CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215859Orig1s000

CLINICAL PHARMACOLOGY REVIEW(S)

Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 215859
Link to EDR	\\CDSESUB1\evsprod\NDA215859
Submission Date	22 Jun 2021
Submission Type	Priority
Brand Name	XARELTO®
Generic Name	Rivaroxaban
Dosage Form and Strength	• Granules (b) (4) for oral suspension to be mixed with 150 mL of water to provide 1 mg/mL suspension • Film-coated immediate-release tablets: 10, 15 and 20 mg
Route of Administration	Oral
Proposed Indication	• The treatment of venous thromboembolism (VTE) and the reduction in risk of recurrent VTE in pediatric patients from birth to less than 18 years after at least 5 days of initial parenteral anticoagulant treatment • Thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease (CHD) who have undergone the Fontan procedure
Applicant	Janssen Pharmaceuticals, Inc.
Associated IND & NDA	IND 064892 NDA 022406 S-001/S-002/S-003 (VTE/PE) NDA 202439 (Atrial Fibrillation)
OCP Review Team	Harisudhan Thanukrishnan, PhD; Jihye Ahn, PharmD; Manuela Grimstein, PhD; Liang Li, PhD; Xinyuan Zhang, PhD; Sudharshan Hariharan, PhD

Table of Contents

1. EXECUTIVE SUMMARY

Rivaroxaban is an oral anticoagulant which is approved under NDA 022406 for (A) i. the prophylaxis of deep vein thrombosis (DVT) in patients undergoing hip replacement surgery or knee replacement surgery; ii. to reduce the risk in the recurrence of DVT and/or pulmonary embolism (PE) in patients at risk; iii. for prophylaxis of venous thromboembolism (VTE) in acutely ill patients at a risk for thromboembolic complications and not at high risk of bleeding, and for (B) the treatment of DVT and/or PE. For the prophylactic indications above, the general approved dosing regimen is 10 mg once daily with or without food. For the treatment indication, the general approved dosing regimen is 15 mg twice daily with food for the first 21 days followed by 20 mg once daily with food for the remaining treatment. Rivaroxaban is also approved under NDA 202439 to reduce the risk of major cardiovascular events in patients with coronary artery disease (CAD) and thrombotic vascular events in patients with peripheral artery disease (PAD). It is also approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NAF). For the CAD and PAD indications the approved dosing regimen is 2.5 mg orally twice daily with or without food in combination with aspirin and for the NAF indication the dose is 15 or 20 mg, once daily with food.

To address the Pediatric Research Equity Act requirements and fulfill the FDA's post-marketing requirements, in addition to the approved film coated immediate-release tablets, the Applicant, Janseen Pharmaceuticals Inc., developed granules for oral suspension formulation for use in younger pediatric patients. Pharmacological response to rivaroxaban was assessed for similarity in PK and coagulation PD marker relationships between adults and pediatric patients. A body weight-adjusted dosing was established in pediatric patients with an objective to match the exposures achieved in adults based on the framework of extrapolation. The Applicant is seeking approval of the following two indications under NDA 215859: (1) VTE treatment and reduction of risk of VTE recurrence in pediatric patients from birth to <18 years and (2) Thromboprophylaxis in children with congenital heart disease after the Fontan procedure aged 2 years and above. Please see 'General Dosing section 2.2.1' below for body weight-adjusted dosing regimen for the two proposed pediatric indications.

In the current NDA submission for pediatric use, the Applicant submitted study reports for 7 pediatric clinical studies including two Phase 1 studies (12892, 17992), two Phase 2 studies (14373, 14374), one Phase 1/2 study (17618) and one pivotal Phase 3 study- 14372 (EINSTEIN Jr), totalling to 6 studies in pediatric patients with VTE and one pivotal Phase 3 study- CHD3001 (UNIVERSE), in post-Fontan pediatric patients. In addition, the submission includes six separate Phase 1 biopharmaceutics studies in healthy adults (PH-36262 or 14022, PH-37535 or 16886, PH-38629 or 17769, PH-38690 or 17861, PH-40127 or 19365, PH-40136 or 19366).

1.1 Recommendations

The Office of Clinical Pharmacology (OCP)/ Division of Cardiometabolic and Endocrine Pharmacology and Division of Pharmacometrics have reviewed the information contained in NDA 215859. The OCP review team recommends approval of NDA 215859, rivaroxaban granules for oral suspension and tablets, for use in pediatric patients from birth (at-term) to <18 years of age for the VTE treatment and reduction of risk of VTE recurrence and pediatric patients aged 2 years or older after the Fontan procedure for

thromboprophylaxis. Key review issues with specific recommendations and comments are summarized in the table below:

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	Clinical pharmacology information demonstrated similar exposure-response relationships for clotting time variables (PT, aPTT and anti-factor Xa) between pediatric and adult patients with VTE and pediatric patients with CHD after the Fontan procedure. In addition, the proposed doses in pediatric patients are expected to result in a similar range of steady-state rivaroxaban trough concentrations, as observed in adults. Refer to section 3.3.1 for details.
General dosing instructions	The Applicant proposed body weight-based pediatric dosing regimen (See section 2.2.1) based on pediatric clinical experience from Studies 14372 (EINSTEIN Jr) and CHD3001 (UNIVERSE) to support VTE treatment/recurrent risk reduction and thromboprophylaxis after the Fontan procedure indications, respectively. The appropriateness of proposed dosing regimen is discussed in section 3.3.2. All doses for the VTE indication should be administered with feeding or food. The dose for thromboprophylaxis indication can be administered with or without food. Missed doses can be taken on same day for once or twice daily regimens; missed doses should be skipped for the thrice daily regimen.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Body weight-based starting dosing regimen is required for pediatric patients. • Doses for pediatric VTE indication to be taken with feeding or food. • Avoid use of XARELTO® in pediatric patients with eGFR <50 mL/min/1.73 m^2 or in patients younger than 1 year with serum creatinine results above 97.5th percentile. • Avoid concomitant use with known combined P-gp and strong CYP3A inhibitors or combined P-gp and strong CYP3A inducers in pediatric patients. Avoid concurrent use of XARELTO® with other anticoagulants due to increased bleeding risk unless benefit outweighs risk.
Labeling	The labeling language by Applicant was generally acceptable.
Bridge between the to-be-marketed and clinical trial formulations	The to-be-marketed granules for oral suspension formulation was used in clinical trials. The immediate-release (IR) 10, 15 and 20 mg tablets that were identical in composition to commercial formulation were used in the clinical trials. The granules for oral suspension formulation was shown to meet bioequivalence criteria for AUC and C_{max} in comparison to the commercial IR tablets at the 10 mg dose in fasted state as well as for the 20 mg dose in fed state in healthy adults.
Other (specify)	None

1.2 Post-Marketing Requirements and Commitments

None

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Rivaroxaban is a competitive, selective, and direct oral Factor Xa inhibitor. Factor Xa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation. Rivaroxaban has no direct effect on platelet aggregation, but indirectly inhibits platelet aggregation induced by thrombin. Rivaroxaban produces dose-dependent inhibition of FXa activity. Clotting tests, such as prothrombin time (PT), activated partial thromboplastin time (aPTT) and HepTest®, are also prolonged dose-dependently.

The clinical PK and PD of rivaroxaban were investigated in adult populations and summarized previously under NDAs 022406 and 202439. The clinical pharmacokinetics of rivaroxaban in pediatric studies is summarized below:

Absorption:
PK data following intravenous administration to children are not available, so the absolute bioavailability of rivaroxaban in children is unknown. Rivaroxaban is readily absorbed after oral administration as IR tablet or granules for oral suspension formulation in children. Following multiple doses of rivaroxaban in the EINSTEIN Jr Phase 3 study, median [range] $T_{max,ss}$ values were around 2 [1.8-2.6] h in pediatric subjects aged 6 to <18 years irrespective of formulation (tablet and granules for oral suspension) and around 1.5 [1.3-2.3] h in younger pediatric subjects, all receiving the granules for oral suspension. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was found, as the two formulations were found to be bioequivalent under fed and fasted conditions. In line with data obtained in adults, a decrease in the relative bioavailability for increasing doses (in mg/kg) was found, suggesting solubility-limited absorption for higher doses. However, similar to the findings with IR tablets, the 20 mg granules for oral suspension when taken with food behaved dose-proportionally with regard to rivaroxaban AUC and Cmax compared to 10 mg dose in the fasted state.

Distribution:
In vitro plasma protein binding was evaluated by spiking a nominal concentration of 100 ng/mL rivaroxaban in plasma samples collected from children aged <2 years old, 2-6 years old and >6-9 years old (N=3 donors per age group). The mean unbound fraction (fu %) in pooled pediatric plasma of different age groups: <2 years old, 2-6 years old and >6 years old were 11.1, 11.2 and 9.2%, respectively. In comparison, the mean plasma protein binding in adults was approximately 92 to 95%. Although the mean protein binding in adults is higher, the range of values observed in adults across different studies encompass the values observed in children. It should also be noted that plasma samples were not

collected in any of the pediatric trials of rivaroxaban to evaluate protein binding. Based on population PK (popPK) model in pediatric patients, apparent volume of distribution (Vss/F) increased with body weight in accordance with allometric scaling.

Elimination:
Rivaroxaban is metabolized via the CYP3A4/5 and CYP2J2 enzymes in adults. Rivaroxaban was not a substrate for the fetal isoform of CYP3A7 and the contribution of CYP3A7 to the clearance in pediatric population can be excluded. The popPK model in pediatric patients showed that the clearance (CL/F) increased with body weight in accordance with allometric scaling. Geometric mean values for elimination half-life estimated via popPK modeling decreased with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2 to12 years down to 1.9 and 1.6 h in children aged 0.5-<2 years and less than 6 months, respectively.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant has proposed a body weight-based oral dosing for pediatric patients from at-term birth (weighing ≥2.6 kg) to <18 years for the treatment or reduction in recurrence of VTE and for thromboprophylaxis in patients 2 years or older with congenital heart disease (CHD) after the Fontan procedure. The underlying dosing strategies for VTE treatment and CHD thromboprophylaxis were to achieve rivaroxaban exposures in children that are similar to that observed in adult DVT patients receiving 20 mg rivaroxaban once daily or adults receiving 10 mg rivaroxaban once daily after major orthopedic surgery, respectively. As observed in adults, a decrease in relative bioavailability for increasing doses (in mg/kg bodyweight) was also found in children, suggesting solubility-limited absorption limitations at higher doses. Hence, the pediatric doses for VTE treatment (corresponding to adult 20 mg dose), are recommended to be taken with food.

The Applicant proposed pediatric dosing for VTE treatment following initiation of standard anticoagulant treatment, is shown in Table 1. All doses for the VTE indication should be taken with feeding or food to increase the absorption. Children younger than 6 months should have had oral /(naso)gastric feeding for at least 10 days preceding rivaroxaban administration. The proposed dosing regimen for VTE treatment was evaluated in EINSTEIN Jr, with the only exception of Japan, where 15 mg once daily was used for patients weighing ≥ 50 kg.

Table 1. Dosing table for Xarelto in pediatric patients (<18 years) for treatment of Venous Thromboembolism (VTE) and reduction in the risk of recurrent VTE

Dosage Form	Body weight	1 mg XARELTO = 1 mL suspension			
		Dosage			Total daily dose‡
		Once a day§	2 times a day§	3 times a day§	
Oral Suspension Only	2.6 to <3 kg			0.8 mg	2.4 mg
	3 to <4 kg			0.9 mg	2.7 mg
	4 to <5 kg			1.4 mg	4.2 mg
	5 to <7 kg			1.6 mg	4.8 mg
	7 to <8 kg			1.8 mg	5.4 mg
	8 to <9 kg			2.4 mg	7.2 mg
	9 to <10 kg			2.8 mg	8.4 mg
	10 to <12 kg			3.0 mg	9 mg
	12 to <30 kg		5 mg		10 mg
Oral Suspension or Tablets	30 to <50 kg	15 mg			15 mg
	≥50 kg	20 mg			20 mg

* Initiate XARELTO treatment following at least 5 days of initial parenteral anticoagulation therapy.

† Patients <6 months of age should meet the following criteria: at birth were at least 37 weeks of gestation, have had at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing (b) (4)

‡ All doses should be taken with feeding or with food since exposures match that of 20 mg daily dose in adults.

§ Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart; 3 times a day: approximately 8 hours apart

The Applicant proposed dosing for thromboprophylaxis in pediatric patients with CHD 2 years and older weighing 7 kilograms or more is shown in Table 2. The dose for thromboprophylaxis after Fontan procedure can be taken with or without food. The proposed dosing regimen for thromboprophylaxis in patients weighing <30 kg was identical to the regimen evaluated in UNIVERSE (Table 7). However, a model-based bridging was used to extrapolate dosing for post-Fontan patients ≥30 kg.

Table 2. Dosing table for Xarelto in pediatric patients (<18 years) for thromboprophylaxis in post-Fontan population

Dosage Form	Body weight	1 mg XARELTO = 1 mL suspension		
		Dosage		Total daily dose*
		Once a day†	2 times a day†	
Oral Suspension Only	7 to <8 kg		1.1 mg	2.2 mg
	8 to <10 kg		1.6 mg	3.2 mg
	10 to <12 kg		1.7 mg	3.4 mg
	12 to <20 kg		2.0 mg	4.0 mg
	20 to <30 kg		2.5 mg	5.0 mg
	30 to <50 kg	7.5 mg		7.5 mg
Oral Suspension or Tablets	≥50 kg	10 mg		10 mg

* All doses can be taken with or without food since exposures match that of 10 mg daily dose in adults.

† Once a day: approximately 24 hours apart; 2 times a day: approximately 12 hours apart.

2.2.2 Therapeutic individualization

Body weight and Age:

Due to the expected gain in bodyweight of young children during the course of therapy, dose adjustments and/or change in dosing regimen according to the rivaroxaban dosing table for children (Table 1) are needed to ensure maintenance of a therapeutic dose.

Renal impairment:

Patients 1 year of age or older: No dosage adjustment is required with mild renal impairment (eGFR 50 to ≤80 mL/min/1.73 m^2). Avoid the use of rivaroxaban in pediatric patients with moderate or severe renal impairment (eGFR <50 mL/min/1.73 m^2), as there is limited clinical data in these patients.

Patients less than 1 year of age: Determine renal function using serum creatinine. Avoid the use of rivaroxaban in pediatric patients younger than 1 year with serum creatinine results above 97.5th percentile, as no clinical data is available.

Hepatic impairment:

No clinical data are available in pediatric patients with hepatic impairment.

Drug Interactions:

Rivaroxaban is a substrate of CYP3A4/5, CYP2J2, and the P-gp and ATP-binding cassette G2 (ABCG2) transporters. Concomitant use with strong inhibitors of both P-gp and CYP3A increase exposure to rivaroxaban and may increase the risk of bleeding. Concomitant use with strong inducers of both P-gp and CYP3A decrease exposure to rivaroxaban and may increase the risk of thromboembolic events. Avoid concomitant use of rivaroxaban with known combined P-gp and strong CYP3A inhibitors or combined P-gp and strong CYP3A inducers in pediatric patients.

2.3 Outstanding Issues

None

2.4 Summary of Labeling Recommendations

General labeling recommendations were provided to improve the clarity and relevance of updated information related to pediatric indications that is conveyed to the healthcare provider. Additional recommendation was provided to specify the equations used to estimate renal function in the pediatric population that were enrolled into clinical studies.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Rivaroxaban immediate release tablets (IR) are approved for several adult indications. In the pediatric clinical studies, only 10, 15, and 20 mg dose strengths were used and so the 2.5 mg is not supported for pediatric use. The granules for oral suspension is a new age-appropriate pediatric formulation and was shown to be bioequivalent to the marketed IR formulations.

The Applicant, Janseen Pharmaceuticals Inc., submitted the initial proposed pediatric study request (PPSR) for rivaroxaban in Aug/2012. All the clinical pediatric studies in VTE treatment program are a part of the Pediatric Research Equity Act (PREA) Post-marketing Requirements under NDA 022406. In response to FDA's feedback, a thromboprophylaxis program in pediatric subjects with CHD post-Fontan procedure was developed and included in the Written Request (WR) that was issued on 08 June 2017. Considering comparable pathophysiology of thromboembolism (TE) between adults and children, FDA supported partial extrapolation of safety and efficacy data from adult patients treated with rivaroxaban. However, the partial extrapolation was to be supported by an adequate PK and PD bridge to determine the appropriate dose, as well as sufficient safety and efficacy data to screen for large discrepancies in these endpoints between adults and children that could be caused by differences in underlying coagulation system maturity or TE pathophysiology. Since children of all ages, including neonates, experience VTE, studies for treatment of pediatric VTE were agreed to be conducted in children from birth through late adolescence. The study for prophylaxis after a Fontan procedure was agreed to be done in in children 2 years and older, an age group that was considered relevant to that procedure.

Overall, the clinical pharmacology studies were aimed at (a) deriving dosing regimen across pediatric patients of all ages that targets similar exposures in adults treated with rivaroxaban, (b) comparing correlations for pharmacodynamic coagulation markers like prothrombin time [PT], activated partial thromboplastin time [aPTT], anti-factor Xa activity with plasma rivaroxaban concentrations in pediatric population versus data in adults and (c) development of an age-appropriate formulation to be used in the pediatric clinical studies.

NDA submission overview:
This NDA submission includes a total of 7 open-label, multicenter PK/PD studies (Table 3) of which 6 were a part of the WR and/or PMR studies and the Applicant conducted an additional Phase 1 PK/PD study (Study 17992) in support of inclusion of the granules for oral suspension formulation into Phase 3 trials. In addition, the submission includes 6 supporting biopharmaceutic studies in adult healthy subjects that characterize the pediatric formulations. The PK/PD studies include establishment of pediatric dosing regimen, safety, and efficacy of rivaroxaban in subjects with VTE (across all ages) and CHD post-Fontan (2-8 years). The model-based bridging was used to extrapolate dosing for post-Fontan patients from 9-18 years of age.

Table 3. Overview of pediatric clinical studies for Rivaroxaban in NDA 215859

Study number	Phase	Para meter	Duration	Age range	Description	Number receiving Xarelto /placebo
17992	1	PK	Single dose	2 m to <12 y	Single-dose PK/PD study in subjects with previous thrombosis	47
12892	1	PK/PD	Single dose	6 m to <18 y	Single-dose PK/PD study in subjects with previous thrombosis	59

14373	2	PK/PD	30-days repeated dose	6 y to <18 y	Multiple-dose (30-day) safety, efficacy, and PK/PD study in subjects with VTE	43/20
14374	2	PK/PD	30-days repeated dose	6 m to <6 y	Multiple-dose (30-day) safety, efficacy, and PK/PD study in subjects with VTE	46
17618	1/2	PK/PD	7-day repeated dose	term newborn to <6 m	Multiple-dose (7-day) safety, efficacy, and PK/PD study in subjects with arterial or venous thrombosis	10
14372 EINSTEIN Jr	3	PK/PD	3 months-1 year	birth to <18 y	Efficacy and safety in pediatric subjects with acute VTE	329/162
3001/18226 UNIVERSE	3	PK/PD	1 year	2 y to ≤8 y	Multiple-dose (12 months) safety, efficacy and PK/PD for thromboprophylaxis post-Fontan procedure	76/34

Source: Table 1 in Summary of Clinical Efficacy; For details on individual studies, refer Section 4.2

3.2 General Pharmacology and Pharmacokinetic Characteristics

For detailed information and highlights of clinical pharmacology of rivaroxaban, refer to the clinical pharmacology review under NDA 022406 on 4/6/2009.

Pharmacology	
Mechanism of Action	Rivaroxaban is a direct FXa inhibitor which competitively inhibits human free FXa. Rivaroxaban also inhibits prothrombinase activity. This results in downstream inhibition of the FXa mediated conversion of prothrombin to thrombin via the prothrombinase complex and prevents the fibrin clot formation as well as the activation of platelets by thrombin.
General Information	
Bioanalysis	Plasma concentrations of rivaroxaban were determined by validated HPLC-MS/MS methods. Anti-FXa was determined by colorimetric assay. PT and aPTT were determined using commercial coagulation analyzer.
Drug Exposure at Steady State Following the Therapeutic Dosing Regimen	Refer to section 3.3.1 for comparison of exposures in pediatric patients to adult patients.
Dose Proportionality	The granules-for-oral-suspension formulation behaved dose proportionally for rivaroxaban AUC and C_{max} for the 20 mg taken with food vs. 10 mg dose in the fasted state.
Pharmacodynamics	Overall, the results of PT, aPTT in pediatric subjects were within the adult reference range and as in adults, there is a correlation between plasma rivaroxaban concentrations and the degree of its anticoagulant

	effect in pediatric patients with VTE and CHD post-Fontan for PT. A narrower range of aPTT values was observed in CHD post-Fontan subjects in UNIVERSE compared to adults. The anti-factor Xa activity correlated well with plasma rivaroxaban concentrations in pediatric patients.

3.3 Clinical Pharmacology Review Questions

3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information provides supportive evidence of effectiveness in the similarity of PK-PD relationships and range of steady-state C_{trough} values between adult and pediatric patients with VTE or pediatric patients with CHD after a Fontan procedure. Doses for the pivotal pediatric trials for VTE (Study 14372) and CHD after Fontan (Study CHD3001) were selected with an intent to achieve rivaroxaban exposures comparable to that achieved in the adult patients treated for VTE with a dosing regimen of 20 and 10 mg once daily, respectively.

Overall, PK and PD data from more than 500 children who received single or multiple doses of rivaroxaban were available. Results for PK-PD relationship- and rivaroxaban concentration- comparisons between adults and children are described in the following sections.

