

# Dosing Regimen Prediction and Confirmation With Rivaroxaban for Thromboprophylaxis in Children After the Fontan Procedure: Insights From the Phase III UNIVERSE Study

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## Abstract

Thrombosis remains an important complication for children with single-ventricle physiology following the Fontan procedure, and effective thromboprophylaxis is an important unmet medical need. To obviate conventional dose-finding studies and expedite clinical development, a rivaroxaban dose regimen for this indication was determined using a model-informed drug development approach. A physiologically based pharmacokinetic rivaroxaban model was used to predict a pediatric dosing regimen that would produce drug exposures similar to that of 10 mg once daily in adults. This regimen was used in an open-label, multicenter phase III study, which investigated the use of rivaroxaban for thromboprophylaxis in post-Fontan patients 2 to 8 years of age. The pharmacokinetics (PK) of rivaroxaban was assessed in part A ( $n = 12$ ) and in part B ( $n = 64$ ) of the UNIVERSE study. The safety and efficacy in the rivaroxaban group were compared to those in the acetylsalicylic acid group for 12 months. Pharmacodynamic end points were assessed in both parts of the study. Rivaroxaban exposures achieved in parts A and B were similar to the adult reference exposures. Prothrombin time also showed similarity to the adult reference. Exposure-response analysis did not identify a quantitative relationship between rivaroxaban exposures and efficacy/safety outcomes within the observed exposure ranges. A body weight-based dose regimen selected by physiologically based pharmacokinetic modeling was shown in the UNIVERSE study to be appropriate for thromboprophylaxis in the post-Fontan pediatric population. Model-based dose selection can support pediatric drug development and bridge adult dose data to pediatrics, thereby obviating the need for dose-finding studies in pediatric programs.

## Keywords

anticoagulants, child, congenital heart disease, pharmacokinetics, thrombosis

Despite continuous improvements in the medical management of pediatric patients with congenital heart defects, the risk of thrombotic events remains an important complication for patients with single-ventricle physiology, who have had the Fontan procedure.<sup>1</sup> The Fontan procedure separates pulmonary and systemic circulations by directing all systemic venous return to the pulmonary vascular bed, while the functional single ventricle is committed to supporting the systemic circulation. Several studies have estimated that the prevalence of thromboembolic events occurring after the Fontan procedure ranges from 17% to 33%, with a reported thromboembolism-associated mortality of 25% to 38%.<sup>2–4</sup>

To date, no consensus has been reached in the literature or routine clinical practice for the optimal type or duration of antithrombotic therapy after Fontan surgery. Much of the data for pediatric recommendations are still extrapolated from adult data obtained in non-Fontan clinical settings.<sup>5,6</sup> More optimal thromboprophylaxis strategies should be studied in the post-Fontan population in view of the high prevalence of thrombotic events, difficulties achieving consistent

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protection with current anticoagulant therapy, and the considerable residual risk that remains in children treated with warfarin or acetylsalicylic acid (ASA).

Rivaroxaban, an oral, direct inhibitor of activated factor X has been evaluated for the treatment of acute venous thromboembolism (VTE) in children from birth to 18 years in the EINSTEIN-Jr program<sup>7,8</sup> and was also evaluated in the phase III UNIVERSE study for thromboprophylaxis in children aged 2 to 8 years with congenital heart defects after the Fontan procedure.<sup>9</sup> The population studied in the UNIVERSE study is small ( $\approx 1000$  Fontan procedures performed each year in the United States), and this population is highly vulnerable to postoperative complications due to their underlying conditions and age (mostly 2-5 years old).<sup>10,11</sup>

In the EINSTEIN-Jr program (the VTE treatment studies), a body weight-based dose regimen was first predicted using a physiologically based pharmacokinetic (PBPK) model in the pediatric population.<sup>12</sup> The model-predicted dose regimen was used in the phase I (single-dose) and phase II (multiple-dose) studies and supported the final dose regimen used in all cohorts in the phase III EINSTEIN-Jr studies.<sup>12,13</sup> For the UNIVERSE study (the post-Fontan thromboprophylaxis study), the development path was abbreviated in comparison to the EINSTEIN-Jr program in that the phase II studies were omitted. The rivaroxaban dose selected by the PBPK model, which was adjusted for the pediatric post-Fontan population, was directly evaluated in the UNIVERSE study, as described in the present article. Part A of the UNIVERSE study evaluated the pharmacokinetics (PK) of rivaroxaban in 12 patients to ensure an appropriate range of rivaroxaban exposures and patient safety. This was followed by part B, which was intended to confirm rivaroxaban exposure matching to adults who were treated with a total daily dose of 10 mg of rivaroxaban. This dose was shown to be safe and effective for thromboprophylaxis in adult subjects after major orthopedic surgery (phase III RECORD studies).<sup>14,15</sup> Part B also evaluated pharmacodynamics (PD) anticoagulant responses in post-Fontan pediatric patients for comparison to adults. The pediatric-to-adult drug exposure matching, also known as pediatric bridging, supplemented by PD similarity, is a well-accepted approach to support the extrapolation of efficacy data from adults to the pediatric population in pediatric drug development programs.<sup>16,17</sup> It is expected that children who underwent a Fontan procedure would respond to factor Xa inhibition by rivaroxaban in a similar manner as seen in adults when they achieve matching concentrations.

The UNIVERSE study (NCT02846532) is the first clinical study of rivaroxaban in post-Fontan pediatric patients.<sup>9</sup> This article aims to present a model-informed drug development (MIDD) approach that was applied

to select specific rivaroxaban dose regimens and to summarize PK, PK/PD, and exposure response results from the UNIVERSE study. The results confirmed the appropriateness of the model-based doses selected for pediatric patients after the Fontan procedure.

## Methods

### Physiologically Based PK Modeling and Simulation

A first PBPK model for rivaroxaban administration to healthy children was established previously in the EINSTEIN-Jr program using the generic software tool PK-Sim and was reported in detail.<sup>12,13</sup> Briefly, this model was scaled from the PBPK model for adults by accounting for (1) the age dependency of anthropometric, anatomic, and physiologic parameters (eg, body weight, height, organ volumes, blood flow rates, and tissue composition); and (2) the ontogeny and variability of active processes that are relevant for rivaroxaban PK (eg, cytochrome P450 3A4 activity, transporter activity) and drug-related parameters (eg, protein binding). This model served as a basis for the development of a pediatric Fontan-PBPK model that considered relevant pathophysiologic conditions of post-Fontan patients. Post-Fontan patients in the age range between 2 and 8 years are known to have a reduced cardiac output and a lower body weight for a given age compared to healthy children (for details see Tables S1-S3 and Figures S1-S3). To account for these differences, the log-normally distributed body weights and body heights of the healthy reference children were shifted to lower values to match the weight-by-age and height-by-age relationships in post-Fontan children (Figures S1 and S2). Cardiac index (cardiac output divided by body surface area) was reduced to 70% of a healthy child of the same age (Figure S3). With this Fontan-PBPK model, 7 virtual pediatric post-Fontan populations for each age (2, 3, 4, 5, 6, 7, and 8 years) comprising 2000 individuals per sex were generated as previously described<sup>13</sup> to predict the relationship between dose and exposure of rivaroxaban in post-Fontan patients in comparison to healthy children.

