A R T I C L E

Model-informed bridging of rivaroxaban doses for thromboprophylaxis in pediatric patients aged 9 years and older with congenital heart disease

Stefan Willmann[1] | **Ibrahim Ince[1]** | **Maurice Ahsman[2]** | **Katrin Coboeken[1]** | **Yang Zhang[1]** | **Kirstin Thelen[1]** | **Dagmar Kubitza[1]** | **Peter Zannikos[3]** | **Wangda Zhou[3]** | **Liza Miriam Pina[3]** | **Teun Post[2]** | **Jörg Lippert[1]**

[1]Bayer AG, Research & Development, Pharmaceuticals, Wuppertal/Leverkusen, Germany

[2]Leiden Experts on Advanced Pharmacokinetics and Pharmacodynamics, Leiden, The Netherlands

[3]Janssen Research & Development, LLC, Raritan, New Jersey, USA

Correspondence
Stefan Willmann, Bayer AG, Research & Development, Pharmaceuticals, Pharmacometrics/Modeling & Simulation, Building 0431 42096 Wuppertal, Germany.
Email: stefan.willmann@bayer.com

Abstract

Rivaroxaban is approved in various regions for the treatment of acute venous thromboembolism (VTE) in children aged between 0 and 18 years and was recently investigated for thromboprophylaxis in children aged between 2 and 8 years (with body weights <30 kg) with congenital heart disease who had undergone the Fontan procedure. In the absence of clinical data, rivaroxaban doses for thromboprophylaxis in post-Fontan children aged 9 years and older or ≥30 kg were derived by a bridging approach that used physiologically-based pharmacokinetic (PBPK) and population pharmacokinetic (popPK) models based on pharmacokinetic (PK) data from 588 pediatric patients and from adult patients who received 10 mg once daily for thromboprophylaxis after major orthopedic surgeries as a reference. Both models showed a tendency toward underestimating rivaroxaban exposure in post-Fontan patients aged between 2 and 5 years but accurately described rivaroxaban PK in post-Fontan patients aged between 5 and 8 years. Under the assumption that hepatic function is not impaired in post-Fontan patients, PBPK and popPK simulations indicated that half of the rivaroxaban doses for the same body weight given to pediatric patients treated for acute VTE would yield in pediatric post-Fontan patients exposures similar to the exposure observed in adult patients receiving 10 mg rivaroxaban once daily for thromboprophylaxis. Simulation-derived doses (7.5 mg rivaroxaban once daily for body weights 30–<50 kg and 10 mg once daily for body weights ≥50 kg) were therefore included in the recent US label of rivaroxaban for thromboprophylaxis in children aged 2 years and older with congenital heart disease who have undergone the Fontan procedure.

> **Study Highlights**
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> **WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?**
> Rivaroxaban was shown to be safe and effective for the treatment of acute venous thromboembolism in children from birth to 18 years and for thromboprophylaxis in post-Fontan patients aged between 2 and 8 years.
>
> **WHAT QUESTION DID THIS STUDY ADDRESS?**
> What are suitable rivaroxaban doses for thromboprophylaxis in pediatric post-Fontan patients aged 9 years and older or weighing ≥30 kg?
>
> **WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?**
> A model-based bridging approach was developed using physiologically-based pharmacokinetic and population pharmacokinetic modeling to demonstrate that 7.5 mg rivaroxaban once daily (body weight 30–<50 kg) and 10 mg once daily (body weight ≥50 kg) would yield exposure in pediatric post-Fontan patients similar to the exposure observed in adult patients receiving 10 mg rivaroxaban once daily for thromboprophylaxis after major orthopedic surgeries.
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> **HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?**
> The presented case highlights the importance of modeling and simulation in pediatric drug development and serves as a new example of how model-informed analyses can support regulatory decisions to expedite access of the pediatric population to new therapies.

INTRODUCTION

Rivaroxaban is an oral direct inhibitor of factor Xa that is widely used, among other indications, for the treatment and prevention of venous thromboembolism (VTE) in adults and was recently approved in various regions, including the United States, European Union, United Kingdom, and Japan, for the treatment of acute VTE in children aged between 0 and 18 years.[1–5] With extensive support of physiologically-based pharmacokinetic (PBPK) and population pharmacokinetic (popPK) modeling and simulation,[6–8] a body weight–adjusted dosing regimen was established in six pediatric clinical studies that resulted in exposure similar to the exposure observed in young adult VTE patients treated with 20 mg rivaroxaban once daily (o.d.). The EINSTEIN-Jr phase III study demonstrated similarly low recurrence risk and reduced thrombotic burden without increased bleeding compared with standard anticoagulants.[4] As a second pediatric indication, the use of rivaroxaban for thromboprophylaxis in children with congenital heart disease (CHD) with single ventricle physiology who had undergone the Fontan procedure was investigated in the UNIVERSE study.[9] The Fontan procedure is the most common surgical procedure performed in children with CHD who are older than 2 years of age.[10] Despite continuous improvements in the medical management of pediatric patients with CHD, the risk of thrombotic events remains an important complication following the Fontan procedure.[11] A prevalence of thrombotic events between 17% and 33% has been estimated, with a reported mortality rate of 25% to 38% due to an associated post-Fontan thromboembolism.[12–14] Patients who have finished the Fontan procedure within 3–12 months have the highest risk of thrombotic complications, and the risk diminishes thereafter but may persist during the following years.[15,16] Beyond 10 years of follow-up after the Fontan procedure, a second peak of thrombotic events occurs.[17] Furthermore, post-Fontan patients are at high risk to develop hepatic dysfunction several years after the procedure. This condition is known as Fontan-associated liver disease (FALD) and is a consequence of hemodynamic changes that are associated with a Fontan circulation, such as elevated central venous pressure.[18,19]