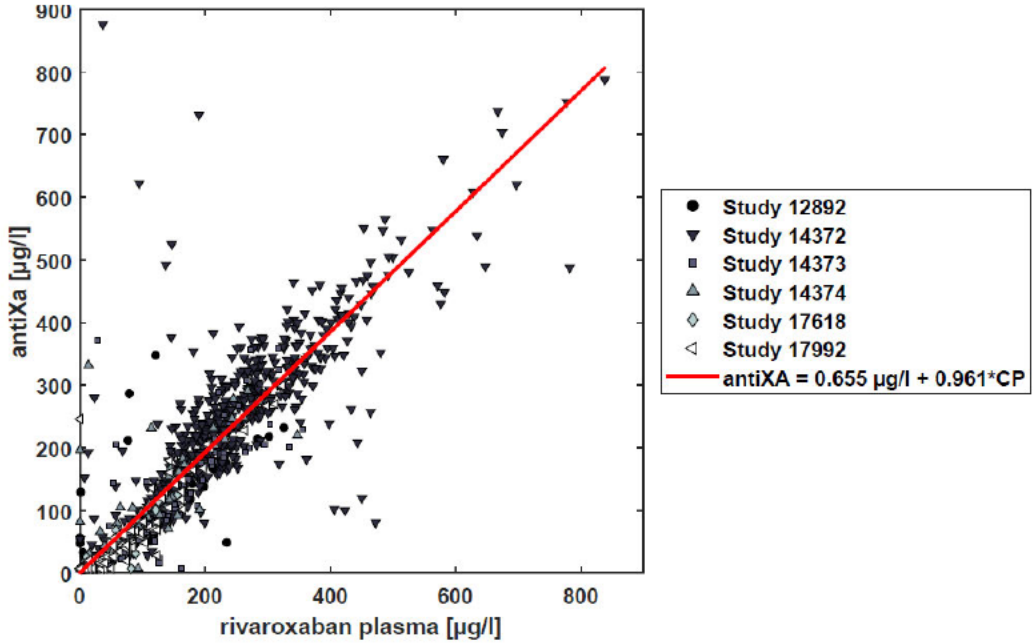
Similar PK-PD relationships for PT, aPTT and anti-factor Xa between adults and pediatric patients:

The Applicant conducted pooled PK/PD relationship analysis for clotting time variables (aPTT and PT) in pediatric VTE patients and compared with the PK/PD relationships observed in adult VTE patients and healthy adults (Figure 2). In addition, the pooled PK/PD relationship for anti-factor Xa activity in pediatric VTE patients is shown in Figure 1, however because calibration using a different set of calibrators and controls were used during assays of pediatric study samples, a direct comparison with results from adult studies was not possible.

Comparison between adults and pediatric patients- VTE treatment

The pooled analysis from pediatric studies showed the anti-factor Xa increased linearly with increasing rivaroxaban concentration (Figure 1). A close correlation between anti-factor Xa activity assay and PK has also been well established in adults. In general, visual inspection did not indicate a relevant difference in the correlation between the pediatric data of different age groups or the dosing regimen (o.d., b.i.d. and t.i.d.).

Figure 1. Linear regression of anti-factor Xa activity versus plasma concentrations of pediatric patients treated with rivaroxaban

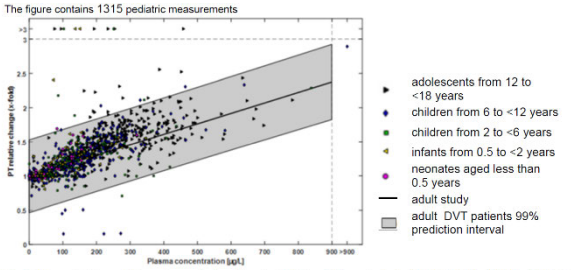


Anti-factor Xa activity (Rivaroxaban) absolute for children of Studies 12892, 14372, 14373, 14374, 17618 and 17992 of all age groups, excluding data from three batches of 14372 which were considered outliers due to technical problems.

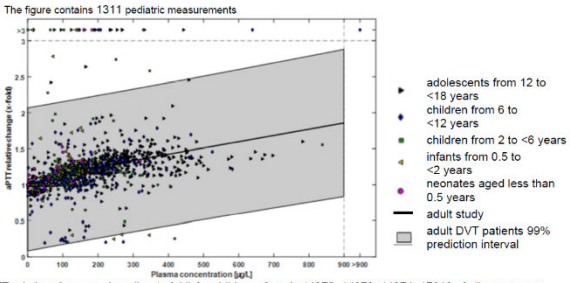
Source: Module 5.3.3.5 Report PH-40947 (20763), appendix 9

PT and aPTT were determined as ratio to the individual baseline and correlated to plasma concentrations. The visual inspection of the pooled data from the pediatric studies (14373, 14374, 17618, 14372) indicated that the correlations of PT and aPTT (as ratio to baseline) versus plasma concentrations in children across the age groups, were mostly contained within the 99% prediction interval of the adult DVT patients who were treated with a 20 mg once daily dose of rivaroxaban.

Figure 2. Correlation of PT and aPTT prolongation versus plasma concentrations in pediatric patients treated with multiple doses of rivaroxaban by age



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



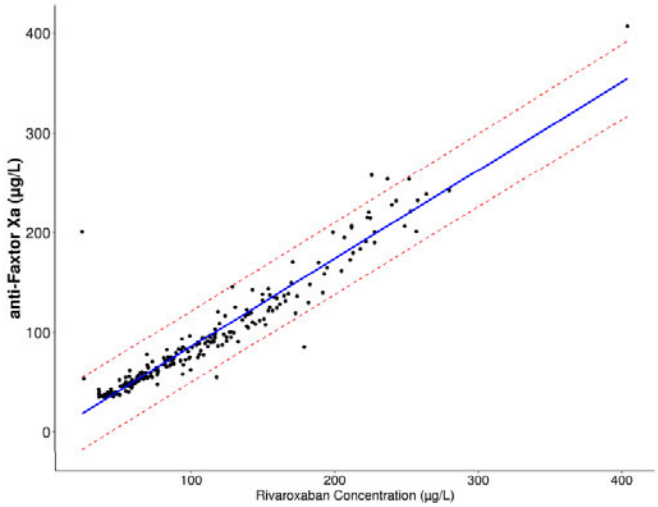
aPTT relative change to baseline (x-fold) for children of study 14372, 14373, 14374, 17618 of all age groups. Lines indicate the 99% prediction interval from adult DVT patients receiving a 20 mg once daily dose of rivaroxaban

Source: Module 5.3.3.5 Report PH-40947 (20763), Appendix 6, Section 1.1.1.2.3 & Section 1.1.1.4.3

Comparison between adults and pediatric patients- Thromboprophylaxis after Fontan procedure:

The linear model describing the relationship between anti-FXa and the plasma rivaroxaban concentrations in UNIVERSE was similar to the pooled analysis from all pediatric studies, as shown in Figure 3 . The absolute values of PT and aPTT determined in UNIVERSE were correlated with plasma concentrations of rivaroxaban (Figure 4). The PT values were within the range of values that were observed in adults (receiving 5 mg twice daily in studies ODIXa-HIP2-10944 and ODIXa-KNEE-10945) and was found to correlate with plasma concentrations of rivaroxaban. A narrower range of aPTT values was observed in pediatric patients in UNIVERSE compared to adults with a weaker correlation of aPTT with plasma rivaroxaban concentrations.

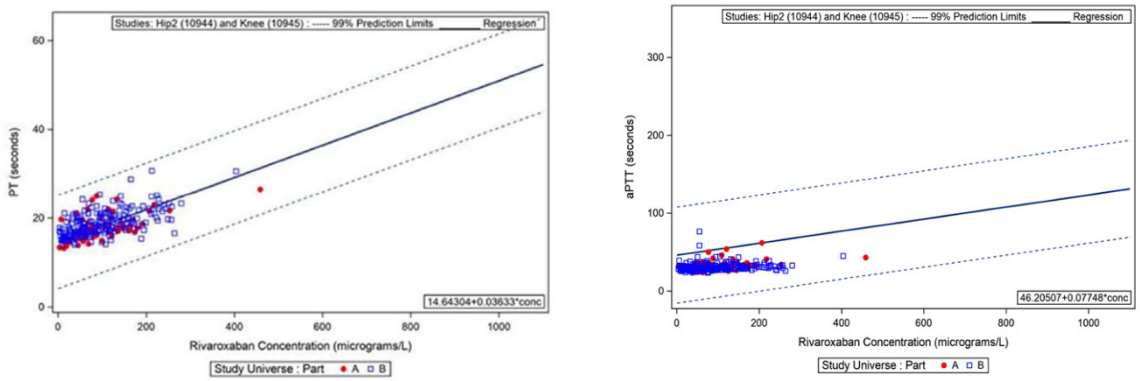
Figure 3. Anti-factor Xa activity as a function of plasma rivaroxaban concentrations in pediatric patients of UNIVERSE



Source: Figure 8 of Population pharmacokinetics report dated 01 Jun 2021 (UNIVERSE);

The solid blue line represents the median of model prediction; the red dashed lines represent the 95% prediction interval. Data are from Day 1 (Parts A and B), Day 4 (Part A), and Month 3 (Parts A and B) of UNIVERSE.

Figure 4. Prothrombin Time and Activated Partial Thromboplastin Time as a function of plasma rivaroxaban concentrations in pediatric patients and adult patients who received a twice-daily regimen of rivaroxaban



Source: Module 2.7.2 Summary of Clinical Pharmacology Studies;
Includes line of regression and 99% prediction intervals of data from the 2.5 to 30 mg rivaroxaban twice daily dose from the adult ODIXa-HIP2 (10944) (Days 3 and 6 or 7) and ODIXa-KNEE (10945) (Days 2 to 9) studies. Observed data (solid red circles and open blue squares) are from Day 1 (Parts A and B), Day 4 (Part A), and Month 3 (Parts A and B) of UNIVERSE.

The observed values for the pediatric patients were contained within the 99% prediction interval based on adult data.

Overall, reasonably similar PK/PD relationships were observed between pediatric patients and adults for all three clotting variables across all pediatric age groups, which provides support to the approach of using adult exposure range for pediatric dose selection.

Pharmacokinetic similarity in range of steady-state concentrations between pediatric and adult patients:

Comparison between adults and pediatric patients- VTE treatment:

The dosing strategy in VTE program was designed to achieve rivaroxaban exposure in children from birth to adolescence (<18 y), that was similar to the adult DVT patients receiving 20 mg once daily. The body weight-based dosing adjustment was derived using a PBPK-based modeling approach (Refer to section 3.3.2 for the details of dose adjustment). The first pediatric formulation used in this program was the ready-to-use oral suspension. Phase 1 data of Study 12892 indicated the need for higher doses in younger cohorts (b) (4) . Hence, subsequent studies in children increased dosing to twice daily regimen and used a new formulation, granules for oral suspension (b) (4) or tablets. In neonates and infants, a thrice daily dosing regimen was required to increase the $C_{trough,ss}$ in comparison to other age cohorts.

The geometric mean plasma concentrations obtained around the steady state maximum and trough concentrations following the Phase 3 dosing regimen (study 14372) across the different pediatric age groups was comparable to the exposures achieved following a 20 mg o.d. dose in adult DVT treatment patients (Table 4).

Table 4. Summary statistics of measured rivaroxaban plasma concentrations (ng/mL) obtained in Phase 3 study 14372 by dose regimen and age categories compared against adult DVT patients (age range 22-87 years) receiving rivaroxaban 20 mg once daily

Adults o.d.	N							
2-4h post	73	215 (22-535)						
24h post	121	32 (6-239)						
Children o.d.	**N**	**12-<18 years**	**N**	**6-<12 years**				
Day 30 / 2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
Day 90 / 20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d.	**N**	**6-<12 years**	**N**	**2-<6 years**	**N**	**0.5-<2 years**		
Day 30 / 2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
Day 90 / 10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
t.i.d.	**N**	**2-<6 years**	**N**	**birth-<2 years**	**N**	**0.5-<2 years**	**N**	**birth-<0.5 years**
Day 30 / 0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
Day 30 / 7-8h post	5	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

Entries are: N, geometric means (5^{th} - 95^{th} percentile)

Source: Module 5.3.5.1 Report PH-40166 (14372), Table 14.4.2/3

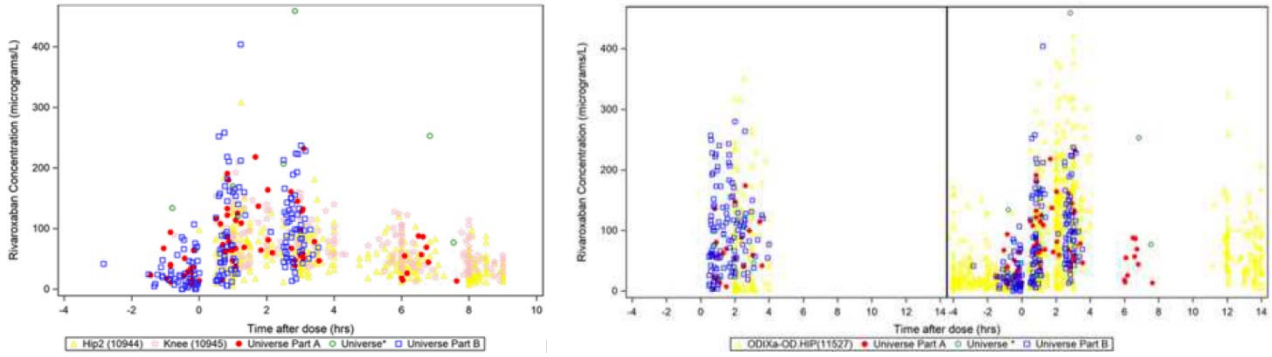
Comparison between adults and pediatric patients- Thromboprophylaxis after Fontan procedure:

The dosing strategy in thromboprophylaxis program was designed to achieve rivaroxaban exposure in children that was similar to the adult patients receiving 10 mg once daily. The dose used in the study was determined via PBPK modeling, which was based on previously established PBPK models for the VTE pediatric indication. The pediatric PBPK model of rivaroxaban incorporated the reported anthropometric differences in this pediatric patient population compared to healthy children. It was reported that post-Fontan patients have lower body weights at a given age and reduced cardiac output (Refer to the PBPK review in the Appendix 4.4 for details). A model-informed bridging approach was used to extrapolate the dose-exposure relationship in 2 to 8-year-old post-Fontan subjects to the 9 to <18-year-old post-Fontan subjects, as no clinical data was generated in older children.

The plasma concentrations of rivaroxaban were obtained at pre-dose and at intervals corresponding to 0.5 to 1.5 h, 1.5 to 4 h, 2.5 to 4 h and 6 to 8 h post-dose. In general, the individual observed rivaroxaban concentrations in the pediatric subjects were within the range of corresponding values that were

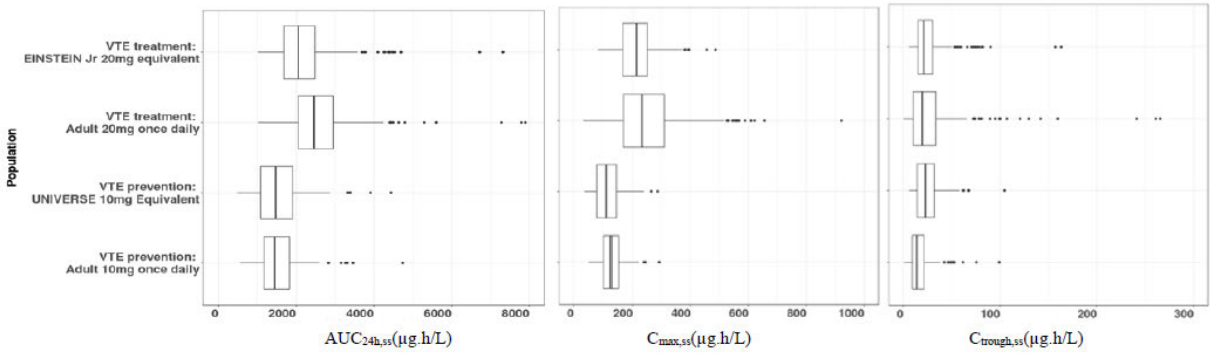
observed in adults after 5 mg twice daily administration of rivaroxaban following total hip- (Studies ODIXa-HIP2 [10944] and [11527]) and knee-replacement (Study ODIXa-KNEE- [10945]) surgeries or after 10 mg once daily administration of rivaroxaban (in Study 11527) (Figure 5).

Figure 5. Rivaroxaban concentrations in plasma as a function of time in pediatric subjects and in adult subjects who received a twice-daily (left panel) or once-daily regimen (right panel) of Rivaroxaban



Source: Figures 4 and 5, Clinical Study Report 39039039CHD3001
Left panel: Data from the rivaroxaban 5 mg twice daily dose from the adult ODIXa-HIP2 (10944) (Days 6 or 7) and ODIXa-KNEE (10945) (Days 5 to 9) studies and from Day 4 (Part A) and Month 3 (Parts A and B) of UNIVERSE; Right panel: Data from the rivaroxaban 10 mg once daily dose from adult ODIXa-HIP-OD [Study 11527] (left side: Day 2; right side: Days 3 or 4, 5 to 7, and 10) and from UNIVERSE (left side: Day 1 (Parts A and B); right side: Day 4 (Part A) and Month 3 (Parts A and B)).
Open green circles represent the values from 2 subjects in Part A of UNIVERSE who prematurely discontinued the study drug.
Source: Mod 5.3.3.5/PH-40947/App2; pop PK reportCHD3001

Figure 6. Comparison of rivaroxaban exposure ($AUC_{24h,ss}$, $C_{max,ss}$, and $C_{trough,ss}$) in the EINSTEIN Jr and UNIVERSE studies with the adult references (for the 20 mg once-daily and 10 mg once-daily dose equivalent, respectively)



EINSTEIN Jr Phase 3: 2.5th to 97.5th percentile exposure ranges of the pediatric subjects (N=320) and adult reference (N=203) are: 1164 to 4295 and 1197 to 4793 µg*h/L; $C_{max,ss}$: 101 to 363 and 90.1 to 568 µg/L; $C_{trough,ss}$: 8.05 to 74.5 and 0.612 to 130 µg/L, respectively.

UNIVERSE Phase 3: 2.5th to 97.5th percentile exposure ranges of the pediatric subjects (N=76) and adult reference (N=140) are $AUC_{24h,ss}$: 579 to 3469 and 820 to 3216 µg*h/L; $C_{max,ss}$: 43.0 to 243 and 70.2 to 216 µg/L; $C_{trough,ss}$: 7.48 to 67.7 and 3.55 to 52.0 µg/L, respectively.

Note: 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 inter-quartile range below and above the 25th and 75th percentile respectively. The solid circles are the outliers.

Source: Mod 5.3.3.5/PH-40947/App2; pop PK reportCHD3001

Overall, the observed plasma concentrations of rivaroxaban in pediatric patients were comparable to adults and was suggestive that the body weight-adjusted rivaroxaban dosing in EINSTEIN Jr for VTE treatment and in UNIVERSE for thromboprophylaxis in CHD, attained the corresponding targeted adult exposures (Figure 5).

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed body weight-based dosing regimens are appropriate for the treatment or reduction in recurrence of VTE in pediatric patients from at-term birth (weighing ≥ 2.6 kg) to <18 years (Table 1) and for thromboprophylaxis in patients 2 years or older with CHD after the Fontan procedure (Table 2) based on clinical PK, efficacy and safety data from Studies EINSTEIN Jr and UNIVERSE, as well as population PK/PD and PBPK modeling and simulation analyses. Refer to clinical review for the assessment of efficacy and safety data from Studies EINSTEIN Jr and UNIVERSE. Rivaroxaban PK assessment and modeling analyses are discussed in detail as follows.

Treatment of VTE and Reduction in Risk of Recurrent VTE in Pediatric Patients:

The Applicant's proposed dosing regimen for this indication is acceptable based on the PK assessment demonstrating that the rivaroxaban exposures in EINSTEIN Jr were generally contained within the adult reference range, and is further supported by clinical efficacy and safety experience in EINSTEIN Jr and exposure-response relationship in the adult VTE treatment program.

The Applicant's proposed dosing regimen is weight-adjusted dosing administered as TID, BID, and QD based on patient's body weight aged from birth to <18 years old and weighing ≥2.6kg (Table 1). The dosing regimen was derived based on evaluations of Phase 1 and 2 studies, PopPK and PBPK modeling and simulation to achieve exposures that match with the targeted exposures in adult VTE patients receiving 20 mg QD. More frequent dosing regimens (e.g., BID and TID) in patients with lower body weight were evaluated due to shorter half life so as to avoid high plasma concentrations at peak and too low concentrations at the end of the dosing intervals. The proposed dosing regimen was further studied in EINSTEIN Jr with a minor difference in the allowed formulations for use in children weighing 20 to <30 kg, i.e,. only oral suspension is recommended for use in this weight group in the proposed USPI while both tablet and oral suspension were administered in EINSTEIN Jr.

The rivaroxaban exposure parameters (AUC0-24h,ss, Cmax,ss and Ctrough,ss) for patients in EINSTEIN Jr, which were derived using the EINSTEIN Jr popPK model (Section 4.3.1.1), are summarized in Table 5 and Figure 7. The Applicant selected the adult reference population consisting of DVT patients (N=203) aged 18 to 45 years from two dose finding studies 11123 or 11528, noting that young adults are physiologically close to children and the elderly patients are more likely to have decreased renal function.

In the exposure summary by age group (Table 5), mean $C_{trough,ss}$ ranged from 20.7 to 31.6 µg/L and was similar among different pediatric age groups and to the adult reference range. AUC0-24h,ss was generally lower in pediatric patients compared to the adult reference: the geometric mean ratios (GMR) were 85% for 12 to <18 years, 79% for 6 to <12 years, 96% for 2 to <6 years, 70% for birth to <2 years,

and 64% in the youngest age group (birth to <6 month old). $C_{max,ss}$ was also lower in the age groups 6 to <12 years, 2 to <6 years and birth to <2 years, as a result of the switch in regimen from QD to BID and TID with decreasing body weight and, thus, age. However, $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ in pediatric patients were generally within the observed range of 1022 to 7900 µg*h/L and 35.3 to 922 µg/L, respectively, in adult patients.

