exploratory evaluation of pharmacodynamics, pharmacokinetics and safety of rivaroxaban in children and adolescents: an EINSTEIN-Junior phase I study. Thromb J 2018;16:31.
14. Monagle P, Lensing AWA, Thelen K, et al. Bodyweight-adjusted rivaroxaban for children with venous thromboembolism (EINSTEIN-Jr): results from three multicenter, single-arm, phase 2 studies. Lancet Haematology 2019; 6: e500–09.
15. 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.

16. Chan A, Lensing AW, Kubitza D, Brown G, Elorza D, Ybarra M, et al. Clinical presentation and therapeutic management of venous thrombosis in young children: a retrospective analysis. Thromb J 2018;16:29.
17. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005;3:692-4.
18. 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.
19. Willmann S, Zhang L, Frede M, Kubitza D, Mueck W, et al. Integrated population pharmacokinetic analysis of rivaroxaban across multiple patient populations CPT Pharmacometrics Syst Pharmacol 2018;5:309-20.
20. Standing JF, Tuleu C. Paediatric formulations - Getting to the heart of the problem. International Journal of Pharmaceutics 2005;300:56–66.
21. Richey RH, Shah UU, Peak M, Craig JV, Ford JL, Barker CE, Nunn AJ, Turner MA. Manipulation of drugs to achieve the required dose is intrinsic to paediatric practice but is not supported by guidelines or evidence. BMC Pediatrics 2013;13:81-8.
22. Richey RH, Hughes C, Craig JV, Shaha UU, Ford JL. A systematic review of the use of dosage form manipulation to obtain required doses to inform use of manipulation in paediatric practice. International Journal of Pharmaceutics 2017;518:155-166.
23. Hart D, Bossert E. Self-reported fears of hospitalized school-age children. J Pediatr Nurs 1994;2:83-90.
24. Kortesluoma R. L., Nikkonen M. 'The most disgusting ever': children's descriptions and views of the purpose of pain. J Child Health Care 2006;10:213-27.
25.

Table 1. Total daily bodyweight-adjusted rivaroxaban doses as evaluated in the EINSTEIN-Jr. Phase 3 study.

Bodyweight, kg		Rivaroxaban dose (mg) regimens used in phase 3	
		Total daily dose	**Regimen**
		2.4	**0.8 TID**
3	<4	**2.7**	**0.9 TID**
4	<5	**4.2**	**1.4 TID**
5	<7	**4.8**	**1.6 TID**
7	<8	**5.4**	**1.8 TID**
8	<9	**7.2**	**2.4 TID**
9	<10	**8.4**	**2.8 TID**
10	<12	**9.0**	**3.0 TID**
12	<30	**10.0**	**5.0 BID**
30	<50	**15.0**	**15.0 OD**
≥ 50		**20.0**	**20.0 OD**

*Dosing regimen, including dosing frequency, was adjusted if the child's bodyweight changed during the study. OD denotes once-daily, BID twice-daily, and TID thrice-daily.

Table 2. PK blood sampling schedule

Children administered rivaroxaban in a once-daily or twice-daily regimen						
	Day 2		**Day 30**		**Day 60**	**Day 90**
			0.5-1.5h post dose	2.5-4h post dose	2-8h post dose	morning trough*
PK sample	-	-	X	X	X	X
Children administered rivaroxaban in a thrice-daily regimen						
	0.5-3h post dose	7-8h post dose	0.5-3h post dose	7-8h post dose	2-6h post dose	10-16h post evening dose
PK sample	X	X	X[#]	X[#]	X	
PK denotes pharmacokinetics; *20-24h / 10-16h after last dose on previous day; in children aged <2 years with catheter-related venous thrombosis, trough sample already taken on Day 30; [#]slightly modified for children weighing <3250 grams at the time of Day 30 visit.						

Table 3. Demographic and clinical characteristics.