The UNIVERSE study enrolled patients between 2 and 8 years of age who had finished the Fontan procedure within 4 months.[9,20] Patients received rivaroxaban as an oral suspension formulation or acetylsalicylic acid (ASA) in the comparator arm for 12 months. The body weight–adjusted rivaroxaban dosing regimen that was applied in the UNIVERSE study was derived using a pediatric Fontan-PBPK model as described in Zhu et al.[20] Targeted exposure for thromboprophylaxis in children with CHD was the daily exposure (measured by the area under the plasma concentration–time curve over 24 h at steady state [$AUC_{(0-24h),ss}$]) observed in adult patients receiving 10 mg rivaroxaban o.d. for the prevention of thromboembolic events after major orthopedic surgery, applying a regimen of two times a day in children.[9,20] The UNIVERSE study

confirmed that the body weight–adjusted dose regimen in post-Fontan patients between 2 and 8 years of age resulted in rivaroxaban exposure that matched the adult reference exposures at 10 mg o.d.[20] The post-Fontan patients who received rivaroxaban had a similar safety profile and fewer thrombotic events, albeit not statistically significant, compared with those in the ASA group.[21] Besides the potential need for continued thromboprophylaxis, rivaroxaban doses for thromboprophylaxis were not clinically investigated for post-Fontan patients 9 years of age or older. Instead, suitable rivaroxaban doses for thromboprophylaxis in post-Fontan children aged 9 years and older or weighing ≥30 kg were derived by a bridging approach using rivaroxaban PBPK and popPK models based on data from adults and children.[6–8,20]

The aim of this article is to report the results of the model-based bridging concept that was designed to obtain suitable rivaroxaban doses for thromboprophylaxis in pediatric CHD patients aged 9 years and older after the Fontan procedure.

DATA AND METHODS

Bridging concept and model qualification

Figure 1 outlines the relevant rivaroxaban data and the bridging concept for post-Fontan patients between 9 and 18 years of age. In total, data from 588 pediatric patients were included in the rivaroxaban bridging database, among them 76 CHD patients from the UNIVERSE study in the age range between 2 and 8 years and body weights between 9.8 kg and 25.3 kg.[20] Of the 512 EINSTEIN-Jr patients, 262 (51.2%) were in the age range between 9 and 18 years, that is, the range for which the dose–exposure relationship had to be extrapolated for post-Fontan patients. Because in adults the prophylactic rivaroxaban dose is 10 mg o.d.,[22] which is half of the dose given for the maintenance treatment of an established thromboembolus (20 mg o.d.), it was deemed reasonable to propose that pediatric post-Fontan patients with a body weight ≥30 kg should receive half of the rivaroxaban doses that are recommended for the treatment of acute VTE in pediatric patients of the same body weight (Table 1).

PBPK and popPK modeling were used to extrapolate the dose–exposure relationship for pediatric post-Fontan patients beyond the clinically investigated age and body weight range. As a starting point, the consistency of exposure observed in the UNIVERSE study with predictions of the Fontan-PBPK model was assessed. If deemed necessary, the PBPK model parameterization was adapted to achieve a PBPK model that is fit for purpose to extrapolate rivaroxaban doses to post-Fontan patients between 9 and 18 years of age following established concepts and accepted workflows for PBPK model development.[23] In a similar way, the consistency of exposure observed in the UNIVERSE study with predictions of the EINSTEIN-Jr popPK model[8] was assessed. First, the predictive capacity of the previously established EINSTEIN-Jr popPK model and its parameter estimates for UNIVERSE rivaroxaban observations were evaluated. Second, model parameters were reestimated, and an adapted popPK model was established to correct potential apparent biases. The choice of parameter(s) was determined via the assessment of goodness of fit (GoF) and other diagnostic plots, and potential covariate effects were reestimated with a particular emphasis on age and body weight. Lastly, the impact of race (Japanese vs. non-Japanese patients) on pharmacokinetic (PK) parameters was exploratively assessed because a first exploration of the potential influence of race

TABLE 1 Rivaroxaban dose regimens established for pediatric patients in the EINSTEIN-Jr study for children with body weight ≥30 kg and proposed dose regimens for thromboprophylaxis in pediatric post-Fontan patients with body weight ≥30 kg

Body weight	EINSTEIN-Jr pediatric doses (matching 20 mg o.d. in adults)	Proposed doses for pediatric post-Fontan patients (targeting 10 mg o.d. in adults)
30–<50 kg	15 mg o.d.	7.5 mg o.d.
≥50 kg	20 mg o.d.[a]	10 mg o.d.

Abbreviation: o.d., once daily.

[a]15 mg in Japan.

age (years)
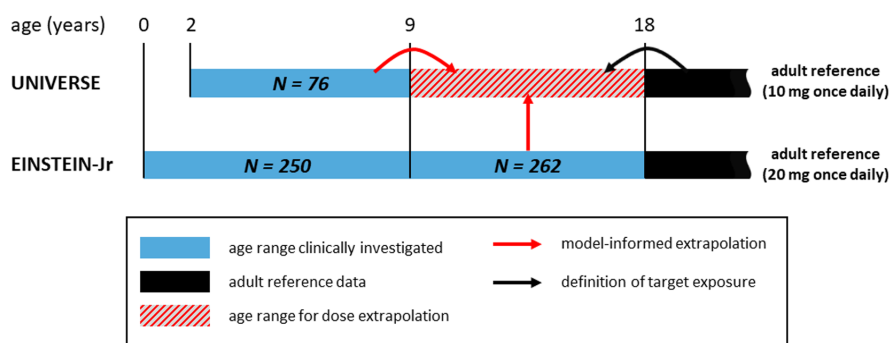
FIGURE 1 Concept for the model-informed bridging approach to extrapolate rivaroxaban doses for thromboprophylaxis in post-Fontan patients aged between 9 and 18 years.

on rivaroxaban PK in post-Fontan patients indicated that Japanese post-Fontan patients tended to have an approximately 35% higher $AUC_{(0-24h),ss}$ and 26% higher maximum concentration at steady state ($C_{max,ss}$) relative to the adult reference (data on file). Eight of the 76 post-Fontan patients were Japanese, and seven were younger than 5 years of age.