Table 5. Geometric mean/%CV (range) of rivaroxaban exposures EINSTEIN Jr patients in comparison to adult reference (PopPK model derived)

Parameter (popPK)	Unit	N	12-<18 years	N	6-<12 years	N	2-<6 years	N	birth-<2 years
$AUC(0\text{-}24)_{ss}$	µg*h/L	174	2120/26.4 (1140-4540)	67	1960/31.7 (1140-4420)	44	2380/40.7 (1400-7330)	35	1740/34.4 (1020-3540)
$C_{max,ss}$	µg/L	174	237/20.6 (123-383)	67	184/36.2 (90.7-487)	44	182/31.2 (120-456)	35	129/28.1 (84.6-218)
$t_{max,ss}$ [a]	h	174	2.23 (1.97-2.60)	67	2.00 (1.80-2.47)	44	1.90 (1.60-2.27)	35	1.57 (1.33-1.83)
$C_{trough,ss}$	µg/L	174	20.7/45.8 (7.74-78.5)	67	21.4/62.7 (7.08-82.3)	44	31.6/70.1 (12.9-163)	35	21.2/62.5 (6.12-81.4)
$t_{1/2}$	h	174	4.17/19.1 (2.70-7.89)	67	3.25/20.4 (2.24-5.83)	44	2.82/25.6 (1.87-6.05)	35	1.78/21.0 (1.15-3.37)
CL	L/h	174	7.29/22.7 (3.37-11.2)	67	4.97/24.6 (3.02-8.93)	44	3.37/25.4 (1.97-4.93)	35	2.65/38.1 (1.26-5.32)
V_{ss}	L	174	92.6/23.6 (45.2-169)	67	49.2/25.3 (33.1-104)	44	28.9/18.2 (20.0-43.5)	35	14.4/42.7 (6.78-29.1)

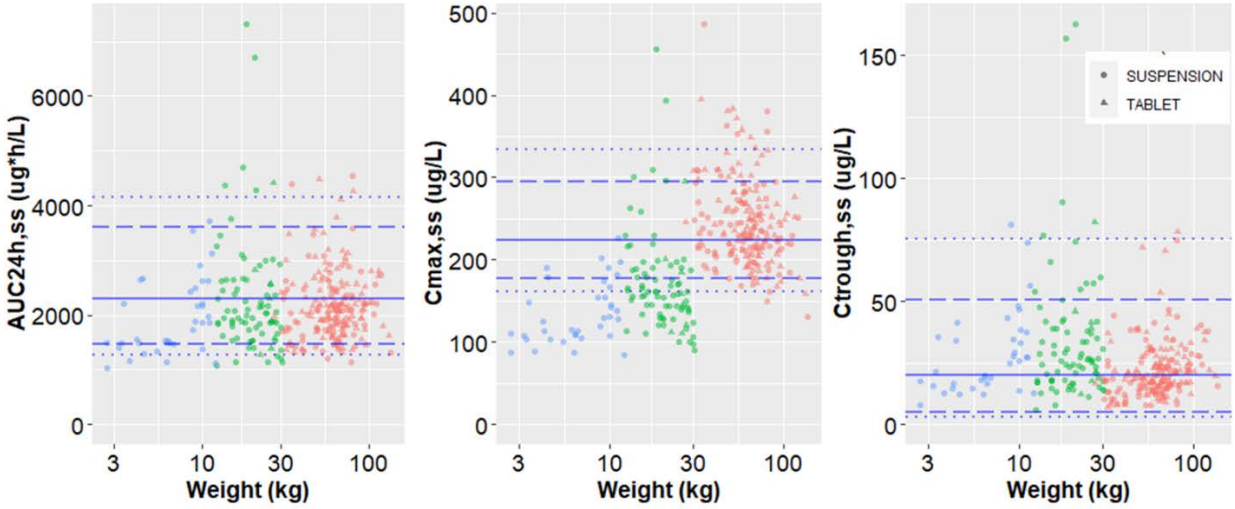
Parameter (popPK)	Unit	N	0.5-<2 years	N	birth-<0.5 years	N	Adults
$AUC(0\text{-}24)_{ss}$	µg*h/L	22	1840/36.4 (1070-3540)	13	1590/29.6 (1020-2660)	203	2484/38.8 (1022-7900)
$C_{max,ss}$	µg/L	22	136/29.4 (84.6-218)	13	119/24.1 (87.9-191)	203	232/50.1 (35.3-922)
$t_{max,ss}$ [a]	h	22	1.60 (1.47-1.83)	13	1.53 (1.33-1.67)	203	2.10 (1.40-2.60)
$C_{trough,ss}$	µg/L	22	22.9/68.6 (6.12-81.4)	13	18.5/50.4 (7.64-41.5)	203	17.4/126 (0.123-266)
$t_{1/2}$	h	22	1.89/20.5 (1.43-3.37)	13	1.61/17.8 (1.15-2.13)	203	6.16/46.6 (1.93-26.9)
CL	L/h	22	3.25/26.6 (1.76-5.32)	13	1.88/25.4 (1.26-2.66)	203	6.84/34.3 (2.12-15.4)
V_{ss}	L	22	18.7/22.5 (12.0-29.1)	13	9.23/21.8 (6.78-13.6)	203	60.9/22.2 (31.5-103)

Source: Applicant's Summary of Clinical Pharmacology Studies – EINSTEIN Jr., Table 3-2, page 146.
[a]median (range); $t_{1/2}$: half-life associated with elimination from the central compartment.

In the exposure summary by body weight (Figure 7), the $C_{max,ss}$ following QD regimen are well within the adult reference range and those following BID and TID regimen are mostly around or below the lower end of the adult reference range. Most $C_{trough,ss}$ values are within the 5th to 95th percentile of the adult reference exposure. While most $AUC_{(0\text{-}24),ss}$ values are within the 5th to 95th percentile of the adult

reference, the $AUC_{(0\text{-}24),ss}$ values in children weighing <12 kg are around the lower end (5^{th} - 10^{th} percentiles) of the adult reference. There is no safety concern from a PK perspective, as both daily AUC and Cmax are similar or at the lower side of the adult reference values.

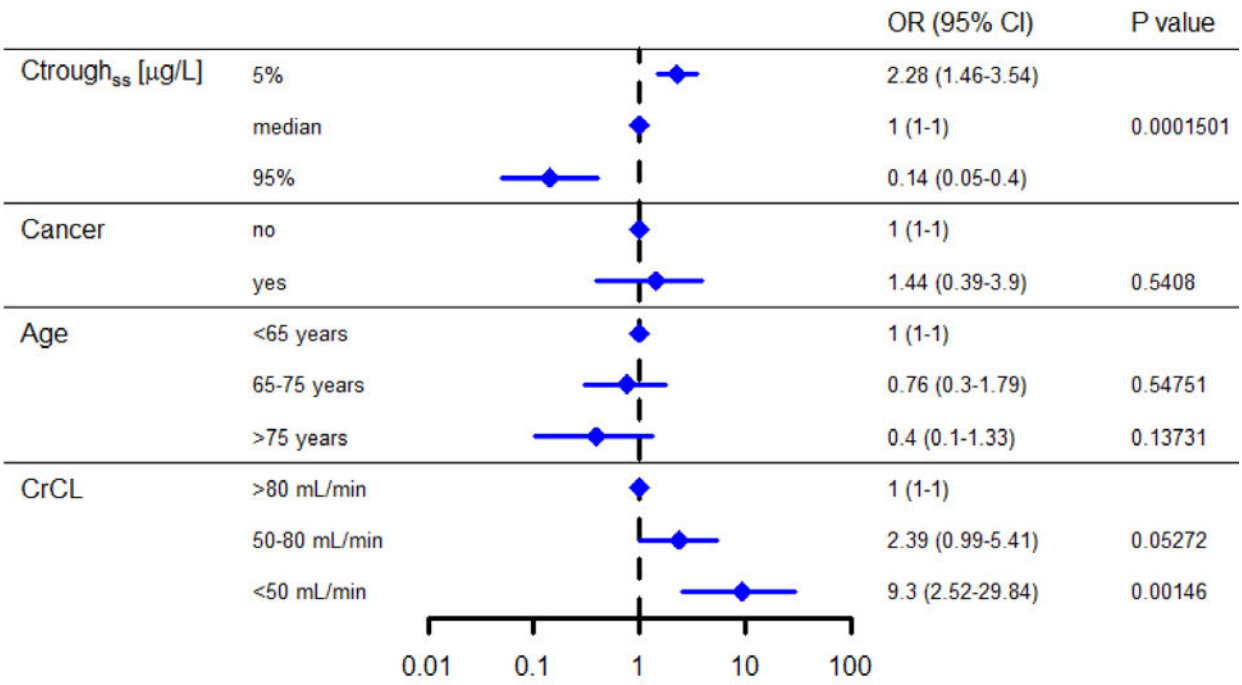
Figure 7. Rivaroxaban exposures for EINSTEIN Jr patients (PopPK derived)



Source: Reviewer's plots generated using the Applicant's reported individual predicted exposures which were predicted by the EINSTEIN Jr PopPK analysis: blue dots (TID regimen), green dots (BID regimen); red dots (QD regimen). Blue lines represent the adult reference exposures ranges (5^{th}, 10^{th}, 50^{th}, 90^{th}, 95^{th}) which were estimated using the popPK model developed for the exploratory analysis of rivaroxaban in patients with acute symptomatic DVT excluding residual unexplained variability (RUV) from IR response dated 10/15/2021.

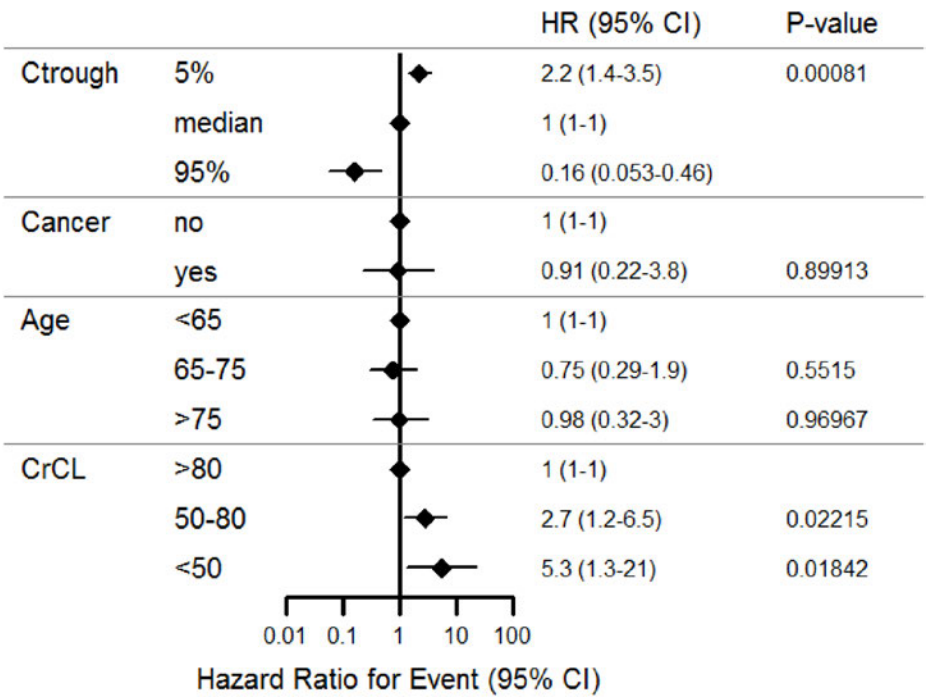
With regard to extrapolation of efficacy, the Applicant provided exploratory E-R analyses using different rivaroxaban exposures ($AUC_{0\text{-}24,ss}$, $C_{max,ss}$ and $C_{trough,ss}$) for adult VTE treatment based on the data from a Phase 3 study (EINSTEIN-DVT/PE, also referred to as Study 11702) where patients received rivaroxaban 15 mg BID for 3 weeks followed by 20 mg QD thereafter. A univariate logistic regression analysis identified $C_{trough,ss}$ as the exposure metric with the strongest association with the probability of the event compared to $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$. In the multivariate E-R analyses performed separately for BID dosing period and QD dosing period, composite endpoint 1 (recurrent DVT and PE) was significantly associated with decreasing $C_{trough,ss}$ during the BID dosing period (Figure 8) and the QD dosing period (Figure 9). Since $C_{trough,ss}$ values achieved in pediatric patients with VTE across the range of age or body-weight were similar to the adult reference range, no clinically significant difference in efficacy between pediatrics and adults is expected. In addition, use of $C_{trough,ss}$ for efficacy extrapolation is consistent with the approach used to support approval of dabigatran in pediatric VTE patients.

Figure 8. Forest plot for composite endpoint 1 during BID period



Source: Applicant's Report 39250, Figure 10-27, page 188.

Figure 9. Forest plot for composite endpoint 1 during QD period



Source: Applicant's Report 39250, Figure 10-42, page 215.

Although the mean values of $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ were found lower in pediatric patients compared to adults, $AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ in pediatric patients were largely within the observed adult reference

range. In addition, in the descriptive E-R assessment based on the pediatric patient data from EINSTEIN Jr, the lower daily AUC or $C_{max,ss}$ does not appear to be correlated to recurrent or worsening of VTE events. The four recurrent VTE events occurred in children aged 12 to 18 years whose $AUC_{(0-24),ss}$, $C_{max,ss}$ and $C_{trough,ss}$ values are predicted to be within the adult reference range. There is no clustering of $AUC_{(0-24),ss}$ values at the lower end of the adult reference range for children with deteriorated or unchanged thrombus burden as compared to children whose thrombotic event normalized or improved. Among the 12 children with lowest $AUC_{(0-24),ss}$ values, there was no child whose thrombus burden deteriorated. In 10 out of 12 children, thrombus burden either normalized or improved. There was no relevant change in thrombus burden in 1 child and the thrombus burden assessment was missing in 1 child. The available data do not indicate a trend between lower daily AUC and worsening of VTE events.

Taken together, the proposed dosing regimen is expected to appropriately provide pediatric patients similar rivaroxaban exposures as the adult patients allowing extrapolation of efficacy. Primarily, the $C_{trough,ss}$, values in pediatirc patients are similar to those for the adult reference range across the range of age or body weight. The E-R relationships in adult VTE patients suggest that rivaroxaban $C_{trough,ss}$ is the most significant predictor for risk of recurrent DVT and fatal/non-fatal PE. The individual $AUC_{(0-24)ss}$ values are largely within the adult reference range, though the mean values for $AUC_{(0-24)ss}$ for lower weight groups were lower than that in the adult reference. The available data in pediatric VTE patients did not indicate a trend between lower daily AUC and worsening of VTE events.

Thromboprophylaxis in Pediatric Patients with CHD after Fontan Procedure:
The Applicant's proposed dosing regimen for this indication is acceptable based on the PK assessment demonstrating that 1) the individual exposure parameters ($AUC_{(0-24h),ss}$, $C_{max,ss}$ and $C_{trough,ss}$) for patients in UNIVERSE aged 2 to 8 years that were largely within the adult reference exposure range, and 2) the population PK modeling and simulation predicted that rivaroxaban exposures for post-Fontan patients aged 9 to 18 years are expected to be similar to the adult reference range. The dosing regimen is further supported by efficacy and safety experience in UNIVERSE, and exposure-response relationship in the adult VTE prevention program.

The Applicant proposed weight-adjusted dosing regimen administered BID or QD depending on body weight for CHD patients with Fontan procedures ages 2 to 18 years and weighing ≥7 kg (Table 2). Dosing strategy for this indication was to target rivaroxaban exposures that correspond to 10 mg QD which is the recommended dose regimen for the prophylaxis of DVT in adult patients undergoing knee or hip replacement surgery. For comparison of rivaroxaban exposures for efficacy extrapolation, the Applicant used an adult reference population consisting of 140 patients aged between 27 and 87 years who participated in a dose ranging study (11527, also referred to as ODIXA-Hip-OD) for the adult VTE prevention program. The Applicant selected this population because Study 11527 contained a data-rich set of PK information including 661 patients across the 4 dose regimens tested including the rivaroxaban dosing regimen of interest i.e., 10 mg QD.

Dosing regimen for pediatric post-Fontan patients weighing 7 to <30 kg:

The Applicant's proposed dosing regimen for pediatric post-Fontan patients weighing 7 to <30 kg was studied in UNIVERSE (Table 2). UNIVERSE enrolled patients ages 2 to 8 years old with body weight ranging from 9.8 kg to 25.3 kg. There was no patient weighing 7 to <8 kg and only one patient weighing 8 to <10 kg in UNIVERSE.

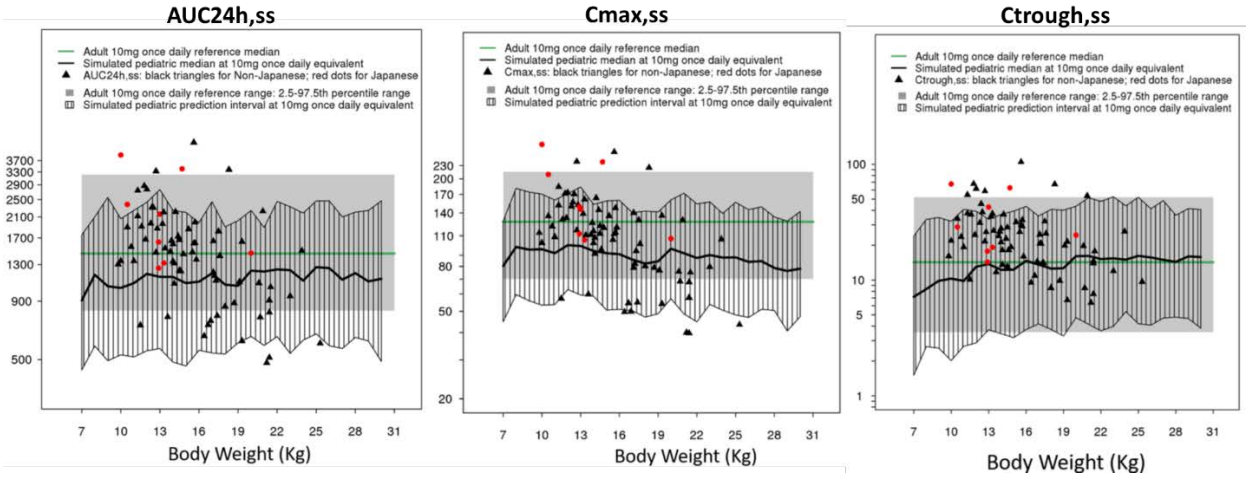
The proposed dosing for 8 to <30 kg was evaluated based on the comparison of rivaroxaban exposures ($AUC_{(0\text{-}24h),ss}$, $C_{max,ss}$ and $C_{trough,ss}$) for patients in UNIVERSE with the adult reference exposure range. The rivaroxaban exposures for patients in UNIVERSE which were derived using the UNIVERSE popPK model (Section 4.3.1.2) are summarized in Table 6. The geometric mean $AUC_{(0\text{-}24h),ss}$ for all patients in UNIVERSE was similar to those the adult reference range. The geometric mean was 13% lower for $C_{max,ss}$, and 64% higher for $C_{trough,ss}$ compared to the median adult reference value. The individual exposure parameters for patients in UNIVERSE are graphically compared to the adult reference as a function of bodyweight (Figure 10). While the individual exposures derived for patients in UNIVERSE are largely contained within the 2.5th to 97.5th percentiles of the adult reference range (grey shade in Figure 10), few values for $AUC_{(0\text{-}24h),ss}$ in the body weight range from 16 to <30 kg are below the lower end (2.5th percentiles) of the adult reference and few values for $C_{max,ss}$ in the body weight range from 10 to 16 kg are above the higher end (97.5th percentiles) of the adult reference.

Table 6. Comparison of rivaroxaban exposures between patients in UNIVERSE and the adult reference

Variables	Exposure Metrics	Japanese	Non-Japanese	All Subjects	Adult Reference 10 mg Once Daily (Study 11527)
N		8	68	76	140
$AUC_{24h,ss}$ (µg*h/L)	Geometric Mean	2013	1385	1440	1494
	(90% CI)	(1568, 2586)	(1261, 1521)	(1317, 1576)	(1425, 1565)
	Median	1896	1472	1477	1452
	(Range)	(1254, 3915)	(484.2, 4444)	(484.2, 4444)	(565.4, 4747)
$C_{max,ss}$ (µg/L)	Geometric Mean	158.4	104.3	109.0	125.8
	(90% CI)	(126.6, 198.3)	(95.8, 113.6)	(100.4, 118.5)	(120.6, 131.3)
	Median	147.6	112.6	113.3	127.6
	(Range)	(105.4, 287.1)	(39.7, 265.2)	(39.7, 287.1)	(54.0, 292.8)
$C_{trough,ss}$ (µg/L)	Geometric Mean	29.8	22.1	22.8	13.9
	(90% CI)	(21.2, 41.8)	(19.6, 24.9)	(20.4, 25.5)	(12.6, 15.4)
	Median	26.6	22.3	23.2	14.3
	(Range)	(14.3, 67.7)	(6.4, 104.7)	(6.4, 104.7)	(0.8, 99.3)

Source: Applicant's Summary of Clinical Pharmacology Studies-CHD3001, Table 2, page 24.