		Birth-<0.5 year	0.5-1 year	2-5 years	6-11 years		12-17 years		Total	
		Suspension	Suspension	Suspension	Suspension	Tablet	Suspension	Tablet	Suspension	Tablet
		n=13	n=21	n=44	n=47	n=18	n=70	n=103	n=195	n=121
Sex	Male, N (%)	10 (77.0)	11 (52.4)	21 (47.7)	28 (59.6)	14 (77.8)	28 (40.0)	49 (47.6)	98 (50.3)	63 (52.1)
Age, years	Mean (SD)	0.2 (0.2)	1.1 (0.48)	3.9 (1.2)	8.8 (1.7)	9.0 (1.8)	15.7 (1.4)	15.7 (1.6)	8.8 (6.0)	14.7 (2.9)
Weight (kg)	Mean (SD)	4.0 (1.0)	9.4 (2.4)	15.7 (3.4)	29.2 (10.0)	34.2 (12.7)	67.1 (19.8)	68.2 (18.9)	35.9 (27.7)	63.1 (21.8)
	Range	2.7 – 6.0	5.4 – 15.1	10.1 – 25.0	17.0 – 71.0	20.8 – 64.1	34.7 – 135.0	27.2–132.5	2.7 – 135.5	20.8–132.5
Race	White	8 (61.5)	12 (57.2)	37 (84.1)	39 (83.0)	10 (55.6)	66 (94.3)	85 (82.5)	162 (83.1)	95 (78.5)
	Black	1 (7.7)	2 (9.5)	1 (2.3)	1 (2.1)	1 (5.6)	0	5 (4.9)	5 (2.6)	6 (5.0)
	Asian	1 (7.7)	4 (19.1)	2 (4.6)	3 (6.4)	6 (33.3)	0	2 (1.9)	10 (5.1)	8 (6.6)
	Other, multiple, or not reported	3 (23.1)	3 (14.3)	4 (9.1)	4 (8.5)	1 (5.6)	4 (5.7)	11 (10.7)	18 (9.2)	12 (9.9)

Index VTE	CVST, N (%)	0	4 (19.1)	21 (47.7)	21 (44.7)	9 (50.0)	6 (8.6)	10 (9.7)	52 (26.7)	19 (15.7)
	CVC-VTE, N (%)	9 (69.2)	15 (71.4)	18 (40.9)	11 (23.4)	5 (27.8)	12 (17.1)	16 (15.5)	65 (33.3)	21 (17.4)
	Non-CVC-VTE, N (%)	4 (30.8)	2 (9.5)	5 (11.4)	15 (31.9)	4 (22.2)	52 (74.3)	77 (74.8)	78 (40.0)	81 (66.9)
Active cancer		0	1 (4.8)	8 (18.2)	6 (12.8)	3 (16.7)	6 (8.6)	10 (9.7)	21 (10.8)	13 (10.7)
Major organ disease		8 (61.5)	8 (38.1)	10 (22.7)	11 (23.4)	5 (27.8)	8 (11.4)	10 (9.7)	45 (23.1)	15 (12.4)
Major trauma /or surgery		4 (30.8)	8 (38.1)	13 (29.5)	15 (31.9)	3 (16.7)	17 (24.3)	17 (16.5)	57 (29.2)	20 (16.5)
Infectious disease		1 (7.7)	9 (42.9)	25 (56.8)	22 (46.8)	6 (33.3)	13 (18.6)	17 (16.5)	70 (35.9)	23 (19.0)

CVST denotes cerebral venous sinus thrombosis, CVC central venous catheter, VTE venous thromboembolism, SD standard deviation.