### UNIVERSE Study Design

The UNIVERSE study was a prospective, open-label, active-controlled, and multicenter study designed to evaluate the PK and PK/PD profiles, safety, and efficacy of rivaroxaban for thromboprophylaxis in pediatric patients 2 to 8 years of age with single ventricle physiology who had completed the Fontan procedure within 4 months before enrollment.<sup>9</sup> The trial was approved by the institutional review board of each participating institution, as well as the appropriate national ethics committee. Written informed consent for trial participation was obtained from the parent or guardian of each patient. Child assent was also

provided, if applicable, according to local requirements. An Independent Data Monitoring Committee ensured patients' safety throughout the trial. A Central Independent Adjudication Committee reviewed all efficacy and safety events.

The UNIVERSE study consisted of 2 parts. Part A was the 12-month, nonrandomized, open-label part of the study, which included a 12-day initial PK, PD, and safety assessment period. By day 12, an internal Data Review Committee assessed the day 1 and steady-state (twice-daily) rivaroxaban PK, PD, and the initial safety and tolerability data available from each patient prior to the patient continuing in the study to complete the planned 12 months of open-label rivaroxaban therapy of part A. Part B was the randomized, open-label, active-controlled part of the study that evaluated the safety and efficacy of twice-daily administration of rivaroxaban compared to ASA (usual standard of care) for thromboprophylaxis for 12 months. Patients randomized to rivaroxaban also had PK and PD assessments.

The transition from part A to part B was predefined on the basis of an interim analysis of the part A PK and PD data. If the geometric mean rivaroxaban exposures observed in part A were within the predefined criteria of 70% to 143% ( $\pm 30\%$  on log scale) of the geometric mean adult reference exposure at 10 mg once daily) in the ODIXa-HIP-OD study (geometric mean area under the plasma concentration–time curve from time 0 to 24 hours at steady state [ $AUC_{ss,24h}$ ], 1494  $\mu\text{g} \cdot \text{h/L}$ ),<sup>18</sup> then the study would continue to part B with the same dose regimen. Otherwise, the dose regimen was to be revised on the basis of part A observations, before starting enrollment into part B.

For both parts A and B, eligible patients were boys or girls 2 to 8 years of age with single-ventricle physiology who completed the initial Fontan procedure within 4 months before enrollment. These patients were considered to be clinically stable by the investigator and able to tolerate oral or enteral administration of a suspension formulation and oral/enteral feedings, and met the requirement of initial post-Fontan transthoracic echocardiographic screening with no reported thrombosis. Patients were not eligible if there was evidence of thrombosis during the screening period or active bleeding or high risk of bleeding contraindicating antiplatelet or anticoagulant therapy. The use of vitamin K antagonists had to be discontinued before the screening visit and baseline laboratory assessments were to be obtained at least 7 days after the last dose of a vitamin K antagonist. Administration of ASA was permitted up to 24 hours before the first dose of the study drug. The use of heparin or any low-molecular-weight heparin was permitted if the study drug was started 0 to 2 hours before the next scheduled dose of

either of these anticoagulants and their administration was stopped thereafter. The use of combined P-glycoprotein and strong inhibitors or combined P-glycoprotein and strong inducers was not permitted within 4 days or 2 weeks, respectively, of enrollment.

#### Study Treatment

Rivaroxaban was administered twice daily in an open-label fashion as a 0.1% (1 mg/mL) oral suspension based on weight as shown in Figure 1. The twice-daily dosing regimen was selected because it was expected to produce less fluctuation and a narrower concentration range (ie, lower maximum plasma concentration [ $C_{max}$ ] and higher  $C_{trough}$ ), relative to once-daily dosing, and increase the likelihood that pediatric exposures fell within the range observed in adults.<sup>19,20</sup> Dose reduction due to impaired renal function was not required because children with an estimated glomerular filtration rate  $<30 \text{ mL/min/1.73 m}^2$  were excluded from the study. Rivaroxaban was to be administered at approximately the same times each day in the morning and evening at 12-hour intervals.