Figure 10. Predicted rivaroxaban exposures for post-Fontan patients (UNIVERSE)

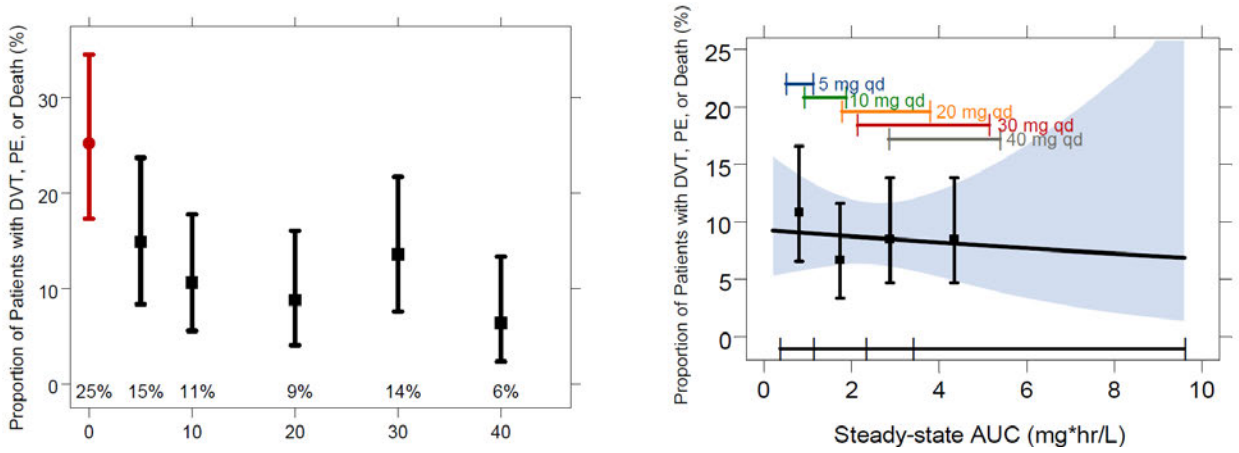


Source: Applicant's Summary of Clinical Pharmacology Studies-CHD3001, Figure 14, page 25.
Black triangles: non-Japanese subjects; Red circles: Japanese subjects; Green line/shaded area: adult 10 mg QD reference median/2.5th-97.5th percentile range; Black line/vertical hatch mark area: simulated pediatric median and prediction interval at 10 mg QD equivalent using EINSTEIN popPK model.

The higher exposures ($AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$) in the lower body weight post-Fontan patients may not be a clinically significant safety concern, because higher rivaroxaban exposures were tested in the EINSTEIN Jr which used a 20 mg adult equivalent dose and achieved a mean (range) $AUC_{(0\text{-}24h),ss}$ of 2120 (1070 to 7330) µg*h/L, and $C_{max,ss}$ of 164 (90.7 to 456) µg/L for the BID regimen.

With regard to efficacy, lower daily AUC values were noted in relatively older children with the Fontan procedure (i.e., 16 to <30 kg) while $C_{trough,ss}$ values were within the adult reference. The Applicant provided an exploratory E-R analysis based on the data from four Phase 3 studies (RECORD 1 THR, RECORD 2 THR, RECORD 3 TKR, and RECORD 4 TKR) where the patients received rivaroxaban 10 mg QD for 2 weeks (knee surgery) or 5 weeks (hip surgery). The efficacy outcome evaluated was the composite of any DVT (proximal and/or distal), non-fatal PE and death none of rivaroxaban exposures ($AUC_{0\text{-}24h,ss}$ and $C_{max,ss}$ and $C_{trough,ss}$) was found as a significant predictor of efficacy in multivariate analysis. Similarly, in the dose-ranging study 11527 for prevention of VTE in adult patients where doses from 5 to 40 mg QD were administered in adults, a shallow dose/exposure-response relationship was observed for effectiveness as evaluated using composite endpoint consisting of any DVT, non-fatal PE, or death from all causes (Figure 11). Particularly, no remarkable difference in efficacy was observed in the range of the daily AUC corresponding to 5 mg to 40 mg QD. Taken together, the available information does not strongly suggest that lower daily AUCs may negatively impact efficacy, particularly when $C_{trough,ss}$ in pediatric patients are similar to the adult reference.

Figure 11. E-R Relationship based on the dose-ranging study 11527 for adult VTE prevention program



Source: FDA review for NDA22406 dated 4/6/2009, Figure 4, page 11. X-axis was dose level (left figure) and steady-state AUC0-24 (right figure). Blue band represents associated 95% CI. The horizontal black bar shows the steady-state AUC0-24 quartiles and the colored bars illustrate the predicted 10-90th AUC and Cmax percentiles following different dose regimens.

As mentioned earlier, there were no patients with body weight between 7 to 8 kg enrolled in UNIVERSE. There are limitations associated with reliably predicting exposures for this weight group using the current pediatric popPK and PBPK models (Refer to Section 4.3.1.3 and Section 4.4). From a clinical perspective, providing a dosing regimen down to 7 kg is important due to the unmet medical need in the indicated patient population and the possibility of patients with CHD after Fontan procedure with lower body weights (Refer to Clinical Review). Given that the post-Fontan patients with body weight 8 to <16 kg receiving 0.25 to 0.4 mg/kg/day exhibited higher rivaroxaban exposures compared to the adult reference range (dots in Figure 10), the proposed dose (2.2 mg daily) for the weight 7 to <8 kg which corresponds to 0.29 mg/kg/day seems reasonable. In the worst-exposure-scenario where post-Fontan patients weighing 7 to <8 kg have similar PK as pediatric VTE patients, the median value for simulated $C_{trough,ss}$ is below the median adult reference, however, majority (>50%) of $C_{trough,ss}$ values in this weight group are within the adult reference range (Figure 10).

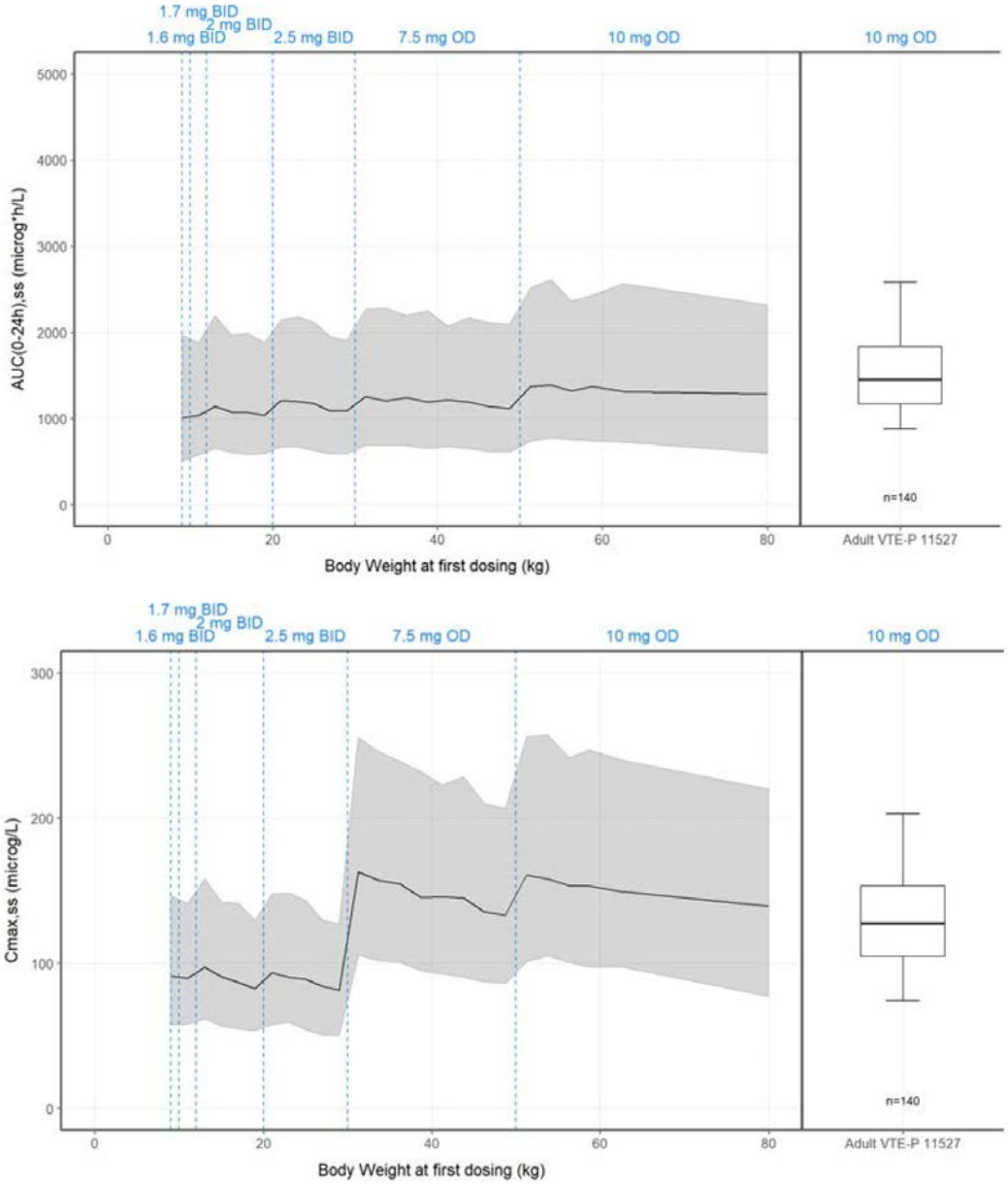
***Dose extrapolation for pediatric post-Fontan patients weighing ≥30 kg**:*
The Applicant proposed a dosing regimen for pediatric post-Fontan patients aged 9 to <18 years based on PopPK modeling and simulations. The proposed dosing regimen for this patient population was 7.5 mg QD for 30 to <50 kg and 10 mg QD for ≥50 kg.

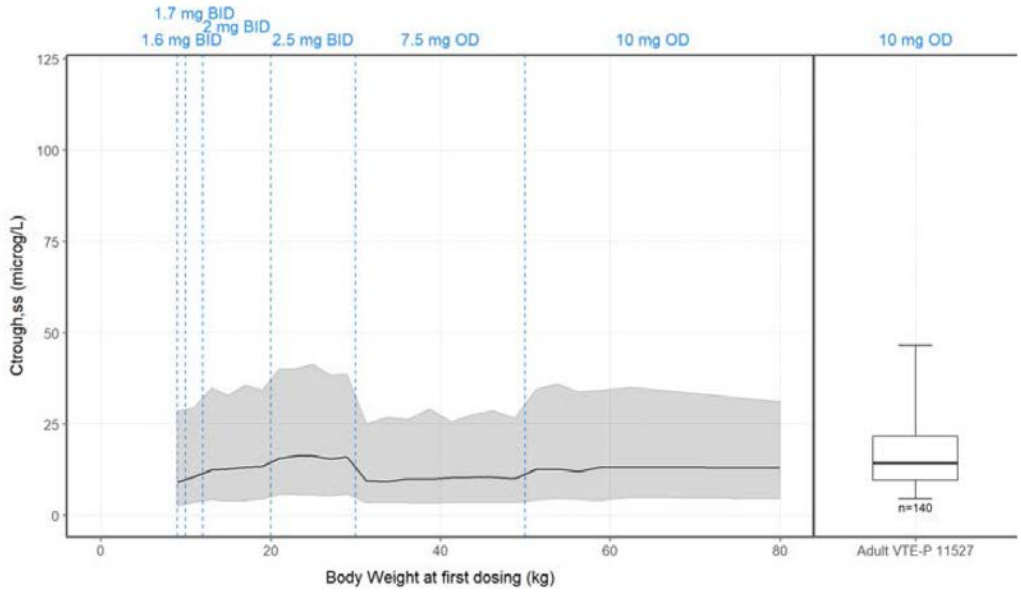
To simulate rivaroxaban exposures for the proposed dosing regimen in pediatric post-Fontan patients ≥30 kg, the Applicant used the EINSTEIN Jr popPK model, which was developed based on data from pediatric VTE patients. While a separate PopPK analysis (referred to as UNIVERSE popPK) was performed based on the data from UNIVERSE, it was noted that UNIVERSE popPK model cannot adequately characterize the PK of post-Fontan patients in UNIVERSE (ages 2 to 8 years) and therefore, not adequate to extrapolate dosing regimen to those aged 9 to 18 years (Refer to Section 4.3.1.3). When EINSTEIN Jr

popPK model was used to predict exposures at the proposed prophylaxis dosing (black line/vertical hatch mark area in Figure 10), there is generally good overlap in exposures observed in post-Fontan patients and those simulated by EINSTEIN Jr popPK model especially at the higher body weight, which corresponds to older post-Fontan patients (5 to 8 years old). Therefore, the review team agrees that use of EINSTEIN Jr popPK model is a reasonable approach to predict rivaroxaban exposures to support the proposed dosing regimen for post-Fontan patients ages 9 to 18 years.

The simulated exposures for post-Fontan patients using EINSTEIN Jr popPK model are presented in Figure 12. The simulated daily AUC across body weight ≥30 kg tends to be lower than those for adult reference patients. This trend is consistent with those observed in post-Fontan patients weighing 16 to <30 kg in UNIVERSE. Following the proposed dose of 10 mg QD for body weight ≥50 kg, the 5^{th} and 95^{th} percentiles for simulated $C_{trough,ss}$ are contained well within the adult reference range. Following the proposed dose of 7.5 mg QD for body weight 30 to <50 kg, the median simulated $C_{trough,ss}$ is lower compared to the adult reference, but the range of 5^{th} and 95^{th} percentiles for simulated $C_{trough,ss}$ are largely within the adult reference range. Therefore, the Applicant's proposed dosing regimen for pediatric post-Fontan patients weighing ≥30 kg appears acceptable.

Figure 12. Simulated rivaroxaban exposure using EINSTEIN Jr popPK model at the proposed prophylaxis dose regimen





Source: Applicant's Report R-13646, Figure 10.1:21 (A), Figure 10.1:22 (A), Figure 10.1:23 (A), on pages 58-60. Grey area represents the median (bold black line) and 5th-95th of the simulated exposure for the post-Fontan population (shaded area). Boxplots and whiskers: 5th, 25th, median, 75th, 95th of exposure metrics for the adult population (VTE-P Study 11527).

3.3.3 Is an alternative dosing regimen and/or management strategy required for subpopulations based on intrinsic factors?

Yes, the use of XARELTO should be avoided in pediatric patients with eGFR <50 mL/min/1.73 m^2 or in patients younger than 1 year with serum creatinine results above 97.5th percentile. No clinical data are available in pediatric patients with hepatic impairment. As per the approved XARELTO USPI, use of rivaroxaban in patients with moderate (Child-Pugh B) and severe (Child-Pugh C) hepatic impairment or with any hepatic disease associated with coagulopathy should be avoided, since drug exposure and bleeding risk may be increased.

Body weight-based dosing regimen is required for pediatric patients from at-term birth (weighing ≥2.6 kg) to <18 years. Due to the expected gain in bodyweight of young children during the course of therapy, dose adjustments and/or change in dosing regimen according to the rivaroxaban dosing table for children (

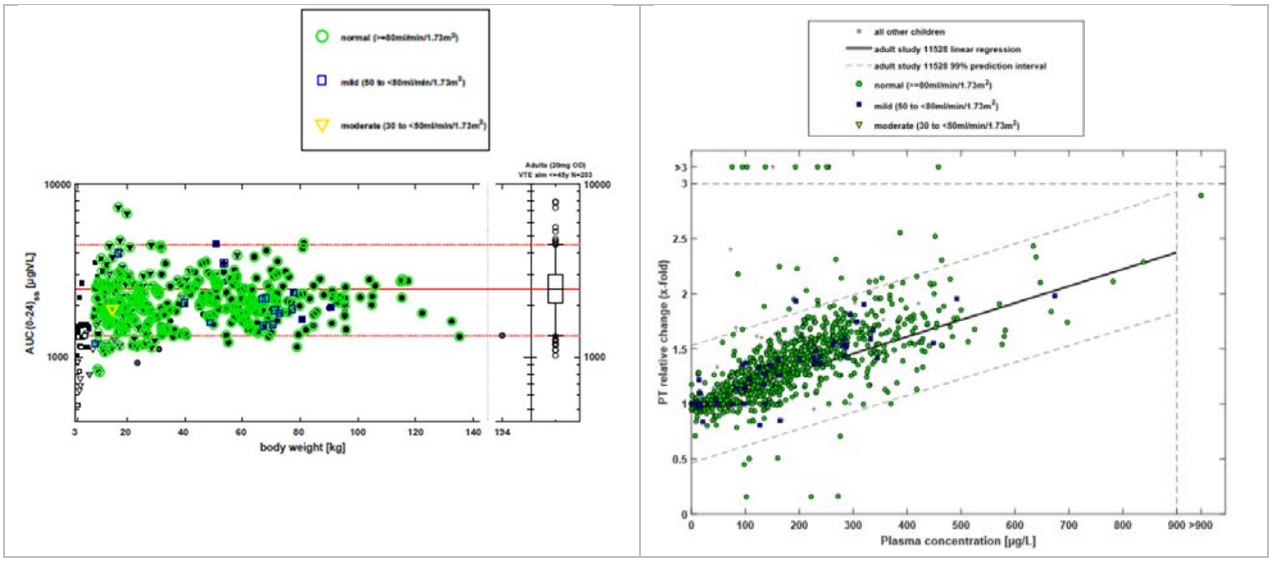
APPEARS THIS WAY ON ORIGINAL

Table 1 and Table 2) are needed to ensure maintenance of a therapeutic dose.

Evaluation of intrinsic factors on PK/PD of rivaroxaban:
Exploratory analyses for intrinsic factors including gender and race did not reveal relevant differences in rivaroxaban exposure within the pediatric population treated for VTE. Following the body weight adjusted dosing, no relevant impact was apparent on the extremities of body weight (underweight or obesity). Minor differences in the PK between age groups were found, which seem to be driven by the close correlation between age and body weight and differences in the applied regimen based on the body weight-adjusted dosing scheme. For additional details see Section 4.3.

Renal impairment:
The impact of renal function on rivaroxaban PK was investigated by a covariate analysis using the comprehensive popPK model for children. Most subjects in the pediatric studies had normal kidney function and only limited data was available from children with renal impairment. Based on the data from the limited number of subjects with mild renal impairment, no obvious differences in the rivaroxaban PK or PD were observed as shown in Figure 13. Log $AUC_{(0\text{-}24)ss}$ vs body weight and Prothrombin time (ratio to baseline) vs plasma concentration separated by renal function The PK and PD values were contained both within the adult reference range and the range of values for children with normal renal function. Therefore, pediatric subjects with mild renal impairment do not seem to need any dose adjustment, consistent with the dosing recommendation in adults. There was data from only one pediatric patient with moderate renal impairment and even though the PK or PD values were within the adult reference range, no meaningful conclusions can be made for this category of subjects based on this data point. Therefore, carrying forward the recommendation in adults, the use of rivaroxaban should be avoided in patients with eGFR <50 mL/min, due to lack of clinical experience and potential concern for significantly higher exposures and bleeding risk.

Figure 13. Log $AUC_{(0\text{-}24)ss}$ vs body weight and Prothrombin time (ratio to baseline) vs plasma concentration separated by renal function



Source: Source: Module 5.3.3.5 Report PH-40947 (20763), Appendix 2 and Appendix 6, Section 1.1.13.2

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Yes, the dosing of rivaroxaban for the VTE indication should be followed immediately by feeding or food to increase the absorption. Based on approved adult dosing instructions, the concomitant use of rivaroxaban with moderate inhibitors or inducers of CYP3A and P-glycoprotein should be avoided in pediatric patients.

Food effect-experience from approved adult dosing with IR tablets:

Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. However, for the 20 mg tablet under fasting conditions, there is a decrease in oral bioavailability due to reduced extent of absorption. When rivaroxaban 20 mg tablets are taken together with food, an increase in mean AUC by 39% was observed when compared to tablet intake under fasting conditions. Rivaroxaban doses of 15 mg and 20 mg are to be taken with food.

Food effect evaluations under this NDA:

As reported previously in adults (NDA 022406 clinical pharmacology review dated 4/2/2009), a decrease in relative bioavailability for increasing doses (in mg/kg) was also found in children, indicative of the solubility-limited absorption at higher doses for both adults and children. The results from a relative BA study in healthy adult volunteers comparing 20 mg granules for oral suspension dose taken with food and the 10 mg granules for oral suspension dosed under fasting condition were dose-proportional, similar to the previous observations for the 10 and 20 mg IR tablets. Because granules for oral suspension behaves similarly to the IR tablets, food is expected to improve the absorption of the higher doses in children and hence, the proposed recommendation for dosing with food is considered adequate for pediatric VTE indication.

3.3.5 Is the granules for oral suspension formulation bioequivalent to the tablet formulation?

Yes, the bioequivalence (BE) for granules for oral suspension formulation versus tablet formulation was demonstrated in two Phase 1 studies in adults (19365 and 19366).

Study 19365 was a single-dose, open-label, randomized, 2-way crossover to assess BE of 10 mg rivaroxaban granules for oral suspension versus 10 mg rivaroxaban immediate-release (IR) tablets under fasted condition in 30 healthy subjects. 10 mg rivaroxaban as an oral suspension was bioequivalent to 10 mg IR tablet when both treatments were administered under fasted state, as shown in Table 10.

Parameter	Ratio	LS mean (90% CI)	Geom. CV%
AUC	10 mg granules for oral suspension / tablet	1.0267 (0.9841 – 1.0712)	9.6690
AUC(0-t_{last})	10 mg granules for oral suspension / tablet	1.0261 (0.9805 – 1.0738)	10.3800
C_{max}	10 mg granules for oral suspension / tablet	1.1283 (1.0400 – 1.2240)	18.7050

Table 7. Study 19365 - Least squares (LS)-mean ratios of PK-parameters (90% confidence interval), geometric coefficient of variation (CV%)

Source: Report PH-40127 (19365), Table 14.4 / 6 to Table 14.4 / 8

Study 19366 was a single-dose, open-label, randomized, 2-way crossover to assess BE of 20 mg rivaroxaban granules for oral suspension versus 20 mg rivaroxaban immediate-release (IR) tablets under fed condition in 30 healthy subjects. 20 mg rivaroxaban as an oral suspension was bioequivalent to the 20 mg IR tablet when both treatments were administered after a standardized high fat, high calorie breakfast, as shown in Table 11 (PK analysis set, n=28). Two subjects were excluded from the PK analysis set because, one did not have a valid PK profile in Period 2 (oral suspension) and the other did not receive study medication in Period 2 (IR tablet).