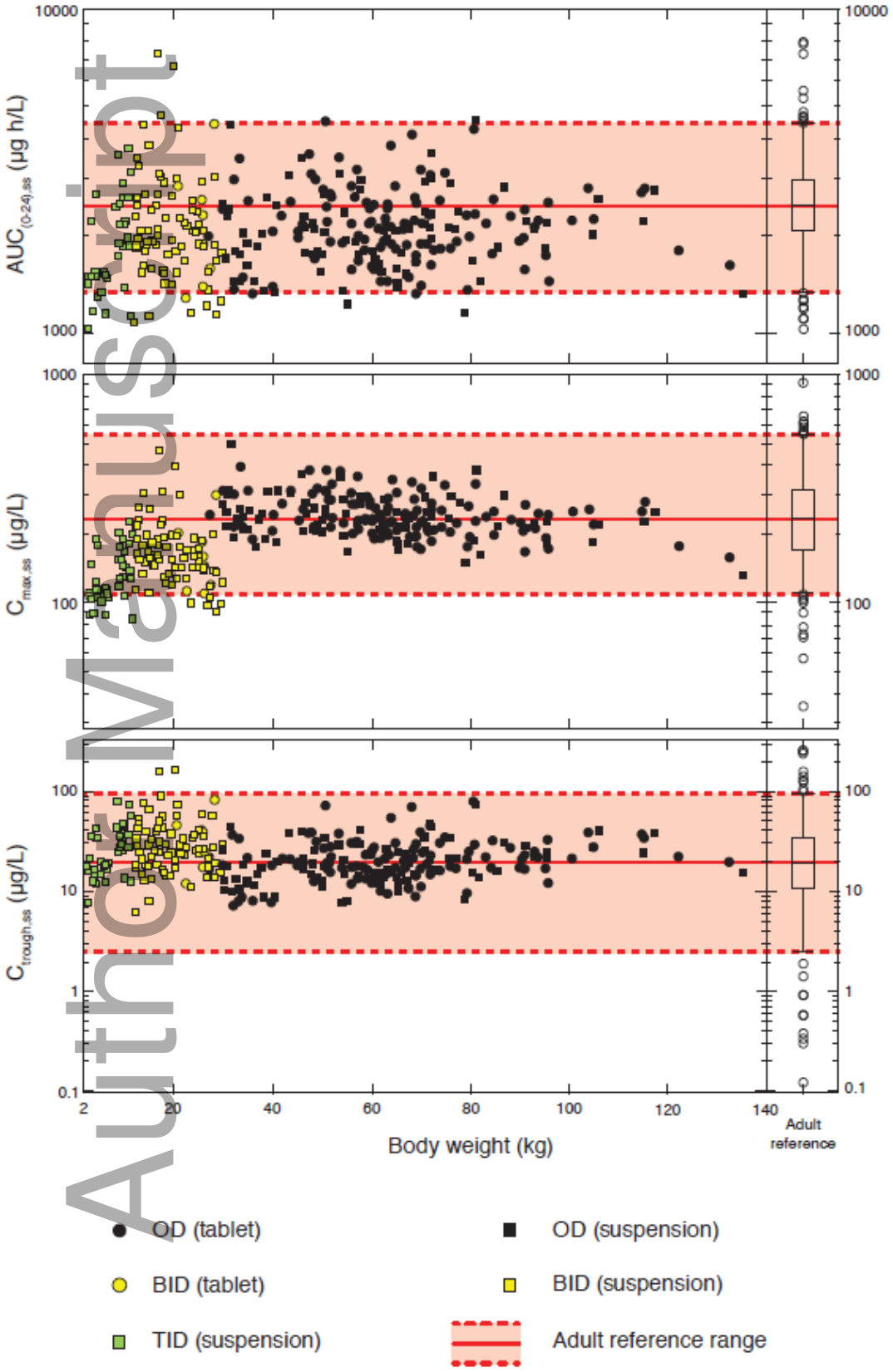
Table 4. Exposures observed in children aged between 6 and 18 years who received rivaroxaban tablets or oral suspension once-daily.

	Children aged 6 to 11 years	Children aged 12 to17 years

PopPK parameter, geometric mean/%CV (range)	Tablet N=10	Suspension N=19	Tablet N=103	Suspension N=70
$AUC(0\text{-}24)_{ss}$ (µg*h/L)	1960/41.4 (1310-3790)	1960/27.0 (1350-4390)	2170/25.2 (1320-4490)	2050/28.0 (1140-4540)
$C_{max,ss}$ (µg/L)	254/26.3 (189-395)	243/21.9 (189-487)	242/19.1 (158-383)	232/21.2 (131-380)
$C_{trough,ss}$ (µg/L)	14.6/78.1 (7.08-53.6)	15.8/45.6 (8.38-44.3)	21.4/43.5 (8.78-78.5)	19.7/49.1 (7.74-74.9)