Simulation of the dose–exposure relationship

Upon successful qualification of the PBPK and popPK models, steady-state exposure estimates $AUC_{(0-24h),ss}$, $C_{max,ss}$, and trough concentrations ($C_{trough,ss}$) were generated for a virtual population of pediatric post-Fontan patients receiving the proposed doses of 7.5 mg o.d. for body weights between 30 and 50 kg and 10 mg o.d. for body weights ≥50 kg (see Table 1). To this end, the previously developed virtual population of post-Fontan patients 2–8 years of age ($N = 28,000$[20]) was extended to 18 years by adding 10,000 virtual pediatric post-Fontan patients 9 years of age and older (500 male and 500 female subjects per 1-year age bin). The same virtual population was used for the PBPK and popPK simulations. An additional set of simulations was performed with the PBPK model under the assumption that liver function is severely impaired in the virtual pediatric post-Fontan population. This scenario was considered relevant as it can be expected that liver function will decrease over time in older post-Fontan children, reflecting the development of FALD. Therefore, the hepatic cytochrome P450 (CYP)-mediated processes relevant to rivaroxaban metabolism were set to zero in this set of simulations. The resulting exposure estimates were graphically compared with relevant adult (including the reference adult population and available exposure data from adult patients with congestive heart failure [CHF]) and pediatric exposure data from EINSTEIN-Jr. Table S1 summarizes the exposure data that are shown for comparison.

RESULTS

PBPK model qualification

Figure S1 shows the distribution of body weight over age that was assumed in the PBPK predictions for post-Fontan patients in the age range between 2 and 8 years superimposed by the individual body weights of the UNIVERSE patients at baseline to confirm that the assumed body weight distribution of the virtual post-Fontan population in the Fontan-PBPK model reasonably resembled the distribution observed in the UNIVERSE study. Figure 2 shows the superimposition of individual rivaroxaban plasma concentrations observed in the UNIVERSE study with the PBPK predictions for post-Fontan patients 2 to 8 years of age on Day 1 (Figure 2a) and at steady state (≥4 days after the first rivaroxaban dose [Figure 2b]). The plasma concentrations observed in the UNIVERSE study are mostly in the range predicted by the Fontan-PBPK model. However, the PBPK model underestimated rivaroxaban concentrations in some pediatric post-Fontan patients younger than 5 years of age. In Figure 3, the predicted rivaroxaban $AUC_{(0-24h),ss}$ is compared with the individual $AUC_{(0-24h),ss}$ estimates obtained from the UNIVERSE popPK model[20] in 1-year age bins (Figure 3a) and per body weight (Figure 3b). This figure demonstrates that $AUC_{(0-24h),ss}$ in post-Fontan patients aged 5 years or older was well in line with the predictions of the Fontan-PBPK model: 19 of 24 (79.2%) of post-Fontan patients aged 5 years or older had a post hoc estimated $AUC_{(0-24h),ss}$ within the 90% prediction interval of the Fontan-PBPK model (Table 2). However, exposure in patients aged 2 to younger than 5 years was, on average, higher than predicted by the Fontan-PBPK model: 22 of 52 (42.3%) had an $AUC_{(0-24h),ss}$ above the 95% prediction interval of the Fontan-PBPK model, and 26 patients (50%) were within the 50%–95% prediction interval (Table 2). The tendency for rivaroxaban exposure to be underestimated in some post-Fontan patients in the age range between 2 and 5 years is also visible in Figure S2, which shows the superimposition of predicted and observed plasma concentrations stratified by age. To quantify the extent by which, on average, rivaroxaban clearance (CL) was underestimated by the PBPK model, the total plasma CL was adjusted in the Fontan-PBPK model to match the observed data in the age range between 2 and younger than 5 years. A reasonable match between the PBPK model and observed plasma concentration–time data was achieved when the CL of the initial Fontan-PBPK model was multiplied with factors of 0.53, 0.64, and 0.45 in the age ranges of 4 to younger than 5, 3 to younger than 4, and 2 to younger than 3 years, respectively (Figure S3).

Despite the underestimation of exposure in post-Fontan patients younger than 5 years, the Fontan-PBPK model was considered adequate and fit for purpose for the extrapolation task because the model described rivaroxaban exposure of pediatric post-Fontan patients 5 years of age or older very well. No adjustments were made to any of the parameters of the initial Fontan-PBPK model to predict the dose–exposure relationship of post-Fontan patients 9 years of age or older.