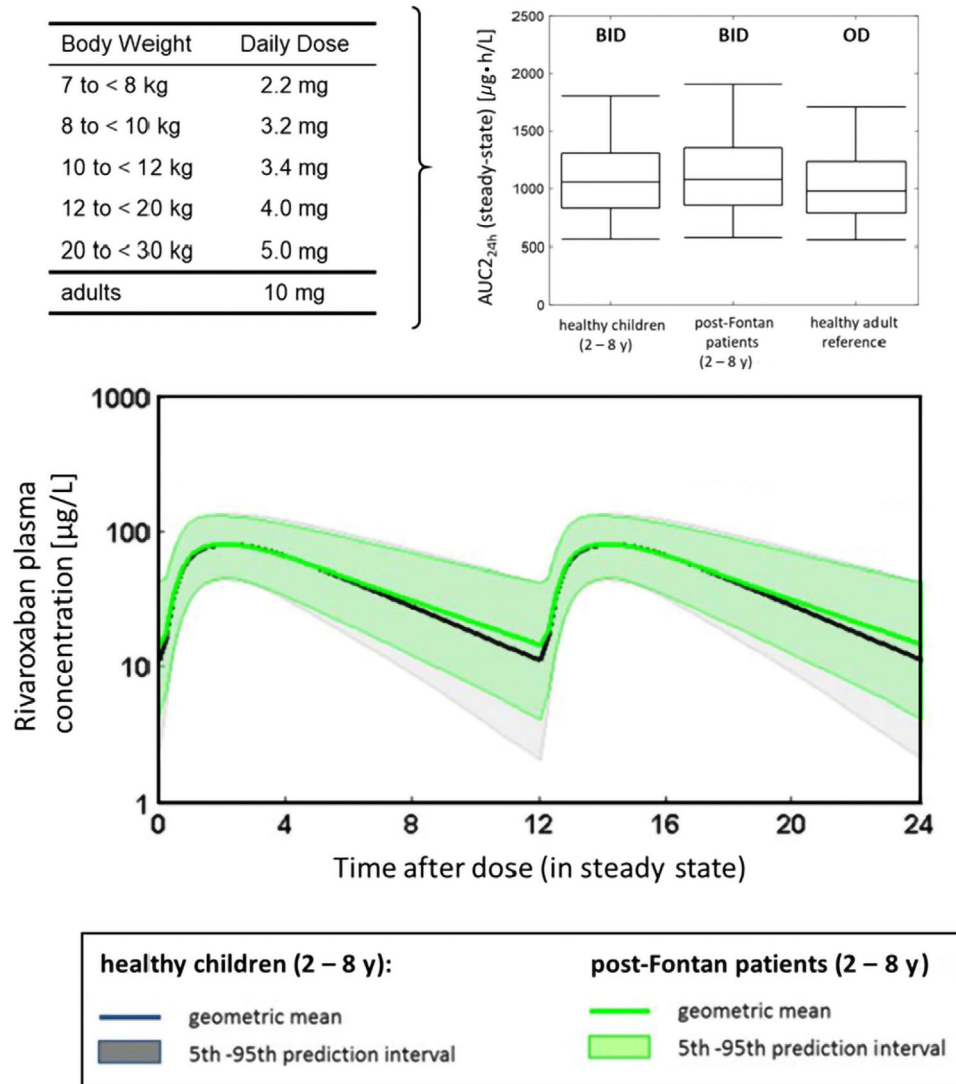
#### Pharmacokinetic and PD Sampling

In part A, blood samples were collected for PK (ie, plasma rivaroxaban concentrations) and full PD (prothrombin time [PT], activated partial thromboplastin time [aPTT], and anti-factor Xa activity) assessments on the first day of dosing between 0.5 and 1.5 hours and again between 1.5 and 4.0 hours after dosing. Additional samples were collected on day 4, just before rivaroxaban administration (PK, PT, and aPTT) and again between 0.5 and 1.5 hours (PK, PT, and aPTT), 1.5 and 4.0 hours (PK, PT, and aPTT), and 6.0 and 8.0 hours (PK and full PD) after dosing. At month 3, samples were collected just before rivaroxaban dosing (PK and full PD) and at 0.5 to 1.5 hours after dosing (PK, PT, and aPTT) and 2.5 to 4 hours after dosing (PK, PT, and aPTT). An additional random sample (PK, PT, and aPTT) was collected at month 12.

In part B, blood samples were collected for assessment of PT and aPTT before the first dosing; PK and full PD samples were collected between 0.5 and 1.5 hours and again between 1.5 and 4.0 hours after the first dose. At month 3, PK and full PD samples were collected just before rivaroxaban administration and again between 0.5 and 1.5 hours, and 2.5 and 4.0 hours after dosing. An additional random sample (PK, PT, and aPTT) was collected at month 12.

#### Sample Analysis

Blood samples for PK or PD assays were centrifuged, and the resulting plasma samples were frozen and stored below  $-15^\circ\text{C}$  until analyzed. Rivaroxaban plasma concentrations were determined using the



**Figure 1.** Body weight-adjusted dosing table proposed for UNIVERSE (daily dose, administered twice daily), comparison of PBPK-predicted rivaroxaban exposure ( $AUC_{24h}$ , steady state), and steady-state plasma concentration-time profile of rivaroxaban predicted for post-Fontan patients aged 2-8 years (green) in comparison to healthy pediatric<sup>(12)</sup> and/or adult<sup>(12)</sup> reference population for the proposed dosing regimen.  $AUC_{24h}$ , area under the plasma concentration-time curve to 24 hours. BID, twice daily; OD, once daily.

validated liquid chromatography-tandem mass spectrometry method with a lower limit of quantitation of  $0.5 \mu\text{g/L}$ . The PD effects of rivaroxaban were assessed by evaluation of PT, aPTT, and anti-factor Xa activity.

PT and aPTT were determined using an electromagnetic mechanical clot detection method at the ARUP Laboratories (Salt Lake City, Utah). The PT assay was performed according to the manufacturers' instructions on the STA Compact Hemostasis Workstation (STA Compact coagulation analyzer) using the PT reagent (STA-Neoplastine Cl Plus; Diagnostica Stago, Inc, Asnières-sur-Seine, France). The primary readout for PT was in seconds with a reportable range between 10 and 120 seconds. STA PTTA agent was used for aPTT (Diagnostica Stago, Inc) analysis. The readout

for aPTT was in seconds with a reportable range between 5 and 180 seconds. Anti-factor Xa activity was determined at Eurofins Biomnis (France) using the STA-COMPACT MAX2 system (Diagnostica Stago). The calibration range of the anti-factor Xa activity assay was 35 to 500 ng/mL.

#### Population PK Assessment

The population PK model used for the UNIVERSE study was similar to that of the EINSTEIN-Jr program.<sup>13</sup> The model was a linear 2-compartment model with first-order oral absorption and first-order elimination from the central compartment, which included the following parameters: the absorption rate constant, the apparent clearance of the central



compartment (CL/F), the apparent central volume of distribution (Vc/F), the apparent peripheral volume of distribution (Vp/F), and the transport rate between the central and peripheral compartments (Q/F) as structural model parameters. CL/F, Q/F, Vp/F, and Vc/F were allometrically scaled with body weight. Other covariates such as renal impairment or hepatic impairment were not assessed in this model due to the limited number of subjects in the UNIVERSE study and the lack of subjects with evaluable covariates. Interindividual variability was identified for absorption rate constant and CL/F. Residual error was described by a proportional error model. The known dose dependency of relative bioavailability ( $F$ ) was described in the population PK model by using the previously reported bioavailability function in adults<sup>18</sup> after replacing the absolute dose in milligrams by dose/weight (DOSE/WGHT) ratio (see Equation 1) using the parameter estimates identified for adult population ( $F_{\min} = 0.590$ ,  $F_{\max} = 1.25$ ,  $D50 = 14.4$  mg).<sup>18</sup>

$$F = F_{\min} + (F_{\max} - F_{\min}) \cdot e^{-\frac{\log_e(2)}{D50} \cdot \frac{\text{DOSE}}{\text{WGHT}}} \quad (1)$$

Exposure metrics of rivaroxaban, the  $AUC_{\text{ss},24\text{h}}$ , the maximum plasma concentration at steady state ( $C_{\text{max,ss}}$ ), and the concentration at the end of the dosing interval at steady state ( $C_{\text{trough,ss}}$ ), were derived using population post hoc parameters.<sup>7,21</sup> Individual exposures in the UNIVERSE study were plotted as a function of body weight and compared with the adult reference range, which was 2.5th to 97.5th percentile range based on adult exposures at 10 mg once daily in the ODIXa-HIP-OD study.<sup>18</sup> Individual exposures in the UNIVERSE study were also compared with the pediatric reference range, which was 2.5th to 97.5th percentile range obtained through simulations of 1000 virtual patients in the EINSTEIN-Jr program assuming the UNIVERSE study weight-based dosing regimen and with a body weight range from 7 to 30 kg.