Table 8. Study 19366 - Least squares (LS) mean ratios of PK-parameters (90% confidence interval), geometric coefficient of variation (CV%)

Para-meter	Ratio	LS mean (90% CI)	Geom. CV%
AUC	20 mg granules for oral suspension / tablet	0.9843 (0.9433 – 1.0271)	9.3534
AUC(0-t_{last})	20 mg granules for oral suspension / tablet	0.9869 (0.9460 – 1.0295)	9.2971
C_{max}	20 mg granules for oral suspension / tablet	0.8822 (0.8146 – 0.9554)	17.6255

Source: Report PH-40136 (19366), Table 14.4 / 6 to Table 14.4 / 8

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 PK Assays

Rivaroxaban was determined in plasma after protein precipitation with acetonitrile/methanol or acetonitrile followed by separation employing high-pressure liquid chromatography and tandem mass spectrometric detection (HPLC-MS/MS). The calibration range of the methods was 0.50 ng/mL (lower limit of quantification [LLOQ]) to 500 ng/mL. Additional data supporting the long-term stability of rivaroxaban in plasma were conducted to allow storage of samples for extended periods of time (at least 39 months).

Several validated methods were used across the different pediatric studies and are summarized in Table 9.

Table 9. Bioanalytical method validation parameters for quantitation of Rivaroxaban in human plasma

Method number	**MW1379V02/ 03/MW1208V 07**	**(b) (4) 10056/ R8686**	**(b) (4) 15049/ R11107**	**(b) (4) 16154/ R11869**	**AJMM2/ P1488**

Matrix	Lithium heparin plasma	Lithium heparin plasma	Lithium heparin plasma	Lithium heparin plasma	Di-potassium EDTA plasma
Internal standard	[D_5,^{15}N] (±) Rivaroxaban	[D_5,^{15}N] (±) Rivaroxaban	[D_5,^{15}N] (±) Rivaroxaban	[D_5,^{15}N] (±) Rivaroxaban	Rivaroxaban-d4
Calibration range, ng/mL	0.5 – 500	0.5 – 500	0.5 – 500	0.5 – 500	0.5 – 500
QCs, ng/mL	1.35, 26.6, 266, 398	1.5, 25, 375	1.5, 25, 375	1.5, 25, 375	0.5, 1.5, 250, 375
Accuracy, % QC L/M/H; LLOQ	96.7-101.1 96.9	102.7 - 105.2 102.2	100.8-104 99.8	102.7-103.7 109.2	98.2-100.1 106.48
Precision, %CV QC L/M/H; LLOQ	1.1-3.1 4.1	2.3-4.4 6.0	2.3-7.2 7.1	2.4-5.4 8.2	2.1-3.3 5.1
PK/PD studies	12892, 14373	17992	14372, 14374	17618	CHD-3001
Biopharm studies	16886, 14022	17769, 17861	-	19365, 19366	-

CV: coefficient of variation; QC L/M/H: Quality controls low, medium, high concentration; LLOQ: Lower Limit of Quantification; Source: Reviewer's summary of based on method validation reports submitted by the applicant

The validated methods for quantifying rivaroxaban in human plasma showed acceptable accuracy and precision of the calibration and QC samples which were ≤15% (and ≤20% at LLOQ) and satisfied the method validation criterion in accordance with the FDA guidance 'Guidance for Industry: Bioanalytical Method Development'.

The in-study performance of the methods during bioanalysis of the pivotal pediatric clinical study samples are summarized in Table 10.

Table 10. In-study performance of bioanalytical methods in the pivotal clinical studies of Rivaroxaban pediatric program

Study number	**14372**	**CHD-3001**
Accuracy, % QC L/M/H; LLOQ	100-100.8 101.6	98.5-101.4 100.1
Precision, %CV QC L/M/H; LLOQ	4.7- 7.2 5.7	3.0-8.9 5.2
Stability	Maximum of 155 days between sample collection and analysis vs 299 days for stability in plasma	Maximum of 759 days between sample collection and analysis vs 1330 days for stability in EDTA plasma
Reproducibility Incurred sample reanalysis	113 out of 1261 samples included, 99.1% passed	89 out of 460 samples included, 94.4% passed

CV: coefficient of variation; QC L/M/H: Quality controls low, medium, high concentration; LLOQ: Lower Limit of Quantification; Source: Reviewer's summary of based on method validation reports submitted by the applicant

Results of selectivity, stability and incurred sample reanalysis using this method were within acceptable limits for the rivaroxaban quantification in clinical samples to be considered acceptable. The validated bioanalytical methods used in analysis of the pediatric study samples fulfilled the required criterion for 'application to routine analysis' provided in the 'Guidance for Industry: Bioanalytical Method Development' and is considered acceptable.

4.1.2 PD Assays

Individual clotting factors- Anti-factor Xa activity:

The factor Xa activity was determined ex vivo using a photometric method according to the recommendations of the manufacturer Technoclone (Technoclone Anti-Xa kit). There is an inverse relationship between the concentration of rivaroxaban in the plasma sample and the color intensity, measured at 405 nm. The calibration range of the assay was 0.1 to 433.3 ng/mL, lower limit of quantification (LLOQ) was 14.5 ng rivaroxaban/mL. The correlations to plasma concentrations determined by HPLC-MS/MS in ng/mL were performed. As the anti-factor Xa activity assay with rivaroxaban-specific calibrators and controls was not available when adult Phase 3 studies were performed, no comparisons between children and adults were made.

Results of all QC samples for the pivotal studies were within the acceptance limits of ± 30% within the working range of 0.1-433.30 ng/mL.

Global clotting tests- Prothrombin time (PT) and activated partial thromboplastin time (aPTT):

Human citrated plasma samples were used for the global clotting tests and stored at -70°C. The assay was done within 12 months from sample collection.

The PT assay was performed according to the manufacturers' instructions on the STA Compact Hemostasis Workstation (STA Compact coagulation analyzer). The PT reportable range was between 10 and 120 seconds. Specimens falling outside that range are reported as "<10" or ">120" seconds and were not diluted. PT values of ≥120 sec was therefore not included in the analysis.

For aPTT, all pediatric studies world-wide were analyzed in one central lab using the STA Compact coagulation analyzer. The read-out for aPTT is in seconds with a reportable range between 5 and 180 seconds. Specimens falling outside that range are reported as "<5" or ">180" seconds and were not diluted. APTT values of ≥180 sec was therefore not included in the analysis.

The PD assays were specified to be in compliance with internal standard operating procedures and local guidelines and the performance for the PD assays were expected to be within the specifications set by the manufacturer.

4.2 Clinical PK and/or PD Assessments

The VTE treatment program, included one key Phase 3 study 14372 (EINSTEIN Jr Phase 3) and three supportive studies (two Phase 2 studies 14373 and 14374, and one Phase 1/2 study 17618). The CHD thromboprophylaxis program included one key Phase 3 study, CHD3001 (UNIVERSE). Two Phase 1 studies, Study 12892 and Study 17992 helped to establish the pediatric dosing recommendations for

both programs. Six of the above 7 studies were a part of the WR and or PMR studies; the seventh study (Phase 1 PK/PD Study 17992) was conducted by Applicant in support of inclusion of the granules for oral suspension formulation into Phase 3 trials. In addition, the submission includes 6 supporting biopharmaceutic studies in adult healthy subjects that characterize the pediatric formulations.

The clinical study report for the Phase 1 study, 12892 to support PMR1966-1 was submitted in NDA 022406 and found to be adequate in the clinical pharmacology review dated 03/10/2017.

4.2.1 Study 17992 (Phase 1 single dose pediatric study)

Title: Single-dose study testing a rivaroxaban dry powder formulation for oral suspension (granules for suspension) in children aged 2 months to 12 years with previous thrombosis

Objectives: The main objective of this PK/PD study was to characterize the pharmacokinetic profile of rivaroxaban administered as granules for oral suspension formulation and to document safety and tolerability of the rivaroxaban granules for oral suspension formulation. To enable a reliable comparison of rivaroxaban PK data, in this study the same individual doses that were used in the previous Phase 1 study 12892 as "low dose" and "as oral suspension dose" in the Phase 2 studies (14373 and 14374) were applied in Groups A and B.

Study Design: Multicenter, single-dose, open-label, cohort study that compared 3 dosing groups (N=47).

Group A: Dosing as low dose in Phase I study 12892; N=22 Group B: Dosing as ready to use suspension dose in Phase II studies 14373 and 14374; N=23	Children with an age between **6 months and <12 years** who have completed anticoagulant treatment at least 10 days prior to the planned study drug administration
Group C: Dosing of 0.4 mg/kg body weight for children weighing 3 to < 12 kg; N=2	Children with an age **≥ 2 months and weight between 3 kg and <12 kg**, who have completed anticoagulant treatment at least 10 days prior to the planned study drug administration, and have Gestational age at birth of at least 37 weeks, and Oral feeding/NG/ gastric feeding for at least 10 days

Table 11. Study 17992- Blood sampling schedule

	Age groups			
	6 to <12 years	**2 to <6 years**	**0.5 to <2 years**	**2 months to <2 years**
PD	pre, 0.5-1.5h, 2-5h, 8-12h and 20-24h	pre, 1.5-5h, 8-12h, and 20-24h	pre, 1.5-5h and 20-24h	no PD samples
PK	0.5-1.5h, 2-5h, 8-12h and 20-24h post	1.5-5h, 8-12h, and 20-24h post	1.5-5h and 20-24h post	10-30 min. 1-2h, 3-5h and 7-8h post

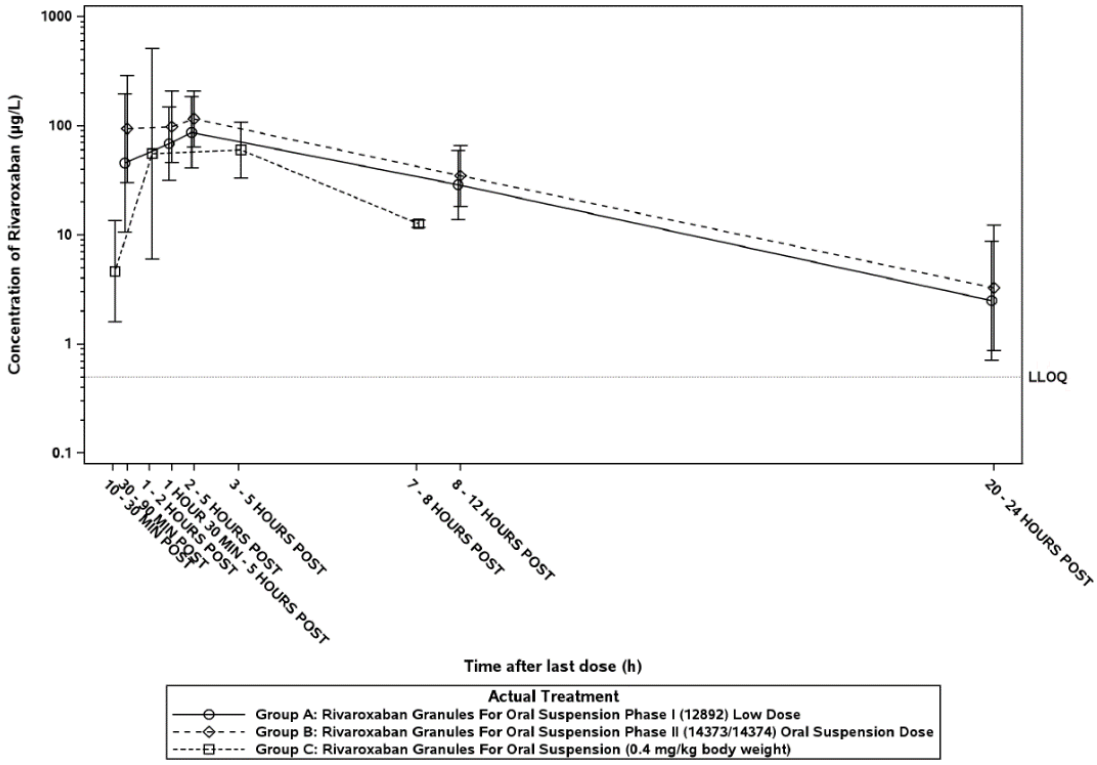
Source: Module 5.3.4.2 Report PH-38996 (17992) Section 9.2.1.1.1 and Section 9.3.1.2.1

PK-pharmacokinetics/ PD-Pharmacodynamics (prothrombin time, activated partial thromboplastin time and anti-factor Xa activity)

PK/PD results:

The plasma concentrations for single dose groups are summarized in the Figure 14 . The values for PD markers PT, aPTT, and anti-factor Xa activity data from study 17992 were within the distribution of adult DVT patients who received 20 mg IR tablets once daily. The Figure 15 shows a representative comparison for the 6-<12 y age group versus adults in the relative change in PT versus plasma rivaroxaban concentrations.

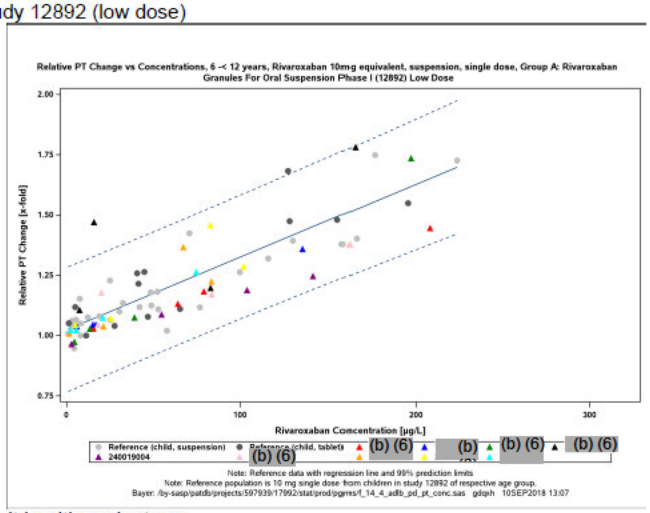
Figure 14. Geometric mean (± SD) for plasma concentrations of Rivaroxaban (ng/mL) by treatment groups



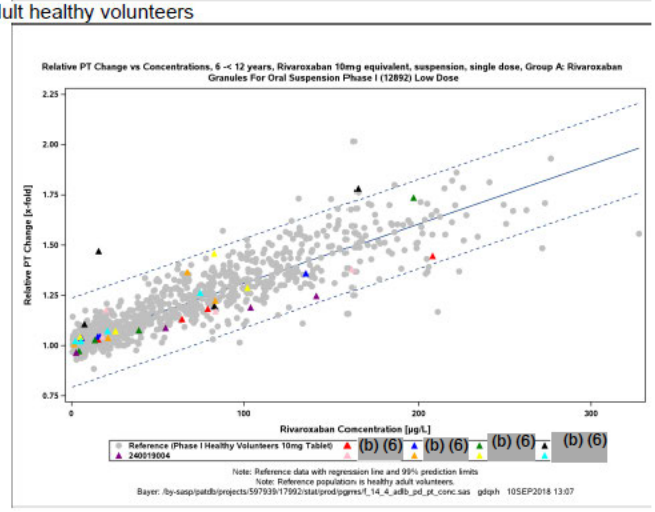
Source: Figure 14.4.2/31 of CSR 17992 / PH-38996

Figure 15. Relative PT change vs rivaroxaban plasma concentrations (single dose rivaroxaban 10 mg dose equivalent, granules for oral suspension in group A – age group 6-<12 years, n=9)

Reference: Study 12892 (low dose)



Reference: Adult healthy volunteers



Source: Figure 9-19 of CSR 17992 / PH-38996

Reviewer's comment: *The granules for suspension showed comparable exposures to the tablet but higher C_{max} compared to undiluted ready-to-use suspension used in previous studies. A trend towards lower AUC was observed in children with lower body weight (< 2 years) compared to older children, despite the higher dose per kg body weight. The PD values for PT and aPTT in children 6 months to 12 years were within the previously observed range of values in adult VTE patients or healthy adult volunteers that received comparable dosing regimens. A linear relationship of anti-Factor Xa activity versus plasma concentrations was observed.*

4.2.2 Study 17618 (Phase 1/2 pediatric study)

Title: A multicenter study evaluating the safety, efficacy and (PK/PD) profile of a 7-day treatment with age- and body weight-adjusted oral rivaroxaban in children younger than 6 months with symptomatic or asymptomatic arterial or venous thrombosis

Objectives: To characterize the PK/PD profile of a 7-day treatment with oral rivaroxaban after a body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban QD.

Study Design: Open label, 7-day treatment with age- and body weight-adjusted oral rivaroxaban in children younger than 6 months with symptomatic or asymptomatic arterial or venous thrombosis who have been treated with anticoagulant therapy for at least 5 days or 2 weeks. (N=10; 9 completed study).

Table 12. Study 17618- Blood sampling schedule

	Birth to less than 0.5 years	
	b.i.d. regimen	t.i.d. regimen
PD	Day 1 at 2-4h post Day 3 at 2-8h post Day 8 at 10-16h post (baseline)	Day 1 at 7-8h post Day 3 at 0.5-3h post Day 8 at 10-16h post (baseline)
PK	Day 1 at 0.5-1.5h and 2-4h post Day 3 at 2-8h post Day 8 at 10-16 h post	Day 1 at 0.5-3h and at 7-8 h post Day 3 at 0.5-3h and at 7-8 h post

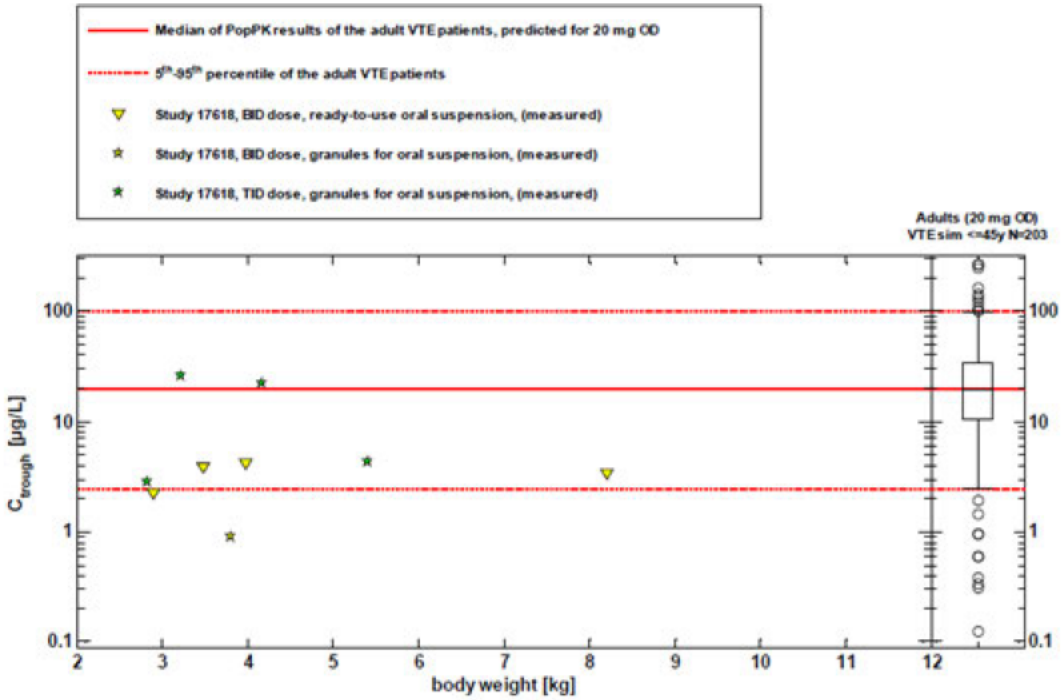
Source: Module 5.3.4.2 Report PH-39733 (17618) Section 9.3.1.1 and Section 9.4.1.2.1

PK-pharmacokinetics/ PD-Pharmacodynamics (prothrombin time, activated partial thromboplastin time and anti-factor Xa activity)

PK/PD results: Initially rivaroxaban was provided as 'ready-to-use suspension' with b.i.d. dosing (4 children), then enrollment changed to 'granules for oral suspension' (1 mg/mL after suspension) with b.i.d. dosing (1 child). The change in formulation was (b) (4) However, PK results of these first 5 children who received the b.i.d. regimen indicated lower rivaroxaban daily exposure ($AUC_{0\text{-}24ss}$ and C_{trough}) than initially expected based on the PBPK model predictions. Following these the dosing regimen was changed from a bid (approx. 12-hour intervals) to a t.i.d. (approx. 8-hour intervals) schedule applying the same individual dose three times a day as previously administered twice daily. Overall, 4 children received diluted rivaroxaban ready-to-use suspension bid, 1 received rivaroxaban granules for oral suspension bid and 5 received rivaroxaban granules for oral suspension tid (4 completed study).

The observed steady state trough concentrations with bid or tid regimens are summarized in the Figure 16. The $AUC_{0\text{-}24h\ ss}$ or C_{max} predicted by population PK models were below adult reference range for both the dosing regimen. In general, the values for PD markers PT and aPTT were within the range of the adult VTE patients receiving 20 mg rivaroxaban once daily (Study 11528) and anti-factor Xa activity showed linear relationship with plasma concentrations of rivaroxaban. The Figure 17 shows a representative comparison for the absolute PT values in this age group in comparison to the adult VTE population that received 10 mg bid or 20 mg qd dose of rivaroxaban.