FIGURE 2 Superimposition of rivaroxaban plasma concentrations observed in UNIVERSE on (a) Day 1 and (b) in steady state on corresponding predictions from the initial PBPK model for post-Fontan patients. Black line, geometric mean of PBPK simulations; gray-shaded area, 5%–95% percentile of PBPK simulations; green dotted line, 95% percentile of PBPK simulations assuming severe hepatic impairment; symbols, individual observations of patients from the UNIVERSE study stratified by age categories 2 to younger than 5 years and 5–8 years.
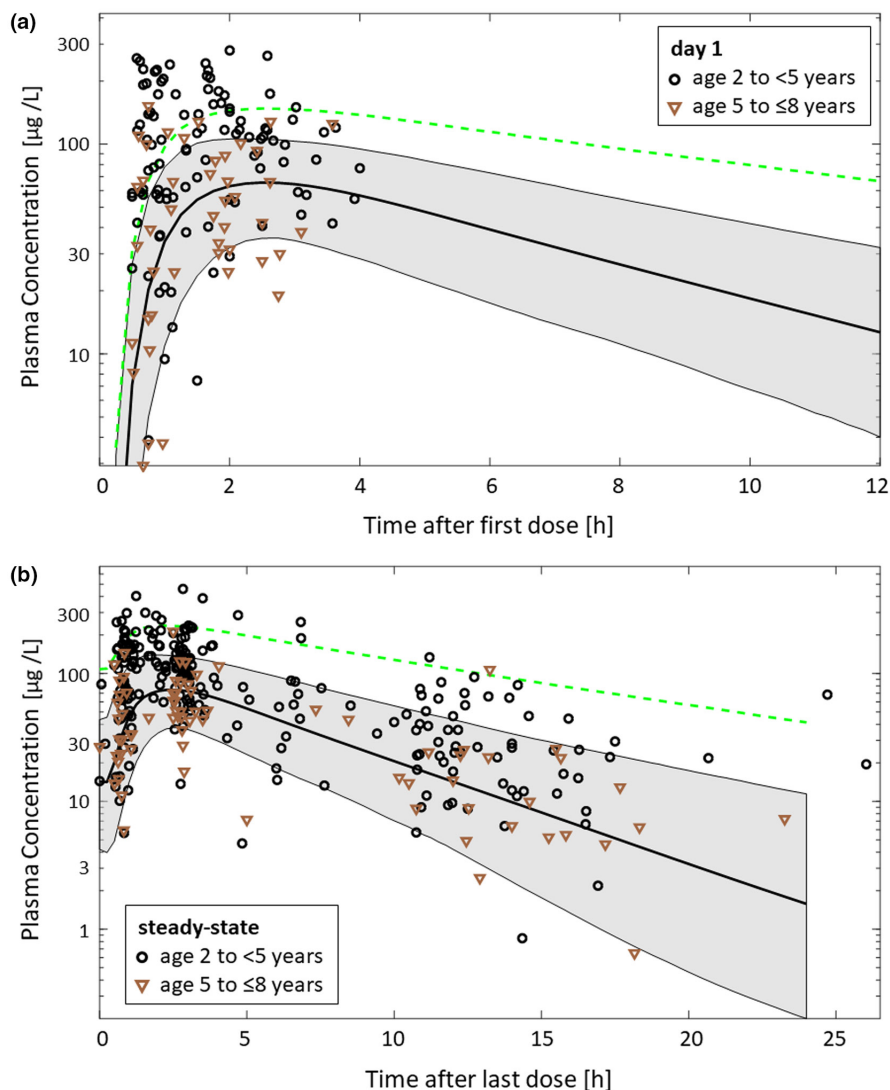
PopPK model qualification

The EINSTEIN-Jr popPK model could generate individual PK estimates that accurately described rivaroxaban PK in the post-Fontan patients in the UNIVERSE study. However, at the population level, a structural underprediction of rivaroxaban concentrations was seen (Figure S4). In particular, young post-Fontan patients tended to have a lower apparent CL than estimated for EINSTEIN-Jr patients of the same age. This observation prompted an investigation to identify factors describing the post-Fontan patient PK using the EINSTEIN-Jr model, starting with fixing all typical PK parameter values except CL while optimizing inter-individual variability on CL and oral bioavailability (F1) and residual variability estimates. Based on a graphical analysis of post hoc CL estimates versus age in 1-year age bins, a binary separation between two separate age groups was considered appropriate. Separate CL estimates were tested for older versus younger post-Fontan patients assuming a range of cutoff age values. A cutoff of younger