#### Pharmacokinetic/Pharmacodynamic Assessment

The PD measurements such as PT and aPTT were known to change instantaneously with varying rivaroxaban concentrations. Individual results of PT and aPTT were plotted against simultaneously observed plasma rivaroxaban concentration measured at the same time point and compared with the adult reference range, which was the 99% prediction range obtained using the linear PT (or aPTT) vs rivaroxaban concentration model in adult patients of the hip and knee replacement studies ODIXa-HIP2 and ODIXa-KNEE.<sup>22,23</sup> Individual results of anti-factor Xa activity were plotted against rivaroxaban concentration. No adult reference

anti-factor Xa data are currently available for comparison.

#### Exposure-Efficacy and Exposure-Safety Assessment

The association between rivaroxaban exposure and thrombosis events was explored visually using box plots. Similarly, the association between rivaroxaban exposure and bleeding events was explored visually using box plots.

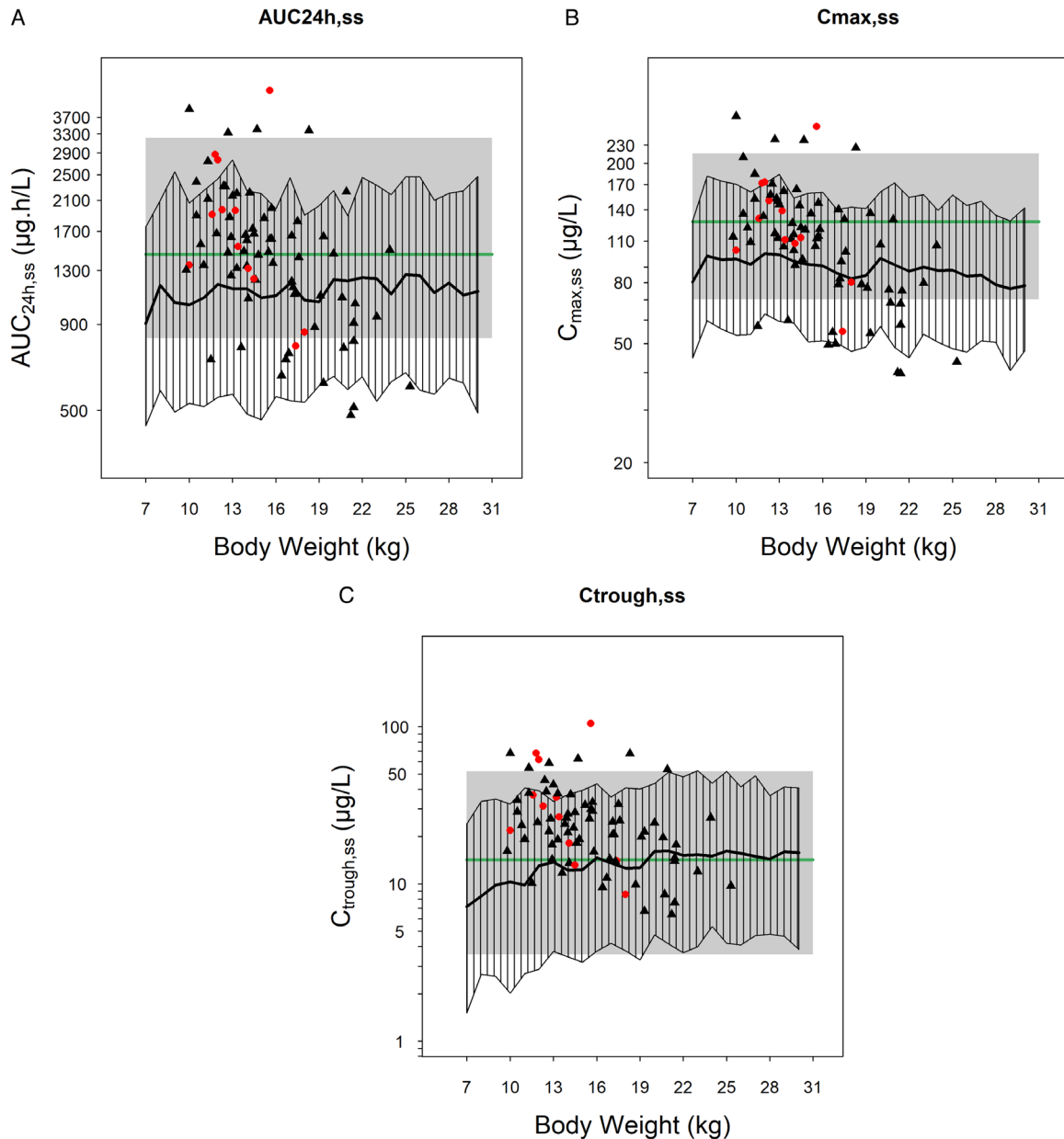
## Results

### Design of a Body Weight-Based Dose Regimen Using PBPK

The relationship between dose and exposure that was predicted by the Fontan-PBPK model for virtual post-Fontan patients 2 to 8 years of age was practically identical to the relationship that was predicted for weight-matched healthy children (based on the initial PBPK model<sup>12</sup>), indicating that the demographic differences as well as the reduced cardiac output that were reflected in the Fontan-PBPK model do not alter the PK of rivaroxaban, in particular the important CL/F metric. The PBPK model simulation suggested a body weight-based dose regimen in pediatric patients following the Fontan procedure, which was expected to produce rivaroxaban exposures similar to the adult reference range at a 10-mg dose. Figure 1 shows the predicted steady-state plasma concentration-time course of rivaroxaban for post-Fontan patients receiving the proposed body weight-adjusted dosing scheme in comparison to healthy children receiving the same dose. This dose regimen was then incorporated and tested in the UNIVERSE study.

### Part A Interim Assessment in the UNIVERSE Study

A total of 12 patients (ages 2-8 years) were enrolled in UNIVERSE part A, with 10 patients completing the PK and PD assessments for 12 months. Since all 12 patients had postdose PK samples taken, they are all included in part A PK assessment. An interim examination of the part A PK run-in results of the 12 patients showed that the rivaroxaban exposures were in a similar range as those observed in adult reference (red circles in Figure 2 and Figure S4). The steady-state exposure of rivaroxaban with the body weight-based dose regimen achieved a geometric mean exposure  $AUC_{\text{ss},24\text{h}}$  of 1698 (90% confidence interval [CI], 1336-2157)  $\mu\text{g} \cdot \text{h/L}$  in part A (Table 1), which was within the predefined range of 70% to 143% of the adult reference exposure at a 10-mg once-daily dose in the ODIXa-HIP-OD study (geometric mean  $AUC_{\text{ss},24\text{h}}$  1494  $\mu\text{g} \cdot \text{h/L}$ ).<sup>18</sup> A noted difference in the steady-state  $C_{\text{trough}}$  was due to different dosing intervals used in adults (once daily) compared to pediatric patients (twice daily). In addition, the PT and aPTT results observed in part A were also