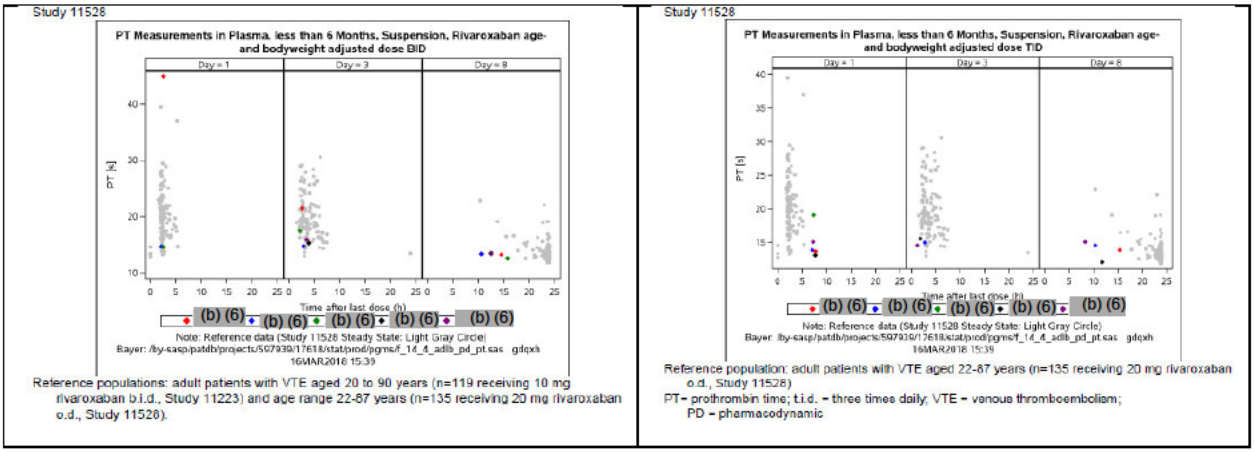
Figure 16. Steady state trough concentrations (C_{trough}) measured 10-16 h (bid) or 7-8 h (tid) after dosing for children less than 6 months receiving rivaroxaban body weight-adjusted doses in bid or tid regimen in comparison to the reference range for adult VTE patients (20 mg od) simulated via population PK modeling (boxwhisker plot indicating the percentiles 5, 25, 50, 75, and 95; open circles show individual values beyond the 5th – 95th percentile range.



C_{trough} = drug concentration in measured matrix at the end of the dosing interval; b.i.d. = twice daily; t.i.d. = three times daily; VTE = venous thromboembolism; o.d. = once daily; PK =pharmacokinetic

Source: Figure 9–19 of CSR PH-39733/17618

Figure 17. PT Measurements in Plasma, less than 6 Months, Suspension, Rivaroxaban age- and bodyweight adjusted dose BID (left panel) and TID (right panel)



Source: Figures 14.4.1.1 / 7 and 14.4.1.1/9 of CSR PH-39733/17618

Reviewer's comment: *For this age group (< 6 months and < 12 Kgs), the change in dosing regimen from b.i.d. to t.i.d. regimen seemed to elevate observed C_{trough} values closer to the targeted mean C_{trough} of the adult DVT treatment population. The values for PD markers PT, aPTT, and anti-factor Xa activity data from study 17992 were within the distribution of adult DVT patients who received 20 mg IR tablets once daily.*

4.2.3 Study 14373 (Phase 2 pediatric study)

Title: A 30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in children with various manifestations of venous thrombosis (**6 to < 18 years**)

Objectives: To characterize the PK/PD profile with sparse sampling after an age and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban QD.

Study Design: Open label, Open-label, multinational, multicenter study in Pediatric subjects between 6 and <18 years of age with documented symptomatic or asymptomatic venous thrombosis treated for at least 2 months or, in case of catheter related thrombosis, treated for at least 6 weeks with LMWH, fondaparinux and/or VKA (Standard of care, SOC) (N=64). The control arm was removed via protocol amendment and the study was completed as single-arm study.

12-18 years:

- 11 children received rivaroxaban o.d. as tablets
- 13 children received comparator

6-12 years:

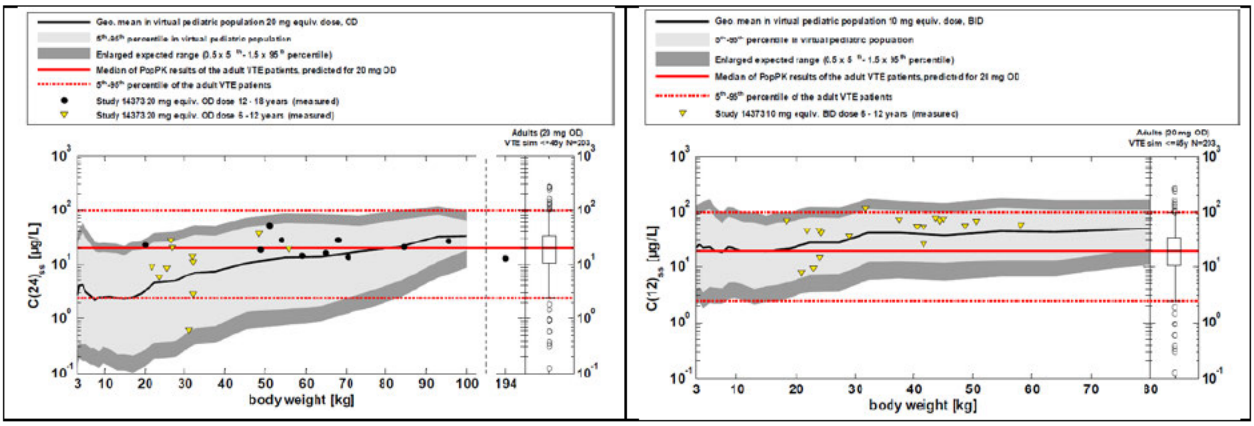
- 13 children received rivaroxaban o.d. as tablets
- 19 children received rivaroxaban b.i.d. as oral suspension (ready-to-use)
- 7 children received comparator

Four blood samples were scheduled for each child:

A predose sample on Day 15, two post dose samples 2-4 and 6-8 h after dosing on Day 15 and a post dose sample after the last dose on Day 31 after 20-24 h for children treated with 20 mg dose equivalents o.d. (tablets) and after 10-16 h for children treated with 10 mg dose equivalents b.i.d. (suspension).

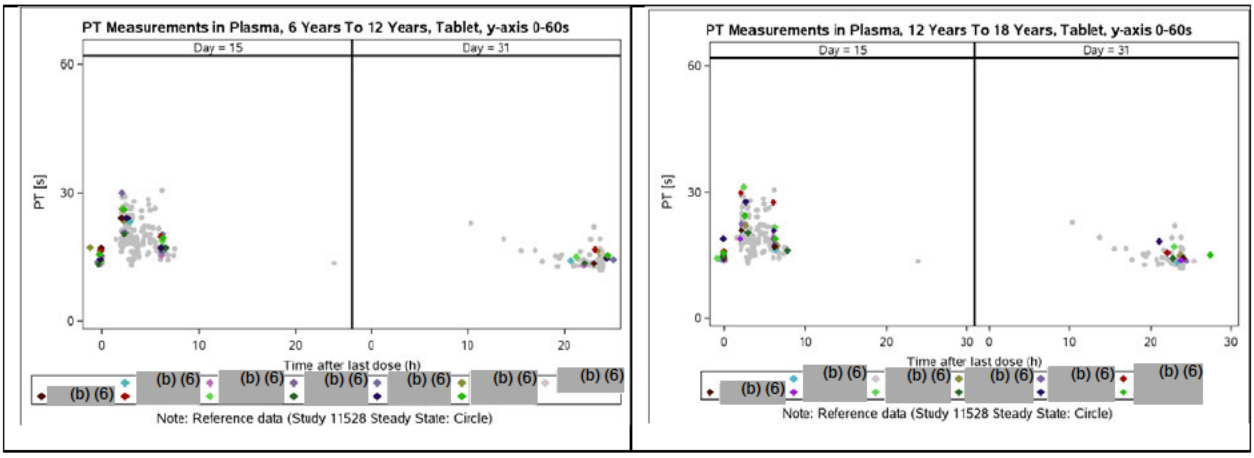
PK/PD results: In children with a body weight > 40 kg, the PK parameters $AUC_{0\text{-}24ss}$, $C_{max,ss}$ and $C_{trough,ss}$ were within the PBPK prediction range and the target exposure range of the adult VTE reference population. The exposures after the bid dosing in the 30-40 kg body weight group were at the higher end of prediction range for adult VTE reference and was suggestive that a od dosing should meet target exposures in this group. In children with a body weight below 30 kg, $AUC_{0\text{-}24ss}$ appears low in comparison to the simulated adult VTE reference population for the o.d. treatment, whereas Ctrough,ss was within the adult VTE reference range, however situated at the lower end of the adult distribution. A b.i.d. dosing with a slightly increased total daily dose is able to target $AUC_{0\text{-}24ss}$ and $C_{trough,ss}$ within the adult VTE reference range for children weighing less than 30 kg. Individual PT and aPTT data in children aged 6 to 18 years were in line with reference data from adult VTE patients treated with 20 mg rivaroxaban o.d. or 10 mg rivaroxaban b.i.d.

Figure 18. Measured PK parameter $C_{(24)ss}$ or $C_{(12)ss}$ (C_{trough}) for children and adolescents receiving rivaroxaban 20 mg (left panel) or 10 mg (right panel) dose equivalent o.d. in comparison to the corresponding PBPK predictions for children/adolescents between 6 months and 18 years of age (grey shaded area) and for adult VTE patients simulated via population PK modeling (box-whisker plot indicating the percentiles 5, 25, 50, 75, and 95; open circles show individual values beyond the 5th -95th percentile range)



Source: Figures 11-26 and 11-29 of CSR PH-38995/14373

Figure 19. Prothrombin time measurements in plasma (sec) in 6 to 12 years (tablet, left panel) and 12 to 18 years (tablet, right panel) after administration of multiple doses of rivaroxaban 20 mg od dose equivalents



Source: Figures 14.4.1.1 / 11 and 14.4.1.1 / 12 of CSR PH-38995/14373

Reviewer's comment: *A twice daily dosing with a slightly increased dose seems to be adequate for children with a body weight of less than 30 kg compared with once daily dosing in higher body weight children.*

4.2.4 Study 14374 (Phase 2 pediatric study)

Title: A 30-day, single-arm study of the safety, efficacy and the pharmacokinetic and pharmacodynamic properties of oral rivaroxaban in young children with various manifestations of venous thrombosis **(6 months to <6 years)**

Objectives: To characterize the PK/PD profile with sparse sampling after an age and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban QD.

Study Design: Study 14374 was a Phase 2 open-label study of a 30-day rivaroxaban treatment in subjects (6 months to <6 years) with documented (symptomatic or asymptomatic) VTE to assess safety, efficacy and the PK/PD properties of oral rivaroxaban. The rivaroxaban dose was adjusted according to body weight to achieve a similar exposure as observed in adults treated for DVT with 20 mg rivaroxaban once daily. All subjects received rivaroxaban as diluted ready-to-use oral suspension in twice daily regimen for a total of 30 days. Before the start of study treatment, subjects were required to have been treated for at least 2 months or, in case of catheter-related thrombosis, for at least 6 weeks with UFH, LMWH, or fondaparinux with or without VKA. The control arm was removed via protocol amendment and the study was completed as single-arm study (N=46)

≥ 2 y to 6 years:

- 25 children received rivaroxaban bid as oral ready-to-use suspension
- 6 children received comparator

6 months -2 years:

- 15 children received rivaroxaban bid as oral ready-to-use suspension

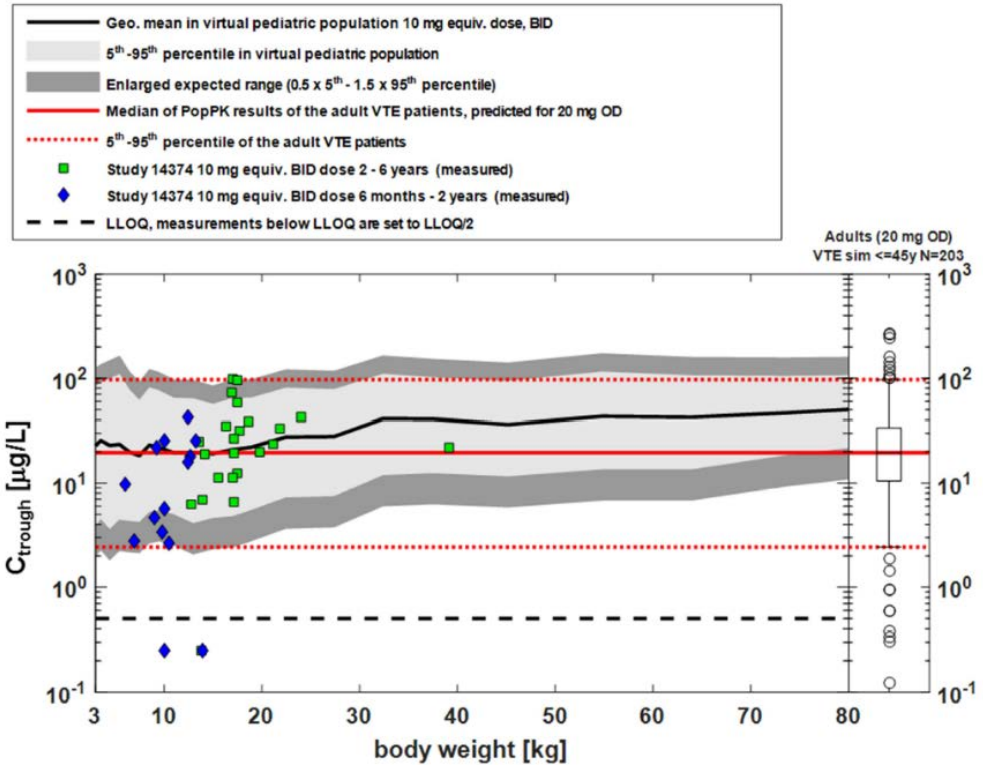
Four blood samples (3 for PD) were scheduled for each child:

Samples were scheduled at 0.5-1.5 h (not for PD) and 2.5-4 h after dosing on Day 1, 2-8 h after dosing on Day 15 and 10-16 h after dosing on Day 30.

PK/PD results: Overall, rivaroxaban plasma concentrations after administration of 10 mg dose equivalents bid to children aged 6 months-6 years were comparable to the adult patient population treated with 10 mg rivaroxaban bid, though C_{trough} values were at the lower end of the adult range, in children of the age group 6 months-2 years.

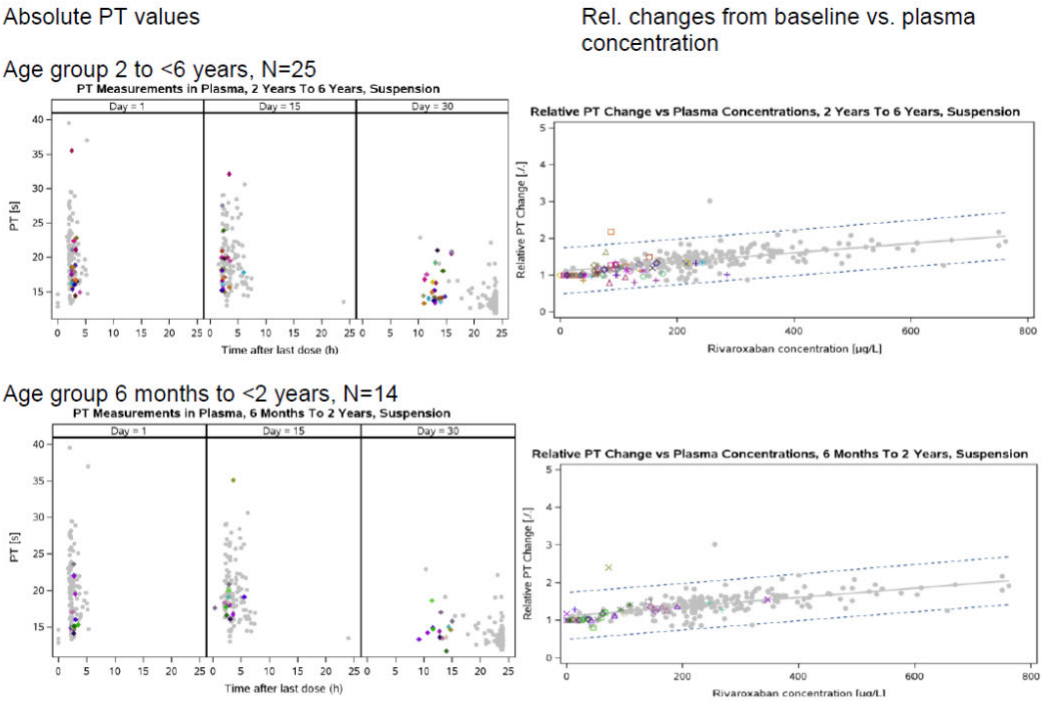
Individual PT and aPTT values in children aged 2 to <6 years and 6 months to <2 years were in line with reference data from adult DVT patients treated with 10 mg rivaroxaban b.i.d. or with 20 mg rivaroxaban once daily as tablets. Correlation of anti-factor Xa activity with plasma concentrations were generally observed but with outliers.

Figure 20. Measured trough concentrations (C_{trough}) 10-16 h after dosing on Day 30 for children and adolescents receiving rivaroxaban 10 mg dose equivalent bid in comparison to the corresponding PBPK predictions (10 mg equivalent dose bid) for children/adolescents between 6 months and 18 y of age (grey shaded area) and for adult VTE patients (20 mg od) simulated via population PK modeling (box-whisker plot indicating the percentiles 5, 25, 50, 75, and 95; open circles show individual values beyond the 5th-95th percentile range)



Source: Figure 11-19 of CSR PH-39333/14374

Figure 21. Study 14374 - Individual Prothrombin time values and relative Prothrombin time changes from baseline versus rivaroxaban plasma concentrations



Colored symbols represent individual data from children.
Light grey circles represent data of adult DVT patients receiving rivaroxaban as 20 mg o.d
Baseline: Day 30 / 10-16 h post dose
Source: Module 5.3.4.2 Report PH-39333 (14374), Figure 14.4.1.1 / 9, Figure 14.4.1.1 / 11, Figure 14.4.1.1 / 10 and Figure 14.4.1.1 / 12

Reviewer's comment: *The PK parameters obtained in this study for children of age group 2-6 years agreed with PBPK based predictions. A consistent decrease in rivaroxaban steady state exposure at lower body weight was observed that fell below the mean values of PBPK predictions, particularly in children with a baseline body weight below 12 kg.*

4.2.5 Study 14372 (Phase 3 pediatric study, EINSTEIN JR)

Title: Multicenter, open-label, active-controlled, randomized study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to standard of care in children with acute venous thromboembolism (**Birth to <18 years**)

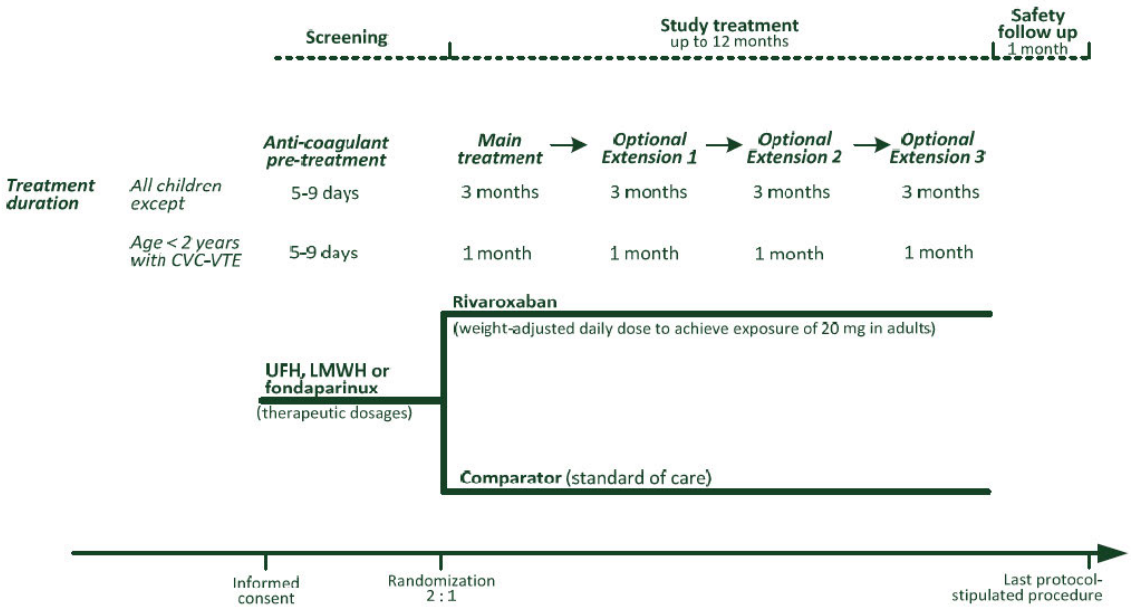
Objectives: Efficacy and safety study after an age and body weight-adjusted dosing of rivaroxaban to achieve a similar exposure as that observed in adults treated for VTE with 20 mg rivaroxaban QD.

Study Design:

Children aged between birth and <18 years with confirmed VTE who received initial treatment with therapeutic dosages of UFH, LMWH or fondaparinux and required anticoagulant therapy for at least 90 days with a plan for 3-month main study treatment period which could be extended with 3 blocks of 3 months each. Children with catheter related VTE aged < 2 years were required to have anticoagulant therapy for at least 30 days with a plan for the main treatment of 1 month which could be extended with 2 blocks of 1 month each. For children younger than 6 months all 3 conditions were to be met:

Gestational age at birth of at least 37 weeks, Oral feeding/nasogastric/gastric feeding for at least 10 days and body weight ≥2600 g.

Figure 22. Study design of 14372 (Phase 3 pediatric study, EINSTEIN JR)



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

Children received body weight-adjusted rivaroxaban in a once daily, twice-daily, or thrice-daily regimen. If a child turned to the next highest age group, he/she continued treatment according to age- and body-weight dependent dosing of his/her inclusion age cohort.