than 5 years of age for CL provided the best improvement in the objective function value (OBJF). This model was then used to test any remaining age dependence of F1. Assuming again a binary division between the two age groups, two F1 values with a cutoff of younger than 5 years of age provided the best improvement in OBJF. After estimation of separate F1 values for post-Fontan patients aged younger than 5 years versus 5 years of age or older, separate CL estimates per age category were no longer required; removal of the age-dependent CL resulted in an insignificant change of OBJF (ΔOBJF = 0.033). A backward deletion procedure with a higher significance level (ΔOBJF = 6.63, $p < 0.01$) was done to confirm whether the implementation of post-Fontan specific CL and F1 estimates were justified. Implementation of the same population CL value for post-Fontan patients as in the existing EINSTEIN-Jr popPK model led to a significantly worsened fit (ΔOBJF = 25.537). Thus, a separate CL estimate for UNIVERSE patients was maintained. Removal of the age-dependent cutoff for estimation of F1 also caused
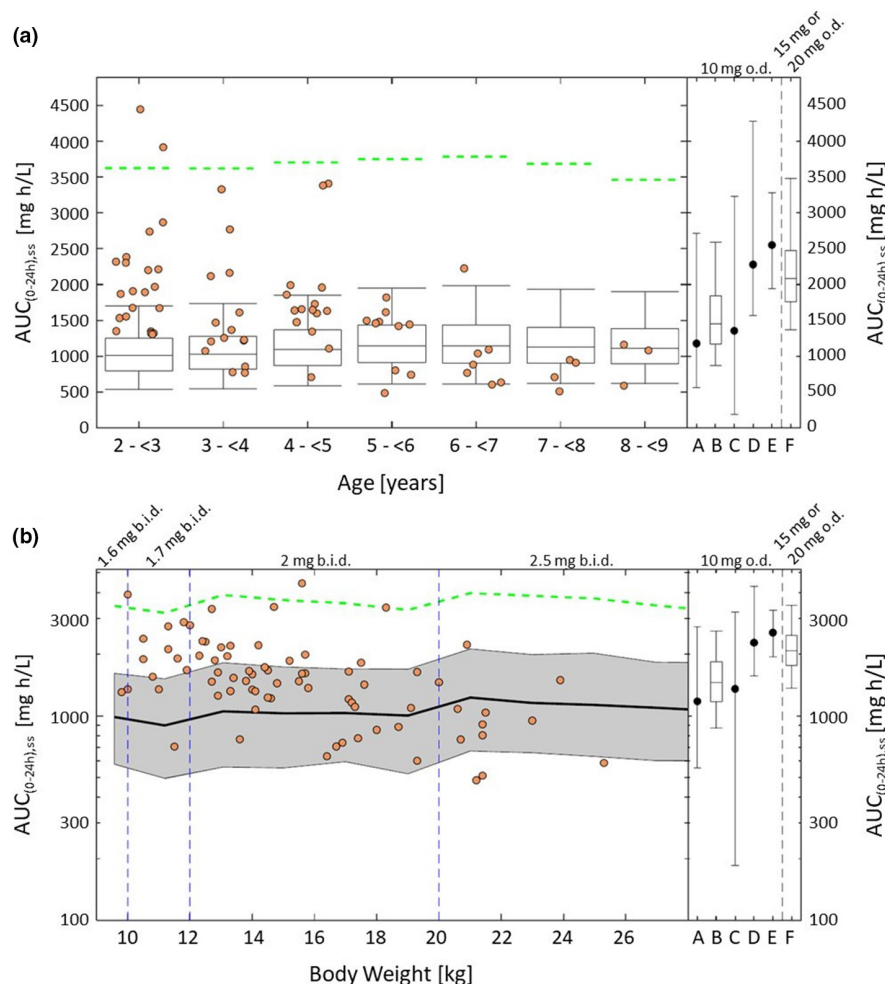
FIGURE 3 Comparison of predictions of AUC$_{(0-24\,h),ss}$ from the initial PBPK model for post-Fontan patients with individual post hoc estimates derived from the UNIVERSE popPK model by (a) age and (b) body weight. Adult and pediatric reference data are shown on the right-hand side for comparison (A, healthy adults receiving 10 mg; B, adults receiving 10 mg once daily for thromboprophylaxis after major orthopedic surgeries; C, medical ill patients receiving 10 mg once daily; D, chronic stable severe congestive heart failure patients receiving 10 mg once daily; E, acute decompensated congestive heart failure patients receiving 10 mg once daily; F, EINSTEIN-Jr patients ≥30 kg receiving 15 or 20 mg once daily; for details, see Table S1). Box, median and interquartile range; whisker, 5th–95th percentile of PBPK simulations; solid black line, geometric mean of PBPK simulations; gray shaded area, 5th–95th percentile of PBPK simulations; green dotted line, 95th percentile of PBPK simulations assuming severe hepatic impairment; symbols, individual post hoc estimates of the UNIVERSE population pharmacokinetic model. AUC$_{(0-24\,h),ss}$, area under the plasma concentration–time curve over 24 h at steady state; b.i.d., two times a day; o.d., once daily; popPK, population pharmacokinetic; s.d., single dose.

a significantly worse fit (ΔOBJF = 24.243) and fixing the F1 value of the age bins younger than 5 years of age or 5 years of age and older to the existing EINSTEIN-Jr popPK model value both caused a significantly worsened fit (ΔOBJF = 10.966 and 7.123, respectively). Lastly, the impact of race (Japanese versus non-Japanese patients) on CL and F1 was explored. No statistically significant effect of Japanese patients on CL was detected, but a tendency toward slightly higher F1 in Japanese patients was seen by the model. The impact of a separate F1 estimate for Japanese patients aged 2 to younger than 5 years was tested but showed an inferior OBJF with the same number of parameters. Effects of Japanese in post-Fontan patients

aged 5 years and older could not be assessed due to an insufficient number of Japanese subjects in this age group (N = 1). Table S2 summarizes the model parameters of the adapted popPK model and shows that all parameters were estimated with good precision. The refined CL estimate was 6.07 L/h for a body weight of 82.48 kg compared with 8.02 L/h for the existing EINSTEIN-Jr popPK model.[8] Relative to a value of 1 for the EINSTEIN-Jr model, F1 was estimated to be 0.752 for patients aged 5 years and older and 1.20 for patients age younger than 5 years. GoF plots for the final adapted popPK model demonstrate an adequate fit at both the population and individual levels (Figure S5), which was confirmed for individual fits in

each weight and dose category (Figure S6). The difference in the individually estimated apparent oral CL values (CL/F1) between VTE patients studied in EINSTEIN-Jr and CHD patients post-Fontan procedure studied in UNIVERSE is visualized in Figure 4 for the age groups 2 to younger than 5 years and 5–8 years. The median CL/F1 was similar (4.59 vs. 4.90 L/h) and $AUC_{(0-24\,h),ss}$ was practically identical for UNIVERSE and EINSTEIN-Jr patients aged 5–8 years. In the age range between 2 and younger than 5 years, however, the ratio of the population medians for CL/F1 in post-Fontan and EINSTEIN-Jr patients was 0.43 (2.09 L/h vs. 4.83 L/h). Japanese subjects are highlighted in this plot to demonstrate that there was no apparent bias in the distribution of CL/F1 in Japanese versus non-Japanese post-Fontan patients in the age range between 2 and younger than 5 years.