**Figure 2.** Comparison of rivaroxaban exposure in UNIVERSE study with the adult reference study ODIXa-HIP-OD and with the simulated pediatric range using the EINSTEIN-Jr population PK model and the UNIVERSE dose regimen. Green solid lines represent adult 10-mg once-daily reference median exposure metrics (A,  $AUC_{24h,ss}$ ; B,  $C_{max,ss}$ ; C,  $C_{trough,ss}$ ); black solid lines represent simulated pediatric median at 10 mg once daily equivalent exposure metrics; black solid triangles (red solid dots) represent individual exposure metrics prediction for part B (part A) of the UNIVERSE study; gray shaded area represents 2.5th and 97.5th percentile range of adult 10-mg once-daily reference; solid shaded area represents simulated pediatric 2.5th and 97.5th prediction interval at 10 mg once daily equivalent. 2.5th-97.5th percentile exposure ranges of the adult reference are  $AUC_{24h,ss}$ : 820–3216  $\mu\text{g}\cdot\text{h}/\text{L}$ ;  $C_{max,ss}$ : 70.2–215.8  $\mu\text{g}/\text{L}$ ;  $C_{trough,ss}$ : 3.55–52.0  $\mu\text{g}/\text{L}$ .  $AUC_{24h,ss}$ , area under the plasma concentration–time curve to 24 hours at steady state;  $C_{max,ss}$ , postdose maximum concentration at steady state;  $C_{trough,ss}$ , predose concentrations at steady state; PK, pharmacokinetics.

within the 99% prediction range observed in the adult reference studies ODIXa-HIP2 and ODIXa-KNEE (red circles in Figures 3 and 4).<sup>22,23</sup> Based on these data, the body weight–based dose regimen proposed by PBPK was considered appropriate and the UNIVERSE study progressed into part B with the same dose regimen.

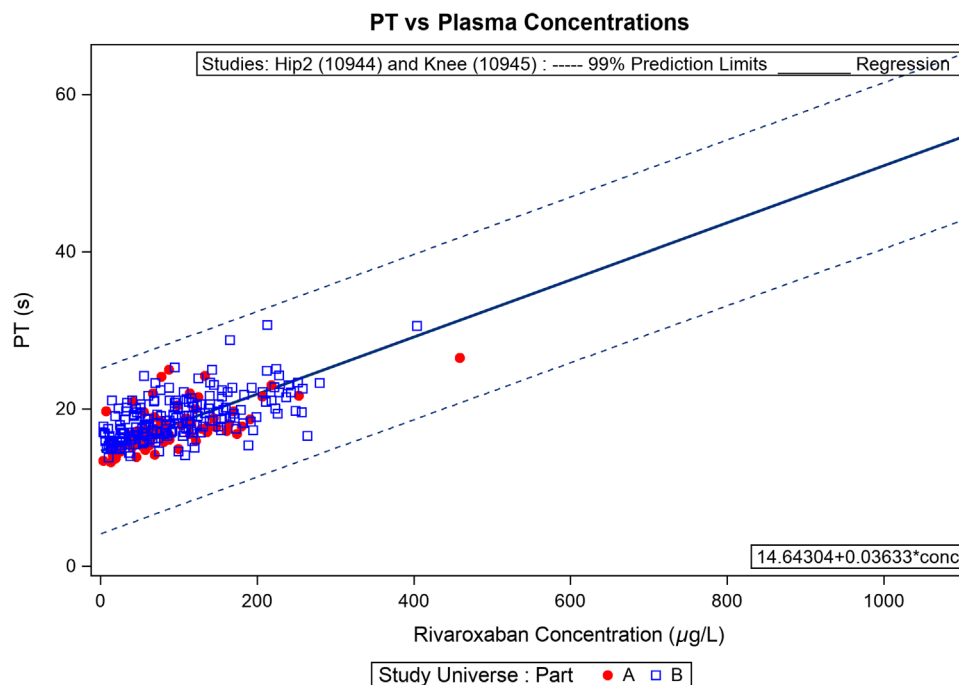
#### Pharmacokinetic Results From Part B of the UNIVERSE Study

Part B included a total of 100 patients: 66 in the rivaroxaban group and 34 in the ASA group. Of the 66 subjects randomly assigned to the rivaroxaban group, 2 did not receive any drug, and 64 received rivaroxaban.

**Table 1.** Comparison of Rivaroxaban Exposures Between the UNIVERSE Study and the Adult Reference Study ODIXa-HIP-OD

Variables	Exposure Metrics	UNIVERSE Part A (Weight-Based Dose Regimen, Twice Daily)	UNIVERSE All Patients (Weight-Based Dose Regimen, Twice Daily)	Adult Reference (10 mg Once Daily)
N		12	76	140
AUC <sub>24h,ss</sub> ( $\mu\text{g} \cdot \text{h/L}$ )	Geometric mean (90%CI)	1698 (1336-2157)	1440 (1317-1576)	1494 (1425-1565)
	Median (range)	1718 (776.8-4444)	1477 (484.2-4444)	1452 (565.4-4747)
	Geometric mean ratio UNIVERSE/adult (90%CI)			0.96 (0.87-1.07)
C <sub>max,ss</sub> ( $\mu\text{g/L}$ )	Geometric mean (90%CI)	123.9 (102.4-149.9)	109.0 (100.4-118.5)	125.8 (120.6-131.3)
	Median (range)	121.8 (54.8-265.2)	113.3 (39.7-287.1)	127.6 (54.0-292.8)
	Geometric mean ratio UNIVERSE/adult (90%CI)			0.87 (0.79-0.95)
C <sub>trough,ss</sub> ( $\mu\text{g/L}$ )	Geometric mean (90%CI)	28.6 (20.2-40.6)	22.8 (20.4-25.5)	13.9 (12.6-15.4)
	Median (range)	29 (8.6-104.7)	23.2 (6.4-104.7)	14.3 (0.8-99.3)
	Geometric mean ratio UNIVERSE/adult (90%CI)			1.64 (1.41-1.90)

AUC<sub>24h,ss</sub>, area under the plasma concentration–time curve to 24 hours at steady state; CI, confidence interval; C<sub>max,ss</sub>, postdose maximum concentration at steady state; C<sub>trough,ss</sub>, predose concentrations at steady state.