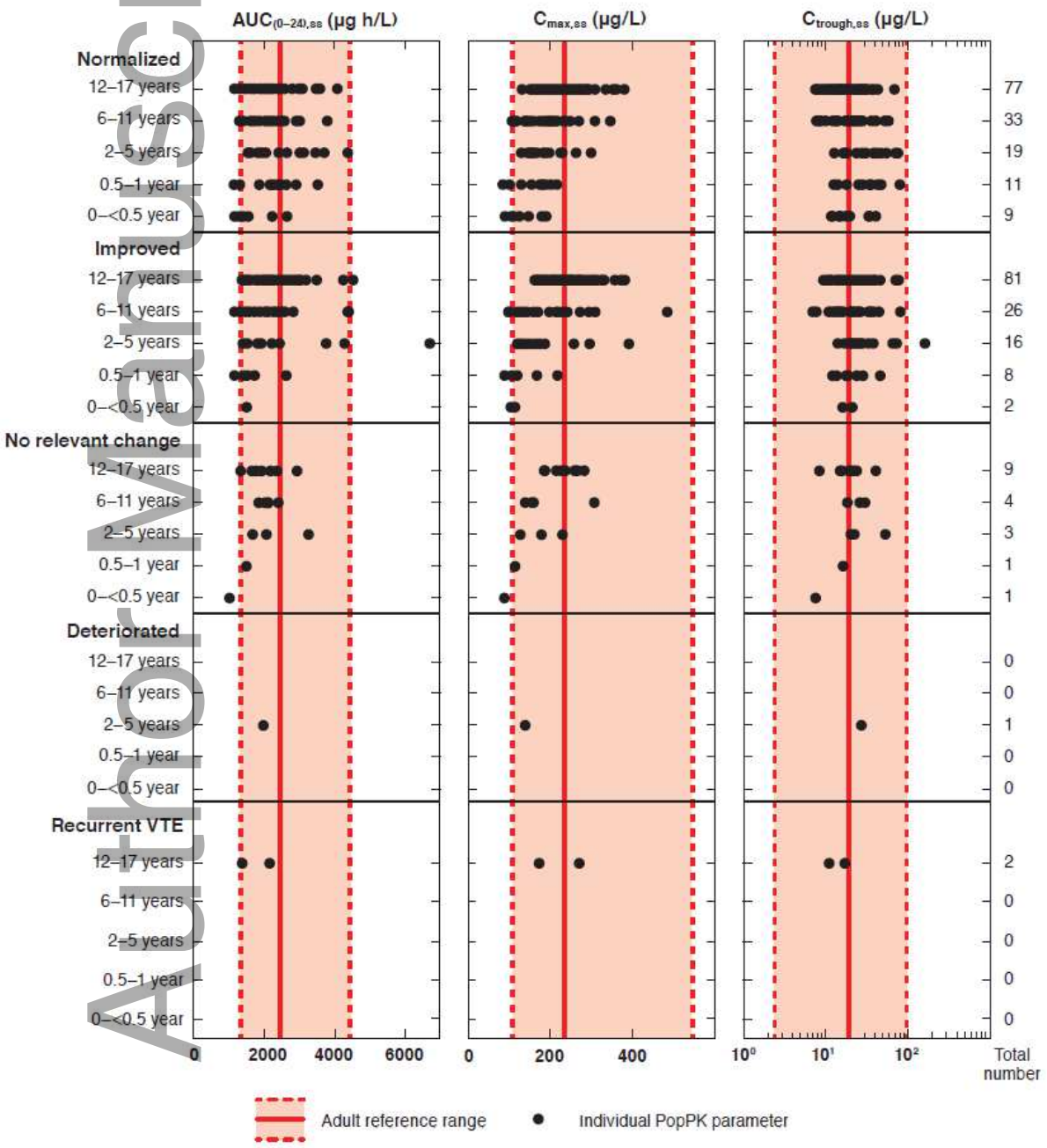
PopPK denotes population pharmacokinetics, %CV coefficient of variation (%), µg microgram, h hour(s), L liter, $AUC(0\text{-}24)_{ss}$ area under the curve from 0 to 24h at steady state, $C_{max,ss}$ maximum drug concentration at steady state, $C_{trough,ss}$ trough concentration at steady state.

Figure 1. Population PK modeling results for children receiving bodyweight-adjusted rivaroxaban in comparison to adult VTE patients.



Box-whisker plot indicates the 5th, 25th, 50th, 75th, and 95th percentiles; extremes as open circles show individual values beyond the 5th-95th percentile range of the adult VTE patient population. OD denotes once-daily, BID twice-daily, TID thrice-daily, and VTE venous thromboembolism.

Figure 2. Correlation of rivaroxaban plasma concentrations in children with outcomes of repeat imaging or recurrent VTE in comparison to the adult reference range.