Based on the similarity in the dose–exposure relationship between the UNIVERSE and EINSTEIN-Jr patients aged 5–8 years and the observed predictive performance in UNIVERSE patients with the same range of ages, the original EINSTEIN-Jr model (without parameter changes) was considered fit for purpose to simulate the exposure in post-Fontan patients aged between 9 and 18 years.
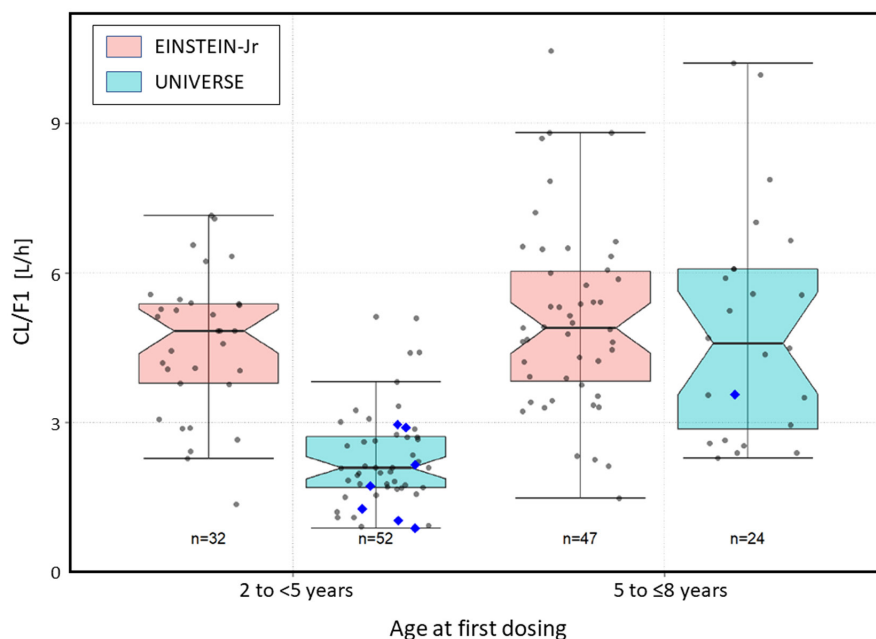
Simulations of the dose–exposure relationship

Figure 5 shows a comparison of rivaroxaban $AUC_{(0-24\,h),ss}$ simulated with the EINSTEIN-Jr popPK and Fontan-PBPK models for pediatric post-Fontan subjects with body weights between 30 and <50 kg receiving 7.5 mg o.d. and body weights ≥50 kg receiving 10 mg o.d., respectively. The $AUC_{(0-24\,h),ss}$ based on the EINSTEIN-Jr popPK model are in line with those simulated with the post-Fontan PBPK model. The simulated $AUC_{(0-24\,h),ss}$ values were within the range observed for adult VTE patients, healthy adults, and medically ill patients treated with 10 mg o.d. The simulated $AUC_{(0-24\,h),ss}$ is slightly below that observed in adult chronic and acute CHF patients receiving the same dose as well as patients in EINSTEIN-Jr with a body weight of ≥30 kg receiving a daily dose of 15 or 20 mg (see Table S1 for a summary of respective PK data and Figures S7 and S8 for corresponding simulated data for $C_{max,ss}$ and $C_{trough,ss}$ as well as PBPK simulations for $AUC_{[0-24\,h],ss}$, $C_{max,ss}$, and $C_{trough,ss}$ as a function of body weight, including the 95th

TABLE 2 Distribution of rivaroxaban $AUC_{(0-24\,h),ss}$ estimates of patients from UNIVERSE in comparison to the prediction intervals of the Fontan-PBPK model for children aged between 2 and younger than 5 years and between 5 and 8 years

	2–<5 years of age	5–8 years of age
Number of patients	52 (100)	24 (100)
Above 95% prediction interval	22 (42.3)	1 (4.2)
Within 50%–95% prediction interval	26 (50.0)	7 (29.2)
Within 5%–50% prediction interval	4 (7.7)	12 (50.0)
Below 5% prediction interval	0 (0.0)	4 (16.7)

Note: Data are provided as *n* (%).

Abbreviations: $AUC_{(0-24\,h),ss}$, area under the plasma concentration–time curve over 24 h at steady state; PBPK, physiologically-based pharmacokinetic.