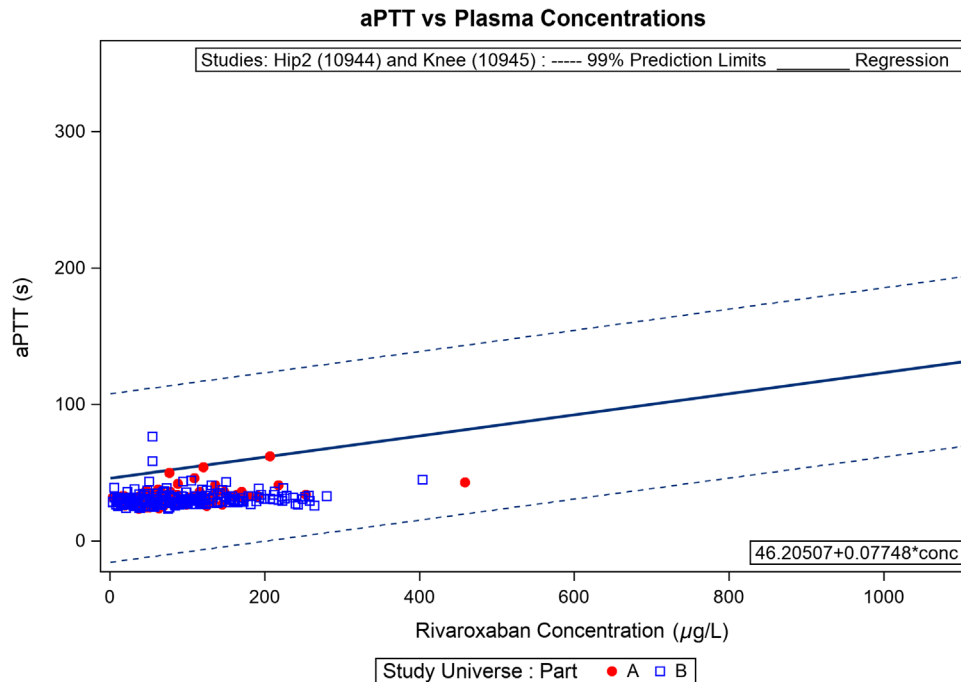


**Figure 3.** Prothrombin time (PT) vs plasma rivaroxaban concentrations: comparison between the UNIVERSE study and the adult reference in studies ODIXa-HIP2 and ODIXa-KNEE. The solid blue line represents the median of the adult reference; the blue dashed lines represent the 99% prediction range of the adult reference.

The observed plasma concentration–time data of rivaroxaban of the full UNIVERSE data set were adequately described by a 2-compartment population PK linear model. The model was parameterized in terms of CL/F estimated at 3.30 L/h, the Vc/F estimated at 17.6 L, Q/F estimated at 1.09 L/h, and Vp/F estimated at 33.4 L/h for a subject with body weight of 15 kg (median weight of the UNIVERSE study population). Rivaroxaban CL/F and Vc/F were scaled exponentially with body weight, and the exponent was estimated to be 1.01 and 1.20, respectively. The first-order absorption

rate constant was estimated to be 1.12/h. As in the EINSTEIN-Jr population PK model (submitted for publication), the dose-dependent relative bioavailability,  $F$ , was adequately described by the previously reported  $F$  function of adults<sup>18</sup> after normalization of dose by weight.

The rivaroxaban concentrations observed in this study were superimposed onto the adult reference range of simulated concentrations from the study ODIXa-HIP-OD (Figure S1).<sup>18</sup> The adult reference range was defined as the 2.5th–97.5th percentile range of



**Figure 4.** Activated partial thromboplastin time (aPTT) vs rivaroxaban concentrations: comparison between the UNIVERSE study and the adult reference studies ODIXa-HIP2 and ODIXa-KNEE. The solid blue line represents the median of adult reference; the blue dashed lines represent 99% prediction range of the adult reference.

simulated concentrations based on the adult reference study ODIXa-HIP-OD, which enrolled adults who underwent a total hip replacement and were administered a 10-mg once-daily dose of rivaroxaban.

The steady-state exposure metrics ( $AUC_{24h,ss}$ ,  $C_{max,ss}$ , and  $C_{trough,ss}$ ) of rivaroxaban in the UNIVERSE study are descriptively summarized in Table 1. The geometric mean  $AUC_{24h,ss}$ , the primary PK metric for exposure matching, was similar between patients in this study and the adult reference. Furthermore, the 90% CIs of the geometric means for these 2 groups largely overlapped. Since patients in the UNIVERSE study received a twice-daily dosing regimen that was intended to match the 10-mg once-daily dosing in adults, the rivaroxaban concentrations in the pediatric patients had a narrower range, with slightly lower  $C_{max,ss}$  and slightly higher  $C_{trough,ss}$  in comparison to the adult reference ranges, which was based on a once-daily regimen. Ratios of geometric mean exposures ( $AUC_{24h,ss}$ ,  $C_{max,ss}$ , and  $C_{trough,ss}$ ) for patients in the UNIVERSE study were compared with the adult reference (Table 1). The ratio for  $AUC_{24h,ss}$  was 0.96 and the corresponding 90% CI was 0.87 to 1.07. As expected for the twice-daily dosing regimen in this study in comparison to the once-daily regimen in the adult reference, the geometric mean ratio for  $C_{max,ss}$  was slightly lower than 1, and the geometric mean ratio for  $C_{trough,ss}$  was slightly higher than 1. These results demonstrated overall similarity in rivaroxaban

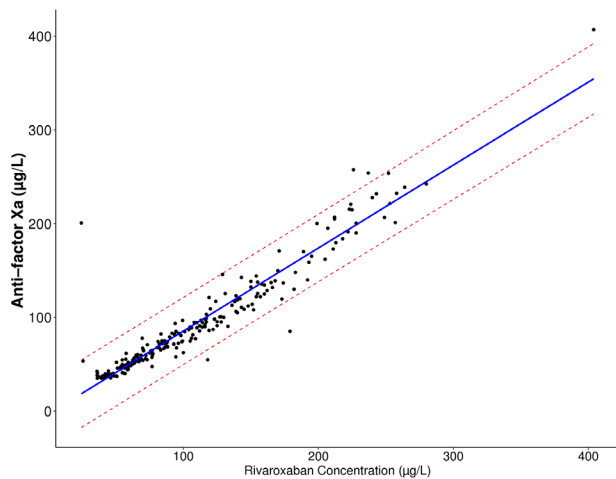
exposures between this pediatric population and the adult reference.

Scatter plots were constructed to compare the exposure metrics ( $AUC_{24h,ss}$ ,  $C_{max,ss}$ , and  $C_{trough,ss}$ ) vs body weight between results from the UNIVERSE study and the adult reference at rivaroxaban 10 mg once daily (Figure 2). The  $AUC_{24h,ss}$  from this study was largely contained within the 2.5th to 97.5th percentile range of the adult reference, indicating that the overall rivaroxaban exposures in patients in the UNIVERSE study were similar to those in adults. As shown in Figure 2, patients in the UNIVERSE study who had relatively lower body weights tended to have slightly higher exposure as compared to the adult reference and predictions using the EINSTEIN-Jr population PK model. However, the overall PK characteristics were similar between the UNIVERSE study and the EINSTEIN-Jr program, with exposure metrics ( $AUC_{24h,ss}$ ,  $C_{max,ss}$ , and  $C_{trough,ss}$ ) largely overlapping with the pediatric prediction range based on the EINSTEIN-Jr population PK model assuming the same dose regimen as the UNIVERSE study (Figure 2).