Rivaroxaban/comparator: 329/162; total N=491

(Rivaroxaban suspension/ tablet/comparator: 204/125/162)

Age groups:

12 to <18 years: 180/89

6 to <12 years: 67/34

2 to <6 years: 46/22

0.5 to <2 years: 21/9

<0.5 years: 15/8

Four blood samples were scheduled for children older than 6 years, 3 blood samples for younger children covering intervals 0.5-1.5 h after dosing (t.i.d: 0.5-3 h), 2.5-4 h and 2-8 h (t.i.d.: 2-6 h), 20-24 h after last dose for o.d. and 10-16 h after b.i.d. and t.i.d. administration.

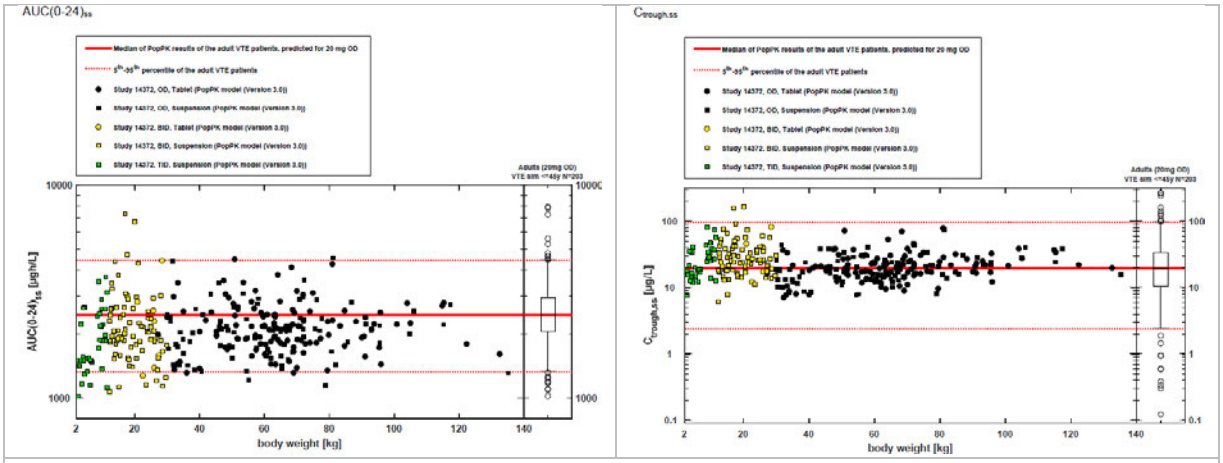
PK/PD results:

Population PK parameters $AUC_{0\text{-}24ss}$, $C_{max,ss}$ and $C_{trough,ss}$ were compared to the corresponding PK parameters derived via PopPK modeling for adult VTE patients with acute symptomatic DVT ≤45 years receiving 20 mg rivaroxaban in o.d. regimen.

For individual PopPK parameter values of $AUC_{0\text{-}24ss}$ and C_{maxss}, most values scatter well within the 5th – 95th percentile of the adult exposure range. For children <7 kg most values for AUC_{ss} and C_{maxss}, were located below the median of the adult reference range. Several values were located below the 5th –95th percentile but fall into the range of individual values beyond the 5th percentile of the adult reference population. For $C_{trough,ss}$ a minor trend towards higher values in bid and tid regimen compared to od regimen was evident, however the individual values scattered around the median of the adult reference population.

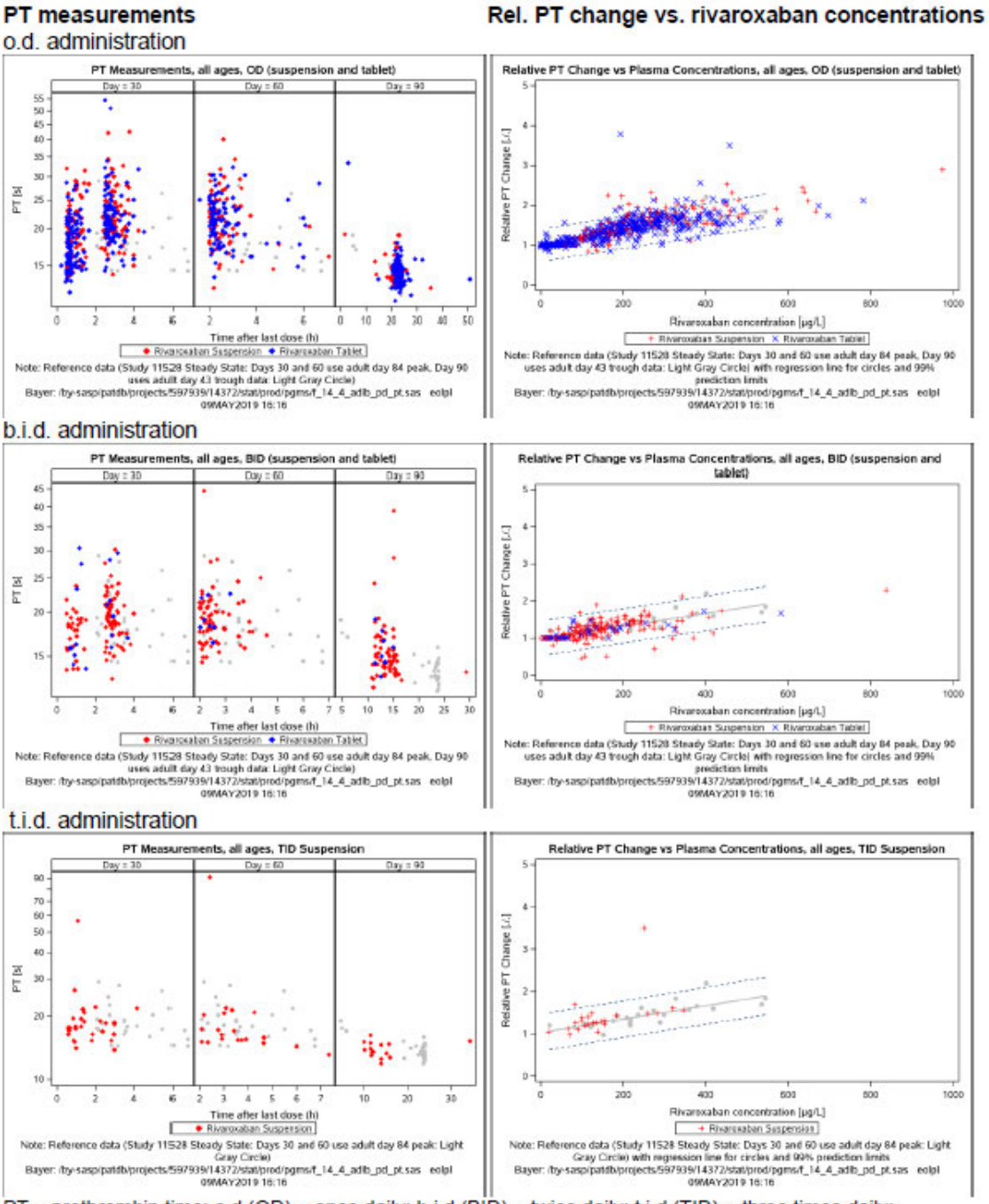
Overall, PT and aPTT prolongation was similar after od, bid and tid administration of rivaroxaban. No relevant difference was observed between the tablet and the suspension formulation. Children with a weight > 12 kg, between 6-12 kg and < 6 kg showed comparable PT and aPTT responses as expected due to weight adjusted dosing. With few exceptions, individual PT and aPTT data in children of all age groups were in line with reference data from adult VTE patients treated with 20 mg rivaroxaban od.

Figure 23. Body weight-dependence of $AUC_{(0\text{-}24)\ ss}$ and $C_{trough,ss}$ (popPK) derived by PopPK in children aged <18 years for the 20 mg daily dose equivalent on a semi-log scale. PopPK results for adult VTE patients (20 mg od) are shown as box whisker plot, which indicate the percentiles 5, 25, 50, 75, and 95 and individual values beyond the 5th – 95th percentile as open circles



Source: Figure 9-36 of CSR PH-40166/14372

Figure 24. Prothrombin time profiles (sec) and Prothrombin time relative changes vs. plasma concentration (all children)



PT = prothrombin time; o.d.(OD) = once daily; b.i.d.(BID) = twice daily; t.i.d.(TID) = three times daily;
Blue symbols: tablet, red symbols: suspension, grey circles: reference population
PT change to baseline (x-fold) is individual PT divided by individual PT at baseline (Day 90)
A linear relationship was assumed for the concentration-response curve of the reference populations. 99% prediction intervals were used to depict the variability in the reference population (dashed lines).
Reference population: adult VTE patients treated with 20 mg tablets once daily in study 11528
Source: Figure 14.4.1.1 / 10, Figure 14.4.1.1 / 11, Figure 14.4.1.1 / 16, Figure 14.4.1.1 / 17, Figure 14.4.1.1 / 22 and Figure 14.4.1.1 / 23

Reviewer's comment: *The PK parameters obtained in this study for children across the age groups were within range for the target adult exposures. The absolute PT and aPTT values as well the correlation of the PT or aPTT as ratio to baseline versus plasma concentration are within the adult reference range after the age and body weight-based dosing regimen.*

4.2.6 Study CHD3001 (Phase 3 pediatric study, UNIVERSE)

Title: A Prospective, Open-label, Active-controlled Study to Evaluate the Pharmacokinetics, Pharmacodynamics, Safety, and Efficacy of Rivaroxaban for Thromboprophylaxis in Pediatric Subjects 2 to 8 Years of Age after the Fontan Procedure (**2-8 years**)

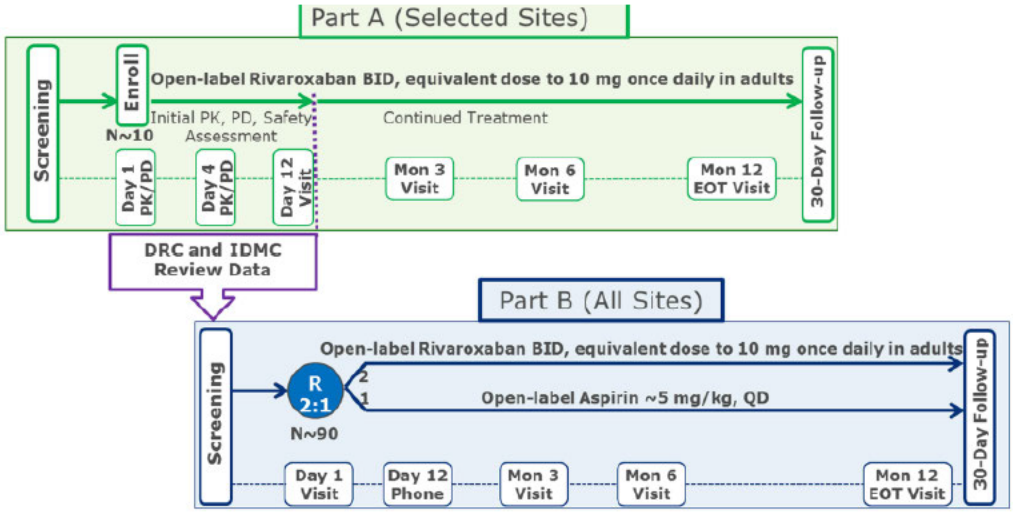
Objectives: Part A was for initial PK assessment in this pediatric patient population; Part B- Efficacy and safety study after an age and body weight-adjusted dosing of rivaroxaban for thromboprophylaxis in patients after Fontan procedure and to achieve a similar exposure as that observed in adults treated for VTE with 10 mg daily dose of rivaroxaban.

Study Design:

Open label with single-arm Part A and 2-arm, randomized, active (aspirin) controlled Part B in Pediatric subjects between 2 - 8 y of age, who had Fontan procedure within 4 months prior to enrollment.

Part A: To characterize the single- and multiple-dose PK and PK/PD profiles after oral rivaroxaban therapy administered to pediatric subjects 2 to 8 y of age with single ventricle physiology. Subjects from Part A did not participate in Part B.

Figure 25. Study design of CHD3001 (Phase 3 pediatric study, UNIVERSE)



BID=twice daily, DRC= Data Review Committee, EOT=end of treatment; IDMC=Independent Data Monitoring Committee, Mon=month; PD= pharmacodynamics, PK= pharmacokinetic(s); QD=once daily; R=randomization.

Note: An internal DRC assessed by Day 12 the PK, PD, and the safety data from each subject, prior to the continuing subject in the study to complete the planned 12 months of open-label rivaroxaban therapy.

Enrollment in Part A ended, and enrollment in Part B was started, once the cumulative data from all subjects in the Initial PK, PD, and Safety Assessment Period of Part A were deemed acceptable by the IDMC.

Part B: To evaluate the safety and efficacy of rivaroxaban, administered bid (exposure matched to rivaroxaban 10 mg QD in adults) compared to aspirin, given od (approximately 5 mg/kg) for thromboprophylaxis in pediatric subjects 2 - 8 y of age with single ventricle physiology

Children received body weight-adjusted rivaroxaban twice-daily with the oral granules for suspension formulation. If a child turned to the next highest age group, he/she continued treatment according to age- and body-weight dependent dosing of his/her inclusion age cohort.
Rivaroxaban part A/part B/aspirin part B: 12/64/34; total N=112
The median age was 2 y (2-4) in part A and 4 y (2-8) in Part B of this study.
Pharmacokinetic and PD samples were collected on Day 1, Day 4, Month 3, and Month 12 of rivaroxaban treatment in Part A. Pharmacokinetic and PD samples were also collected on Day 1, Month 3, and Month 12 in Part B.

PK/PD results:

The observed rivaroxaban concentrations in pediatric subjects who received a body weight-adjusted dosing regimen of rivaroxaban, when depicted as a function of time, are within the range of corresponding values that were observed in adults who received a daily dose of 10 mg rivaroxaban for the prevention of VTE (Refer to Sec 3.3.1). The observed PT and aPTT values in pediatric subjects that received a body weight-adjusted dosing regimen of rivaroxaban, when depicted as a function of time, were within the range of corresponding values that were observed in adults after daily administration of 10 mg rivaroxaban. PT values showed a linear relationship and good correlation while aPTT values had a narrower range and weaker correlation with plasma rivaroxaban concentration in pediatric subjects after Fontan procedure as compared to adults. A linear relationship was observed between anti-FXa activity and plasma rivaroxaban concentrations in these pediatric subjects.

Reviewer's comment: *The body weight-based dosing regimen for thromboprophylaxis in post-Fontan patients aged 2-8 years was shown to achieve exposures comparable to the adults after a 10 mg daily dose of rivaroxaban.*

4.2.7 Study 14022 (Relative BA study, food effect, Healthy volunteers)

Title: Single-dose, open-label, randomized, 4-way crossover study to compare 10 and 20 mg of an oral suspension of rivaroxaban under fasting and 20 mg of an oral suspension of rivaroxaban under fed conditions to 10 mg of an immediate release tablet under fasting conditions in healthy subjects

Objectives: To characterize the PK of 10 and 20 mg of rivaroxaban administered as an oral suspension in comparison to a 10 mg immediate release (IR) tablet. The potential for a food effect was investigated for 20 mg oral suspension.

Study Design:

Open-label, randomized, non-placebo controlled, 4-way crossover, single-dose study in healthy men aged 18-55 y. Following are the 4 groups:

- Rivaroxaban 10 mg oral ready-to-use oral suspension fasted (n= 16)
- Rivaroxaban 20 mg oral ready-to-use oral suspension fasted (n= 16)
- Rivaroxaban 20 mg oral ready-to-use oral suspension with food (n= 16)
- Rivaroxaban 10 mg tablet fasted (n= 17)

The point estimates and 90% confidence intervals of PK parameters (AUC,C_{max}) for the different treatment ratios were compared.

PK results:

Table 13. Assessment of rivaroxaban bioavailability in plasma [LS mean (90% confidence interval)], all subjects valid for PK, n=16

Para-meter	10 mg susp. fasted / 10 mg tab fasted	20 mg susp. fasted / 10 mg tab fasted	20 mg susp. fed / 20 mg susp fasted	20 mg susp. fed / 10 mg tab fasted	20 mg susp. fed / 10 mg susp fasted
AUC/D	0.925 (0.847, 1.009)	0.691 (0.634, 0.754)	1.466 (1.344, 1.600)	1.013 (0.929, 1.106)	1.0962 (1.005, 1.196)
C_{max}/D	0.871 (0.772, 0.982)	0.529 (0.470, 0.597)	2.025 (1.796, 2.284	1.072 (0.951, 1.209)	1.231 (1.092, 1.388)

Source: Table 14.4 / 5 of CSR BAY 59-7939 / 14022

The dose-normalized results shown in Table 16 indicated that systemic exposure was dose proportional between the 10 mg standard IR tablet / oral suspension in the fasted state and the 20 mg oral suspension taken with food. A slightly lower C_{max} was observed for the oral suspension at 10 mg in comparison to the IR tablet.

Reviewer's comment: *The administration with food compensated for the loss in bioavailability of the 20 mg oral suspension dose in the fasted state.*

4.2.8 Study 16886 (Relative BA study, food effect, Healthy volunteers)

Title: Single-dose, open-label, randomized, 4-way crossover study to compare 10 mg of an oral suspension of rivaroxaban under fasting (2 different batches) and 20 mg of an oral suspension of rivaroxaban under fed conditions to 10 mg of an immediate release tablet under fasting conditions in healthy male subjects

Objectives: The study was conducted as a single-dose, open-label, randomized, 4-way crossover to compare 10 mg of the ready-to-use oral suspension of rivaroxaban under fasting conditions (batches BN03501 and BR05701) and 20 mg of an oral suspension of rivaroxaban under fed conditions to 10 mg of the standard IR tablet under fasting conditions in healthy male subjects. It was investigated whether PK results obtained in children, indicating a delay in absorption, could be reproduced in adults using the same batch of medication as previously used in children. Comparisons were made with a new batch of the ready-to-use suspension as well as the IR tablet.

Study Design:

Open-label, randomized, non-placebo controlled, 4-way crossover, single-dose study in healthy men aged 18-55 y. Following are the 4 groups:

- Rivaroxaban 10 mg oral ready-to-use oral suspension fasted-batch BN03501 (n= 14)
- Rivaroxaban 10 mg oral ready-to-use oral suspension fasted-batch BR05701 (n= 14)
- Rivaroxaban 10 mg oral ready-to-use oral suspension with food (n= 14)

- Rivaroxaban 10 mg tablet fasted (n= 14)

The point estimates and 90% confidence intervals of PK parameters (AUC,C_{max}) for the different treatment ratios were compared.

PK results:

Table 15. Assessment of bioavailability in plasma [LS mean (90% CI)], all subjects valid for PK, n=14

Parameter	Ratio		Geometric LS mean	90% CI
AUC/D	10 mg suspension BN03501 fasted	10 mg IR tablet fasted.	0.9973	(0.9009, 1.1040)
	20 mg suspension BN03501 fed	10 mg suspension BN03501 fasted	1.1203	(1.0120, 1.2402)
	10 mg suspension BR05701 fasted	10 mg suspension BN03501 fasted	0.9280	(0.8383, 1.0273)
	10 mg suspension BR05701 fasted	10 mg IR tablet fasted	0.9255	(0.8360, 1.0245)
C_{max}/D	10 mg suspension BN03501 fasted	10 mg IR tablet fasted.	0.8848	(0.7668, 1.0210)
	20 mg suspension BN03501 fed	10 mg suspension BN03501 fasted	1.1227	(0.9722, 1.2965)
	10 mg suspension BR05701 fasted	10 mg suspension BN03501 fasted	0.9499	(0.8226, 1.0970)
	10 mg suspension BR05701 fasted	10 mg IR tablet fasted	0.8405	(0.7278, 0.9706)

Source: Module 5.3.3.1 Report PH-37535 (16886), Table 14.4 / 7 to Table 14.4 / 10

Table 14. Pharmacokinetic parameters of rivaroxaban [geometric mean/%CV (range)], n=14

Parameter	Unit	n	10 mg suspension fasted (BN03501)	n	20 mg suspension fed (BN03501)	n	10 mg suspension fasted (BR05701)	n	10 mg IR tablet fasted
AUC	µg*h/L	13	921/28.8 (541-1332)	13	2057/22.0 (1407-2987)	14	865/21.7 (559-1148)	13	920/21.0 (669-1316)
AUC/D	h/L	13	0.0921/28.8 (0.0541-0.133)	13	0.103/22.0 (0.0704-0.149)	14	0.0865/21.7 (0.0559-0.115)	13	0.0920/21.0 (0.0669-0.132)
AUC(0-t_{last})	µg*h/L	14	917/28.2 (531 – 1285)	14	2073/21.9 (1388 – 2945)	14	853/21.4 (554-1134)	14	915/20.6 (663-1297)
C_{max}	µg/L	14	107/27.0 (75.5-186)	14	240/31.3 (129 – 452)	14	101/20.9 (69.8-163)	14	120/21.3 (87.2-174)
C_{max}/D	1/L	14	0.0107/27.0 (0.00755-0.0186)	14	0.0120/31.3 (0.00644-0.0226)	14	0.0101/20.9 (0.00698-0.0163)	14	0.0120/21.3 (0.00872-0.0174)
$t_{1/2}$	h	13	7.89/33.9 (5.12-13.0)	13	8.16/34.8 5.00-15.3)	14	7.56/34.8 (4.15-18.7)	13	7.17/29.7 (4.73-10.5)
t_{max}[a]	h	14	2.00 (0.500-4.00)	14	4.00 (1.50-11.9)	14	1.75 (0.700- 4.00)	14	1.50 (0.700-4.00)

a median (range)

Source: Module 5.3.3.1 Report PH-37535 (16886), Table 14.4 / 2 and Table 14.4 / 4

As in study 14022, comparison between the 10 mg doses as a standard IR tablet and as ready-to-use oral suspension in the fasted state showed comparable AUC values whereas C_{max} values were slightly lower for the ready-to-use oral suspension (both batches) than for the standard IR tablet with values slightly (12 and 16%) lower after the oral suspension BN03501 and BR05701 (107 and 101 ng/mL, respectively) than after the standard IR tablet (120 ng/mL). Comparison between the two batches of the ready-to-use suspension showed comparable AUC and C_{max} values.