FIGURE 4 Individual apparent oral clearance value (CL/F1) estimates versus age groups for patients in EINSTEIN-Jr and UNIVERSE. Patients from Japan are highlighted as blue diamonds. Black horizonal line, median; box, interquartile range; whisker, range between the 5th and 95th parameter value; notches, 95% confidence interval of the median; symbols, individual parameter estimates (gray dots, non-Japanese patients; blue diamonds, Japanese patients).
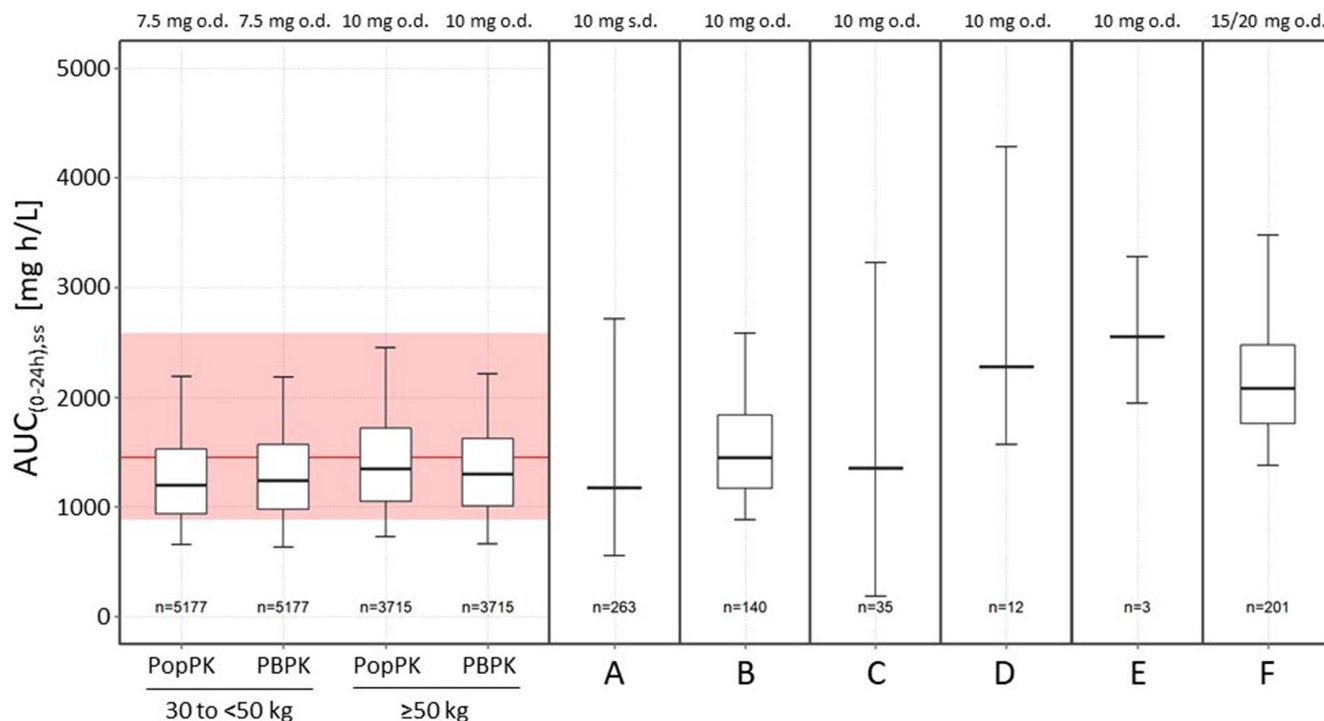
FIGURE 5 Comparison of rivaroxaban $AUC_{(0-24\,h),ss}$ predicted by the EINSTEIN-Jr popPK and Fontan-PBPK models for pediatric post-Fontan patients with body weights between 30 and <50 kg receiving 7.5 mg once daily and body weights ≥50 kg receiving 10 mg once daily. Adult and pediatric reference data are shown on the right-hand side for comparison (A: healthy adults receiving 10 mg; B: adults receiving 10 mg once daily for thromboprophylaxis after major orthopedic surgeries; C: medical ill patients receiving 10 mg once daily; D: chronic stable severe congestive heart failure patients receiving 10 mg once daily; E: acute decompensated congestive heart failure patients receiving 10 mg once daily; F: EINSTEIN-Jr patients ≥30 kg receiving 15 or 20 mg once daily; for details, see Table S1). Box-and-whisker-plots: black solid line, median; box, interquartile range; whisker, 5% to 95% range. Whisker plots: black horizontal line, geometric mean; whisker, range from minimum to maximum. Red solid line, median of the adult reference data (adult patients receiving 10 mg once daily for thromboprophylaxis after major orthopedic surgeries); red-shaded area, 5% to 95% interval of the adult reference data (adult patients receiving 10 mg once daily for thromboprophylaxis after major orthopedic surgeries). $AUC_{(0-24\,h),ss}$, area under the plasma concentration–time curve over 24 h at steady state; b.i.d., two times a day; o.d., once daily; PBPK, physiologically-based pharmacokinetic; popPK, population pharmacokinetic; s.d., single dose.

percentile of the severe hepatic impairment scenario for completeness).

DISCUSSION

The strategy for the prevention of thrombosis in pediatric CHD patients has been considerably debated in the past, and limited evidence-based guidelines have been established.[24,25] The UNIVERSE study investigated the use of rivaroxaban versus ASA for thromboprophylaxis in children 2–8 years of age with single ventricle physiology after the Fontan procedure.[9] Although this randomized study was not powered for efficacy, the participants who received rivaroxaban had a lower prevalence of thrombotic events, albeit not achieving statistical significance, and a similar safety profile compared with those patients who received ASA.[21] Although the available data indicate a need for continuous thromboprophylaxis,[24,25] to our

knowledge no clinical data are available, and no rivaroxaban dose has been clinically established for pediatric post-Fontan patients older than 8 years or above 30 kg to date. To close this gap, a model-informed bridging approach employing PBPK as well as popPK modeling and simulation was developed to extrapolate the rivaroxaban dose–exposure relationship for thromboprophylaxis that was established in the UNIVERSE study for post-Fontan patients in the age range between 2 and 8 years to post-Fontan patients aged 9–18 years. The bridging approach made use of (i) available dose–exposure data of rivaroxaban from another pediatric program, EINSTEIN-Jr, which investigated rivaroxaban for the treatment of acute VTE in children between 0 and 18 years of age[1–5] and (ii) pre-existing PBPK and popPK models of rivaroxaban in pediatric patients.[6–8,20] At first, the predictive performances of the Fontan-PBPK model[20] and the EINSTEIN-Jr popPK model[8] for the UNIVERSE data were retrospectively assessed. Both models showed a tendency toward