#### Pharmacokinetic/Pharmacodynamic Results From the UNIVERSE Study

Since the adult PK reference study ODIXa-HIP-OD used an insensitive PT assay and could therefore not be used for reference, adult PD reference ranges were alternatively obtained from the adult phase II hip and





**Figure 5.** Anti-factor Xa activity as a function of plasma rivaroxaban concentrations in the UNIVERSE study. The solid blue line represents the median of model prediction; the red dashed lines represent the 95% prediction interval. Regression line:  $y = -3.14 + 0.885x$ ;  $R^2 = 0.901$ .

knee replacement studies ODIXa-HIP2 and ODIXa-KNEE,<sup>22,23</sup> during which rivaroxaban was administered twice daily. As the PK/PD relationship is independent of the dosing frequency, it is appropriate to use these data for reference. PT values as a function of rivaroxaban concentration were similar to the adult reference range as illustrated in Figure 3. Activated thromboplastin time as a function of time is illustrated in Figure 4. The slope for aPTT vs rivaroxaban concentration relationship was less steep in comparison to the adult reference, which may be due to the low sensitivity of aPTT assays and its known large variability between studies due to sensitivity to reagents and experimental conditions.<sup>24</sup> Anti-factor Xa activity correlated strongly ( $R^2 = 0.901$ ) with rivaroxaban concentrations in UNIVERSE (Figure 5).

#### Exposure-Efficacy and Exposure-Safety Results From the UNIVERSE Study

Within the rivaroxaban treatment group, 2 thrombotic events, including 1 venous thrombosis and 1 pulmonary embolism, were observed in 2 patients, respectively. Bleeding events were observed in 27 patients. Three patients experienced multiple bleeding events and 24 patients experienced 1 event. Among the bleeding events, 1 major bleeding, 5 clinically relevant nonmajor bleeding, and 24 trivial bleeding events were observed.

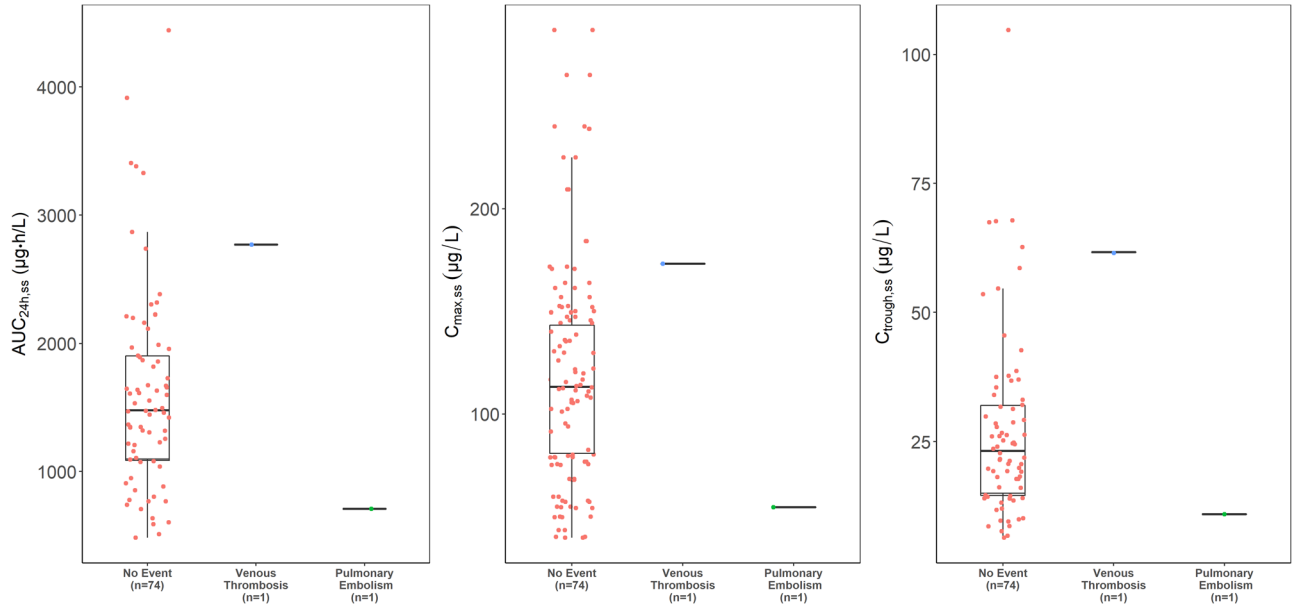
Exposure-response relationships in patients treated with rivaroxaban were visually investigated by comparing the exposure metrics ( $AUC_{24h,ss}$ ,  $C_{max,ss}$ , and  $C_{trough,ss}$ ) in patients with or without thrombotic or bleeding events, and with or without bleeding events (Figures 6 and 7). The ranges of  $AUC_{24h,ss}$ ,  $C_{max,ss}$ , and  $C_{trough,ss}$  largely overlapped between patients with or without thrombosis or bleeding events. In addition,

when logistic regression was performed between the bleeding events and  $AUC_{24h,ss}$ , no statistically significant correlation was detected. These results suggest that, within the exposure range observed, there was no apparent exposure-response relationship between rivaroxaban exposure and thrombosis or bleeding events.