PopPK denotes population pharmacokinetics, VTE venous thromboembolism, $AUC(0\text{-}24)_{ss}$ 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.

Figure 3. Correlation of rivaroxaban plasma concentrations with treatment-emergent bleeding events.

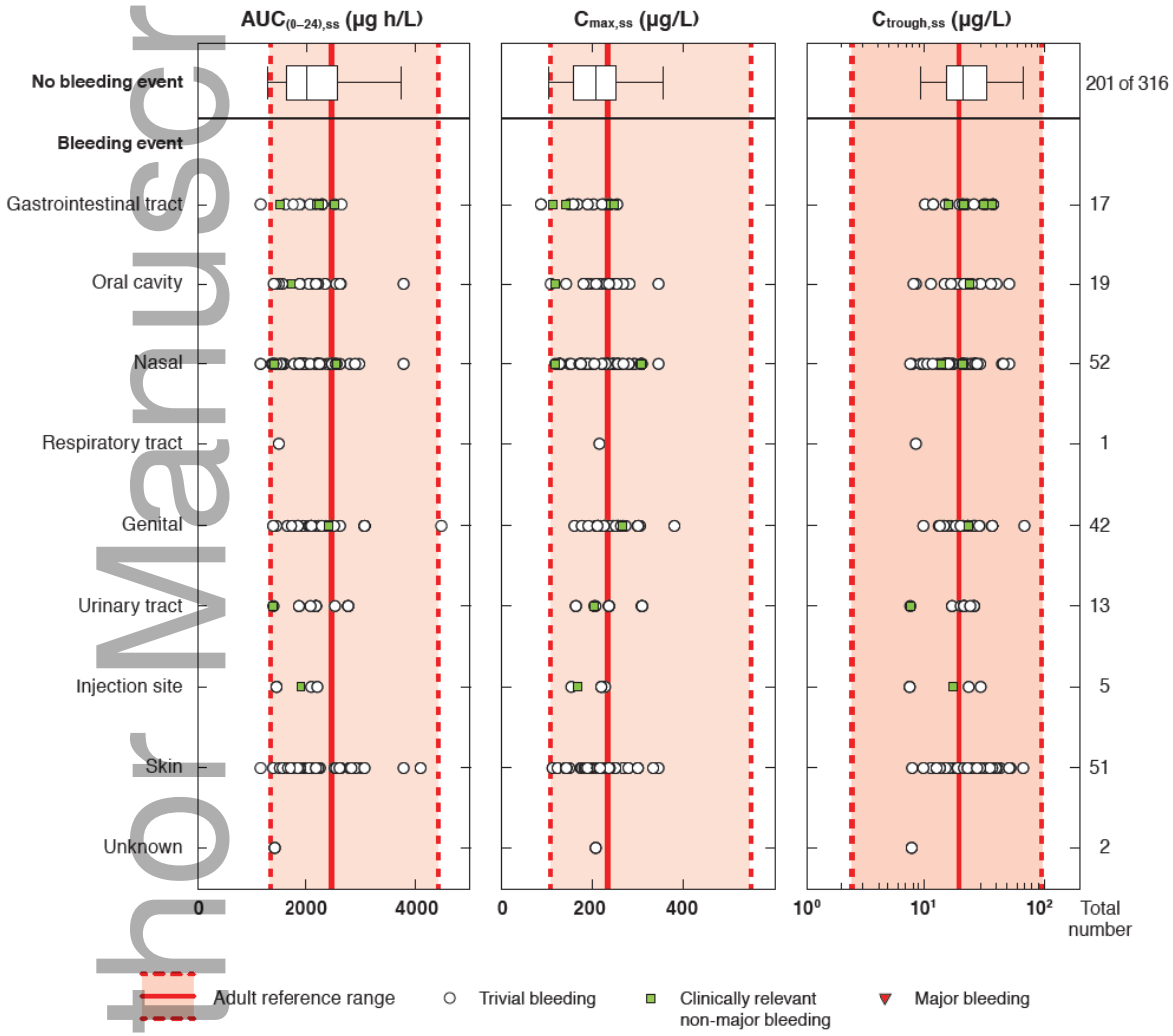


Figure 4. Correlation of rivaroxaban plasma concentrations with treatment-emergent adverse events.