underestimating rivaroxaban exposure in post-Fontan patients in the age range between 2 and younger than 5 years. In the case of PBPK modeling, this cutoff was established by visual inspection of the plots superimposing predicted and observed data in 1-year age bins (Figure S2). The same cutoff age of younger than 5 years was more rigorously confirmed by an assessment of OBJF values using popPK modeling. Such an underestimation of exposure can, in theory, be caused by an overestimation of CL, an underestimation of F1, or a combination of both. A clear separation of the influence of CL and F1 on exposure, however, would require PK data after intravenous administration in children, which is not available for rivaroxaban. The PBPK model could adequately describe the observed plasma concentrations in post-Fontan patients aged 2 to younger than 5 years after multiplying the initially assumed total CL of rivaroxaban with factors of 0.53, 0.64, and 0.45 in the age ranges of 4 to younger than 5, 3 to younger than 4, and 2 to younger than 3 years, respectively, without modifying the extent of absorption (i.e., unchanged F1). The popPK model partially attributed the higher exposure in post-Fontan patients aged between 2 and younger than 5 years to a 24% lower CL estimate in Fontan subjects versus EINSTEIN-Jr patients (6.07 L/h compared with 8.02 L/h for a body weight of 82.48 kg for the existing EINSTEIN-Jr model[8]) and partially to a 37% higher F1 in post-Fontan patients aged 2 to younger than 5 years compared with 5–8 years (Table S2). Seven of the eight Japanese subjects in UNIVERSE were younger than 5 years of age, and when these seven Japanese post-Fontan patients were compared with non-Japanese subjects in the same age range, there was no apparent difference in CL/F1 (Figure 4). Explorative analyses of additional covariates did not reveal any further insights into what could have caused the unexpectedly high exposure in young post-Fontan patients. For example, the estimated glomerular filtration rate values at baseline in the UNIVERSE study were in the normal range and very similar for the age groups 2 to younger than 5 years (geometric mean, 121.8 ml/min/1.73m^2) and 5–8 years (126.9 ml/min/1.73m^2; data on file). Concomitant medications that could potentially affect rivaroxaban exposure (e.g., CYP3A4 inhibitors) were reviewed but could not explain the findings. Also, the duration between the end of the Fontan procedure and the start of rivaroxaban administration was explored as a potential covariate for exposure because it was known from adult VTE prophylaxis (VTE-P) studies that major orthopedic surgeries can reduce the CL of rivaroxaban by approximately 20% in the first 72 h after surgery.[26,27] However, the start of rivaroxaban treatment relative to the end of the Fontan procedure could also not explain the higher plasma exposure in post-Fontan patients aged between 2 and younger than 5 years.

Thus, the reason for the higher-than-expected rivaroxaban exposure in post-Fontan patients aged 2 to younger than 5 years remains unclear to date. It should be noted that the direction of the deviation from the expected exposure in young post-Fontan patients is opposite to what was previously observed in EINSTEIN-Jr patients younger than 2 years of age, for which CL was underpredicted and rivaroxaban exposure was overpredicted by the PBPK model.[8] Consequently, the presented PBPK and popPK models should not be used to extrapolate the dose–exposure relationship toward post-Fontan patients younger than 2 years of age.

On the other hand, both models, the Fontan-PBPK model and the EINSTEIN-Jr popPK model, accurately described pediatric post-Fontan patients in the age range between 5 and 8 years and were, therefore, considered fit for purpose to extrapolate the dose–exposure relation toward post-Fontan patients aged 9 years and older or weighing ≥30 kg. Simulations in virtual post-Fontan patients with body weight ≥30 kg receiving half of the rivaroxaban doses for the same body weight as pediatric patients treated for acute VTE (Table 1) led to an $AUC_{(0–24\,h),ss}$ that was within the adult reference range that is defined by adult patients receiving 10 mg o.d. for thromboprophylaxis after major orthopedic surgeries and slightly below that observed in adult chronic and acute CHF patients receiving the same dose (Figure 5). The Fontan-PBPK model further delivered estimated rivaroxaban exposures in case the liver of the post-Fontan patients becomes severely impaired, for example, in the context of FALD.[18,19] The simulation results suggest that, under such circumstances, rivaroxaban exposure will increase to an extent that is comparable with adult patients with chronic stable severe CHF (Figure S8). Furthermore, it must be emphasized that potential alterations in the PK/pharmacodynamic (PD) relationship of rivaroxaban that could be the consequence of the development of a coagulopathy in patients with FALD were not considered in the assessment of the suitability of the proposed dosing regimen.

In summary, the dose–exposure relationship of rivaroxaban was extrapolated to pediatric post-Fontan patients aged 9 years or older or ≥30 kg using the PBPK model for pediatric post-Fontan patients and the EINSTEIN-Jr popPK model. Under the assumption that hepatic function is not impaired in post-Fontan patients, the PBPK and popPK simulations supported that 7.5 mg rivaroxaban o.d. (for body weights 30–<50 kg) and 10 mg o.d. (for body weights ≥50 kg) would yield exposure in pediatric post-Fontan patients similar to the exposure observed in adult VTE-P patients receiving 10 mg rivaroxaban o.d. In case that the post-Fontan patients develop severe dysfunction of the liver, rivaroxaban exposure may, on average, increase (to an extent

similar to that seen in adults with chronic stable severe CHF) and lead to more pronounced PD effects. It is known for adult patients with moderate hepatic impairment that the sensitivity of the anticoagulant activity of rivaroxaban in relation to its plasma concentration was significantly altered.[28]

In December 2021, the US Food and Drug Administration approved the use of rivaroxaban for the treatment of VTE in patients from birth to younger than 18 years and for thromboprophylaxis in children aged 2 years and older with CHD who have undergone the Fontan procedure. The US label thus includes the doses for post-Fontan patients ≥30 kg that were based on this model-informed bridging approach. The presented case highlights the importance of modeling and simulation in pediatric drug development and serves as a new example how model-based analyses can support regulatory decisions[29] to expedite access of the pediatric population to new therapies.

AUTHOR CONTRIBUTIONS

S.W., I.I., M.A., D.K., K.T., P.Z., W.Z., L.M.P., T.P., and J.L. wrote the manuscript. S.W., I.I., M.A., K.C., Y.Z., D.K., K.T., P.Z., W.Z., L.M.P., T.P., and J.L. designed the research and analyzed the data. S.W., I.I., M.A., K.C., Y.Z., and T.P. performed the research.

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CONFLICT OF INTEREST

ORCID

Stefan Willmann https://orcid.org/0000-0001-8322-965X
Maurice Ahsman https://orcid.org/0000-0002-6084-2571
Teun Post https://orcid.org/0000-0001-9183-2678
Jörg Lippert https://orcid.org/0000-0002-0683-2874

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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