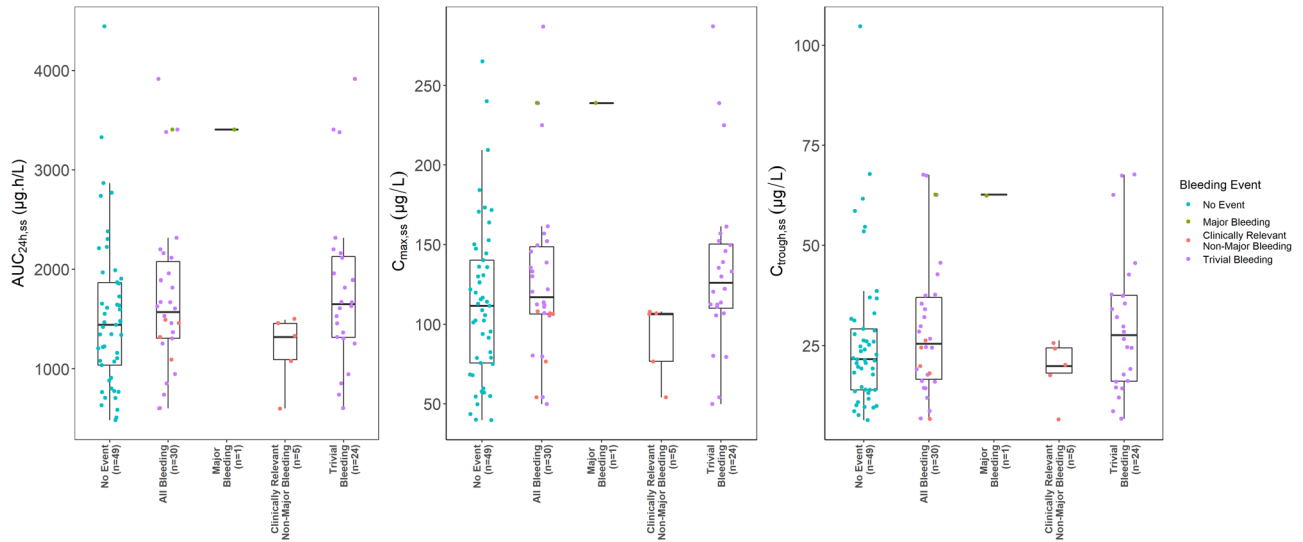
## Discussion

Identifying effective and safe dosing regimens of rivaroxaban for post-Fontan pediatric patients was expedited using an MIDD strategy in comparison to that of the VTE treatment indication (ie, the EINSTEINJr program). Instead of conducting a phase II dose-finding study, we took advantage of the large amount of pediatric PK data previously collected in multiple phase I studies in the EINSTEIN-Jr pediatric program.<sup>13,25</sup> By integrating the preexisting pediatric PK knowledge, and further incorporating the disease-specific physiology of post-Fontan patients, a rivaroxaban PBPK model for post-Fontan patients was developed. Simulations with this PBPK model were used to design a body weight-based dose regimen for thromboprophylaxis to be tested in post-Fontan children. This dose regimen was then tested in part A (PK run-in) of the phase III UNIVERSE study to verify that the dose regimen achieved rivaroxaban exposures comparable with the adult reference range at 10 mg once daily with a preset criterion of 70% to 143% for the geometric mean of  $AUC_{24h,ss}$ . Once the exposure criterion was met, the UNIVERSE study continued to part B, in which the dose regimen was confirmed to be appropriate with additional PK and PD results collected from a larger number of post-Fontan patients. If the exposure criterion had not been met, we would have had an opportunity to adjust the dose regimen based on observed part A data, refine the PBPK model, and then move on to part B.

This MIDD-based approach saves time and resources by obviating the need for a full phase II dose-finding or dose-confirmation study. Given the challenges faced in the conduct of a pediatric study as well as the range of possible doses over the range of body weight that needed to be tested, the MIDD-based strategy, as appropriately verified and validated in the UNIVERSE study, can significantly reduce the time needed for dose-finding for a pediatric indication. MIDD approaches may not necessarily work for every drug. In our case, the successful application of such an approach in rivaroxaban post-Fontan thromboprophylaxis could be attributed to the following 4 major factors: first, the PK of rivaroxaban was noncomplex (time linear and approximately dose linear) and generally consistent between adult and pediatric populations, which made the body



**Figure 6.** Exposure-thrombosis event relationship of rivaroxaban in the UNIVERSE study. Individual values are provided where  $n = 1$ . The solid line in the box is the median. The boundaries of the box represent the 25th and 75th percentiles. The whiskers are the nearest values within 1.5 times the interquartile range below and above the 25th and 75th percentiles, respectively.  $AUC_{24h,ss}$ , area under the plasma concentration–time curve to 24 hours at steady state;  $C_{max,ss}$ , postdose maximum concentration at steady state;  $C_{trough,ss}$ , predose concentrations at steady state.



**Figure 7.** Exposure-bleeding events relationship of rivaroxaban in the UNIVERSE study. All bleeding includes the 3 bleeding categories: major, trivial, and CRNM. The solid line in the box is the median. The boundaries of the box represent the 25th and 75th percentiles. The whiskers are the nearest values within 1.5 times the interquartile range below and above the 25th and 75th percentiles, respectively.  $AUC_{24h,ss}$ , area under the plasma concentration–time curve to 24 hours at steady state;  $C_{max,ss}$ , postdose maximum concentration at steady state; CRNM, clinically relevant nonmajor bleeding;  $C_{trough,ss}$ , predose concentrations at steady state.

weight–based exposure-scaling applicable; second, the accumulation of sufficient PK knowledge in the pediatric populations, especially that the dose-finding results collected in the EINSTEIN-Jr program showed in general good agreement with PBPK prediction and further enhanced the confidence of the PBPK

model-based dose simulations; third, the PD, efficacy, and safety were expected to be similar given similar exposures due to the similarity in the mechanisms of action and the magnitude of the drug effect between pediatric patients and adults; and finally, a well-planned PK run-in with sufficient PK (and PD) evaluations in

the phase III study is advantageous to evaluate the validity of the MIDD-selected dose in the relevant population before moving forward to the confirmatory part of the study (part B) in a larger number of patients.

In the MIDD-based dose selection approach, different modeling and simulation tools such as PBPK and population PK, and sometimes quantitative systems pharmacology models can be used for making decision on dosing regimen selection. For supporting pediatric dose adjustments, the choice of modeling tools should depend on the PK characteristics of the compound and the physiologic similarity between the adult and pediatric populations. In many cases, population PK alone can be sufficient if the expected difference between the adult and pediatric population is solely driven by body weight. PBPK modeling can offer advantages over a simpler population PK model if there are patient-specific and/or disease-specific physiologic characteristics that may affect drug PK and/or PD. If there are known PD, efficacy, and safety differences that can be reliably and quantitatively expressed in a model, then a PK/PD-linked model (using PBPK or population PK) or a quantitative systems pharmacology model may be applied as suggested in previous publications.<sup>26,27</sup>

## Conclusions

The PK results of the UNIVERSE study confirmed that the body weight-based dose regimen (shown in Figure 1), in post-Fontan pediatric patients, resulted in rivaroxaban exposure that matched the adult reference exposures at 10 mg once daily. Moreover, the key PD end point, PT, was also similar to the adult reference ranges. The slope for aPTT vs rivaroxaban relationship was less steep in comparison to the adult reference, which may be due to its known variability between studies due to its large sensitivity to reagents and experimental conditions.<sup>24</sup> Furthermore, there was no apparent quantitative relationship identified between rivaroxaban exposure and the reporting of thrombosis or bleeding events within the observed rivaroxaban concentration range. In conclusion, the dose selected by PBPK modeling and tested and confirmed in the UNIVERSE study was shown to be appropriate for thromboprophylaxis in the post-Fontan pediatric population.

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## Conflicts of Interest

P.Z., W.Z., H.Y., L.M.P., T.W., K.N., and P.Z.: employment and equity ownership, Janssen R&D, LLC. S.W.: employment at Bayer AG. A.M.: fees from Janssen Research and Development,

AstraZeneca, Bristol-Myers Squibb/Sanofi-Aventis, Medtronic, and Stasys; grant from Medtronic. B.M.: fees from Janssen R&D, LLC and Mezzion. J.L.: research support; Janssen R&D, LLC. K.H.: consultancy fees; Janssen R&D, LLC. L.L.: consultancy fees, Janssen R&D, LLC.

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## Data Sharing

The data used in these analyses cannot be shared at this time.

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## Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.