Reviewer's comment: *As in the previous study 14022, the administration with food showed dose proportional increase in exposure and a slight delay in peak absorption was observed with the ready-to-use suspension.*

4.2.9 Study 17769 (Relative BA study, Healthy volunteers)

Title: Single-dose, open-label, randomized, 4-way crossover study to compare a dry powder oral suspension (10 mg and 20 mg dose of rivaroxaban) with an oral suspension (10 mg of rivaroxaban) and 10 mg of an immediate release tablet under fasting conditions (10 mg doses) and under fed conditions (20 mg dose) in healthy male subjects

Objectives: The study was conducted to evaluate a new formulation, granules for oral suspension, (10 mg rivaroxaban fasted and 20 mg fed) as a single-dose in comparison to the with the ready-to-use oral suspension (10 mg rivaroxaban fasted) and the IR tablet (10 mg rivaroxaban fasted) in healthy male subjects.

Study Design:

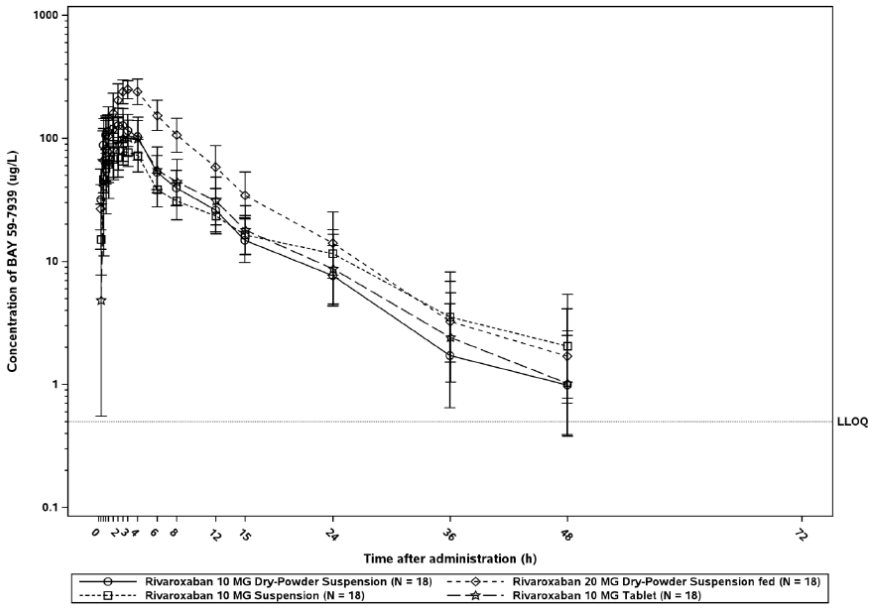
Open-label, randomized, non-placebo controlled, 4-way crossover, single-dose study in healthy men aged 18-55 y. Following are the 4 groups (N=18 each):

- 10 mg dry powder for oral suspension (Treatments A)
- 10 mg ready-to-use oral suspension (Treatment C)
- 10 mg immediate release tablets (Treatment D)
- 20 mg dry powder for oral suspension (Treatment B)

The point estimates and 90% confidence intervals of PK parameters (AUC,C_{max}) for the different treatment ratios were compared.

PK results:

Figure 26. Rivaroxaban plasma concentration following oral administration of 10 mg rivaroxaban as a dry powder oral suspension (A), as a ready-to-use oral suspension (C) and as a standard IR tablet (D) in the fasted state, and following administration of 20 mg as a dry powder oral suspension given with food (B), geometric means and SD- semi-logarithmic scale, n=18



Source: Figure 9.2 PH-38629 CSR

The 10 mg granules for oral suspension met BE criterion for the AUC and C_{max} when compared with the 10 mg IR tablet. The 10 mg granules for oral suspension showed 61% higher C_{max} than the ready-to-use oral suspension with comparable AUC. 20 mg granules for oral suspension dose taken with food showed dose proportional increase in exposure when compared to the 10 mg granules for oral suspension dose.

Table 16. Least squares mean ratios of PK-parameters (90% confidence interval), n=18

Parameter	Nominator	Denominator	LS-mean ratio (90% CI)
AUC	10 mg ready-to-use oral suspension fasted	10 mg tablet fasted	0.8842 (0.8193-0.9543)
	10 mg dry powder oral suspension fasted	10 mg tablet fasted	0.9929 (0.9200-1.0715)
	10 mg dry powder oral suspension fasted	10 mg ready-to-use oral suspension fasted	1.1229 (1.0403-1.2120)
	20 mg dry powder oral suspension fed	10 mg dry powder oral suspension fasted	2.0835 (1.9306-2.2486)
AUC/D	10 mg ready-to-use oral suspension fasted	10 mg tablet fasted	0.8842 (0.8193-0.9543)
	10 mg dry powder oral suspension fasted	10 mg tablet fasted	0.9929 (0.9200-1.0715)
	10 mg dry powder oral suspension fasted	10 mg ready-to-use oral suspension fasted	1.1229 (1.0403-1.2120)
	20 mg dry powder oral suspension fed	10 mg dry powder oral suspension fasted	1.0418 (0.9653-1.1243)
C_{max}	10 mg ready-to-use oral suspension fasted	10 mg tablet fasted	0.7037 (0.6387-0.7754)
	10 mg dry powder oral suspension fasted	10 mg tablet fasted	1.1300 (1.0256-1.2450)
	10 mg dry powder oral suspension fasted	10 mg ready-to-use oral suspension fasted	1.6056 (1.4571-1.7693)
	20 mg dry powder oral suspension fed	10 mg dry powder oral suspension fasted	1.8908 (1.7162-2.0833)
C_{max}/D	10 mg ready-to-use oral suspension fasted	10 mg tablet fasted	0.7037 (0.6387-0.7754)
	10 mg dry powder oral suspension fasted	10 mg tablet fasted	1.1300 (1.0256-1.2450)
	10 mg dry powder oral suspension fasted	10 mg ready-to-use oral suspension fasted	1.6056 (1.4571-1.7693)
	20 mg dry powder oral suspension fed	10 mg dry powder oral suspension fasted	0.9454 (0.8581-1.0416)

Source: Table 2.2 PH-38629 CSR

Reviewer's comment: *The key PK parameters for the newly formulated dry powder granules for oral suspension were comparable to the approved standard IR tablet.*

4.2.10 Study 17861 (Relative BA study, Healthy volunteers)

Title: Single-dose, open-label, randomized, 4-way crossover study to compare a dry powder oral suspension (10 mg and 20 mg dose of rivaroxaban) with an oral suspension (10 mg of rivaroxaban) and 10 mg of an immediate release tablet under fasting conditions (10 mg doses) and under fed conditions (20 mg dose) in healthy male subjects

Objectives: To determine relative bioavailability of Ready-to-use oral suspension under different administration conditions

Study Design:

The study was a single-dose, open-label, randomized, 5-way crossover to compare different administration conditions of 10 mg ready-to-use oral suspension of rivaroxaban in healthy Subjects (N=16):
Conditions:

- A- followed by 10 mL of water
- B- followed by 100 mL of water
- C- followed by 170 mL of water
- D- followed by 240 mL of water
- E- diluted in 30 mL of water and followed by 240 mL of water

The point estimates and 90% confidence intervals of PK parameters (AUC,C_{max}) for the different treatment ratios were compared.

PK results:
The AUC and C_{max} of rivaroxaban administered as 10 mg ready-to-use oral suspension were comparable between administrations with 170- and 240-mL water or diluted with 30 mL water prior to administration, followed by 240 mL water. Thus, in adults, dilution of the ready-to-use suspension prior to administration had no relevant impact on absorption properties. When given with 100 mL water, AUC was slightly reduced whereas C_{max} was similar to the standard administration procedure. When the ready-to-use suspension was administered with only 10 mL of water, AUC and C_{max} values were reduced by 23% and 29%, respectively.

Table 17. Assessment of relative bioavailability of rivaroxaban in plasma [LS mean (90%-confidence interval)], n=15

Para-meter	Nominator (10 mg rivaroxaban ready-to-use suspension)	Denominator (10 mg rivaroxaban ready-to-use suspension)	LS-Mean Ratio (90% CI)
AUC	with 10 mL water	with 240 mL water	0.7653 (0.6790-0.8627)
	with 100 mL water		0.8948 (0.7936-1.0088)
	with 170 mL water		0.9539 (0.8461-1.0755)
	diluted in 30 mL water, followed by 240 mL water		0.9909 (0.8791-1.1169)
C_{max}	with 10 mL water	with 240 mL water	0.7074 (0.6209-0.8058)
	with 100 mL water		0.9409 (0.8257-1.0721)
	with 170 mL water		1.0382 (0.9111-1.1830)
	diluted in 30 mL water, followed by 240 mL water		1.0009 (0.8786-1.1401)

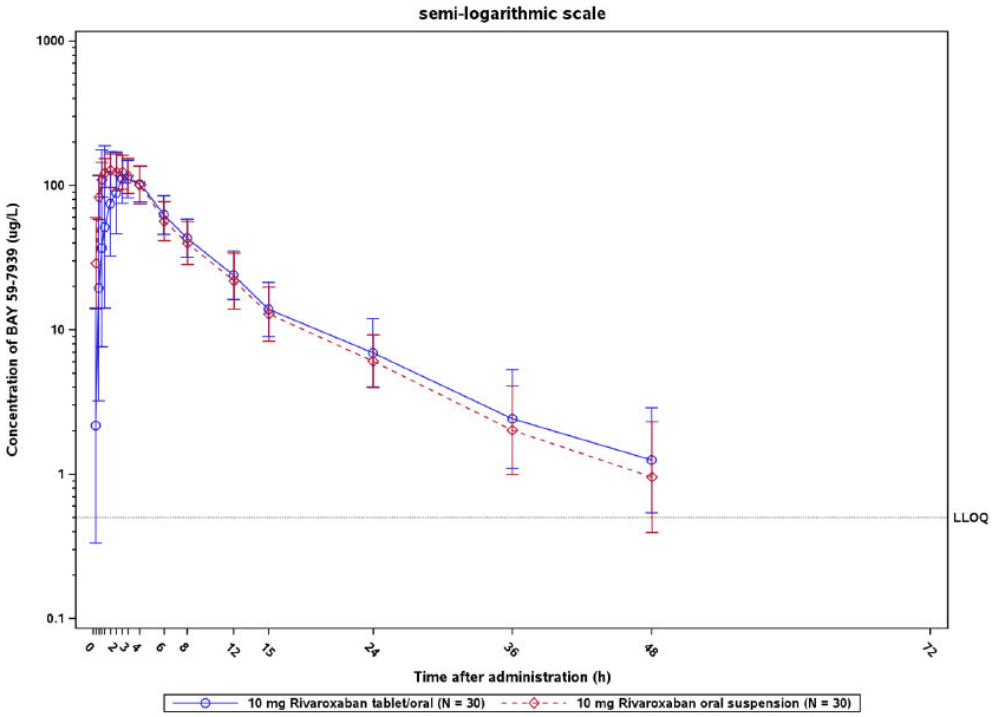
Source: Module 5.3.1.1 Report PH-38690 (17861), Table 14.4 / 6 and Table 14.4 / 7

Reviewer's comment: *In adults, dilution of the ready-to-use suspension prior to administration seemed not to have a relevant impact on absorption properties. In contrast to the healthy adult study findings, the in vitro dissolution results showing higher dissolution with water dilution could be observed only in pediatric studies.*

4.2.11 Study 19365 (BE study, Healthy volunteers)

The study was a single-dose, open-label, randomized, 2-way crossover to investigate BE of 10 mg rivaroxaban granules for oral suspension versus 10 mg rivaroxaban tablets under fasted condition in healthy subjects. 30 healthy male subjects were included in this study. Refer to Sec 3.3.5 for the review of study results. The comparisons of PK and PD profiles are provided in Figure 26 and Figure 27.

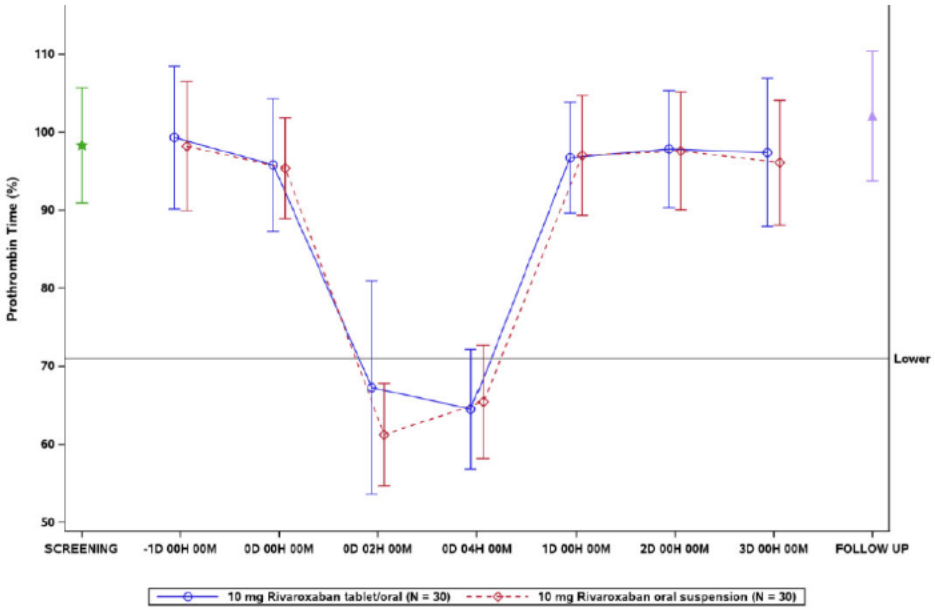
Figure 27. Rivaroxaban plasma concentration following oral administration of rivaroxaban as 10 mg IR tablet and as 10 mg oral suspension in the fasted state, geometric means and SD - semilogarithmic scale (n=30)



.

Source: Figure 9.2 PH-40127 CSR

Figure 28. Means and standard deviations for prothrombin time (%) in plasma, (n=30)

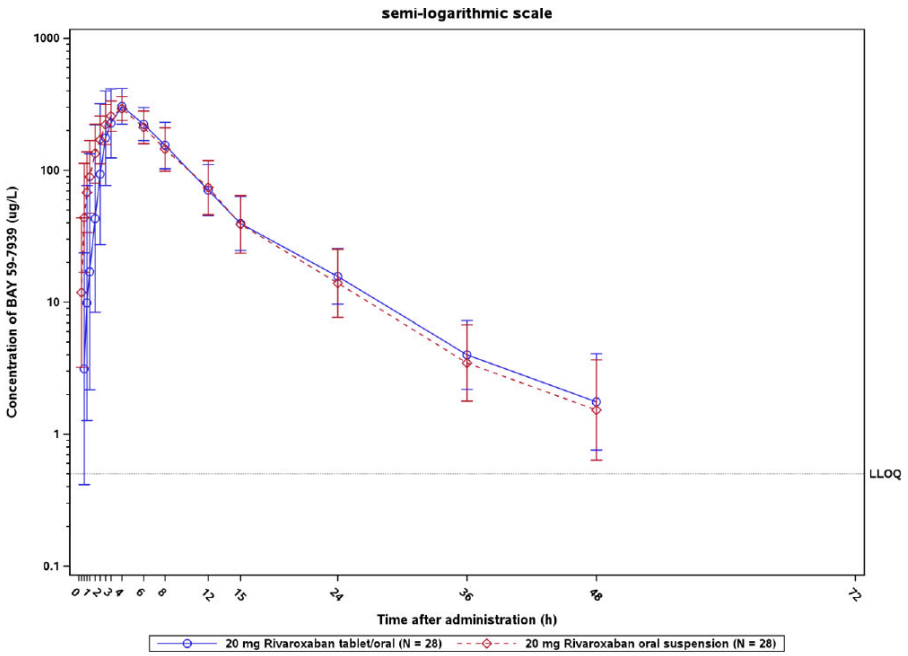


Source: Figure 10.1 PH-40127 CSR

4.2.12 Study 19366 (BE study, Healthy volunteers)

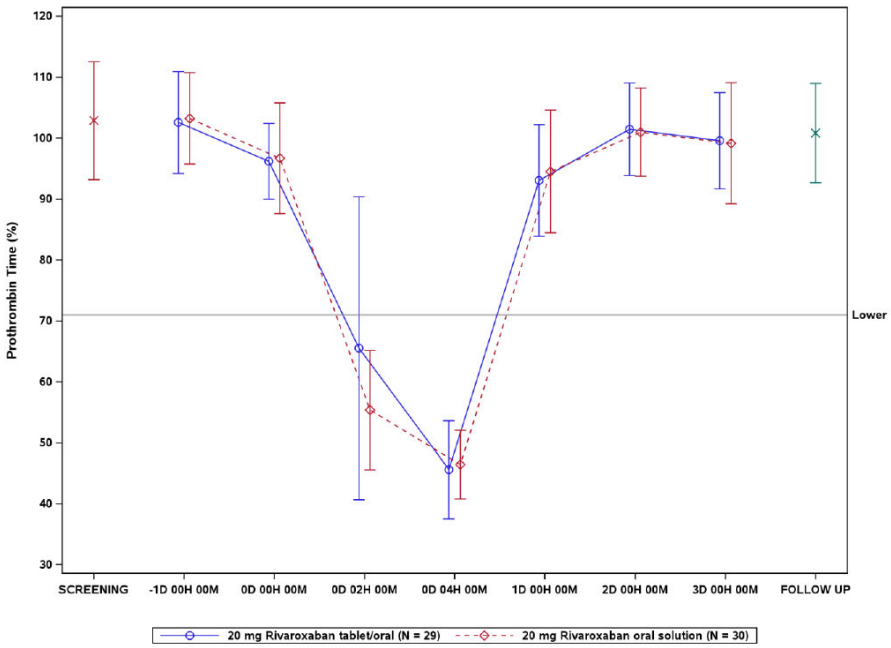
The study was a single-dose, open-label, randomized, 2-way crossover to assess bioequivalence of 20 mg granules for oral suspension rivaroxaban versus 20 mg tablets rivaroxaban under fed condition in healthy subjects 30 healthy male subjects were included in this study. Refer to Sec 3.3.5 for the review of study results. The comparisons of PK and PD profiles are provided in Figure 29.

Figure 29. Rivaroxaban plasma concentration following oral administration of rivaroxaban as 20 mg IR tablet with food and as 20 mg oral suspension with food, geometric means and SD - semilogarithmic scale (n=28)



Source: Figure 9.2 PH-40136 CSR

Figure 30. Means and standard deviations for prothrombin time (%) in plasma (n=30)



Source: Figure 10.1 PH-40136 CSR

4.3 Population PK and/or PD Analyses

4.3.1 Population PK analysis

The Applicant conducted a PopPK analysis separately for 1) VTE treatment program based on the 7 Phase I/II/III studies (Report No. 18376), and 2) CHD thromboprophylaxis program based on UNIVERSE trial (Report No. poppk-chd3001). The clinical studies included in the PopPK analysis and the PK sampling schemes are summarized in Table 18.

Table 18. Summary of studies included in PopPK analysis for pediatric patients

Study Number/Design	PK sampling
Study 12892: Phase I, single-dose study assessing safety, tolerability and PK of rivaroxaban in children ≥6 months and <18 years of age Dosing: Tablets or oral suspension at high dose and low dose groups corresponding to 10 or 20 mg in adults. A dilution step for RTU suspension was introduced based on preliminary PK results in this study	12 to <18 yrs: 0.5-1.5h, 2-4h, 4-8h, 8-12h, 20-24h [a]6 to <12 yrs: 2-5 h, 8-12h, 20-24h [a]2 to <6 yrs: 1.5-5h, 8-12h, 20-24h [a]6 mon to <2 yrs: 1.5-5 h, 20-24h
Study 14374: Phase II study assessing efficacy, safety and PK/PD in children between 6 months and 6 years receiving repeated BID oral doses over 30 days Dosing: Age- and body weight adjusted dosing regimen, BID as RTU oral suspension	Day 1: 30-90 min, 2.5-4h Day 15: 2-8h Day 30: 10-16h
Study 14373: Phase II, a 30-day single-arm study of the safety, efficacy and PK/PD in pediatric patients aged 6 to 18 years with various manifestations of venous thrombosis Dosing: 11 children in 12 to <18 years received tablet QD. 13 and 19 children in 6 to 12 years received tablet QD, and BID oral suspension, respectively.	QD regimen Day 15: predose, 2-4h, 6- 8h post Day 31: 20-24h post BID regimen Day 15: predose, 2-4h, 6- 8h post Day 31: 10-16h post
Study 17618: Phase I/II study of the safety, efficacy and PK/PD of a 7-day treatment in children from birth to <6 months with with symptomatic or asymptomatic arterial or venous thrombosis Dosing: 4 children received diluted RTU BID, 1 child received granules for oral suspension BID, and 5 children received granules for oral suspension TID	BID regimen: Day 1 at 0.5-1.5h and 2-4h post Day 3 at 2-8h post Day 8 at 10-16 h post TID regimen: Day 1 at 0.5-3h and at 7-8 h post Day 3 at 0.5-3h and at 7-8 h post
Study 17992: Phase I, single-dose study to characterize PK profile of granules for oral suspension, in children in the age range between 2 months and <12 years Dosing: granules for oral suspension Group A: Body weight-adjusted dosage from the previous Phase 1 study 12892 (low dose) Group B: Body weight-adjusted dosage used for oral suspension in Studies 14373 and 14374. Group C: 0.4 mg/kg children weighing 3 to <12 kg	6 to <12 yrs: 0.5-1.5h, 2-5h, 8-12h, 20-24 h 2 to <6 yrs: 1.5-5h, 8-12h, 20-24h 6 mon to <2 yrs: 1.5-5h, 20-24 h 2 mon to < 2 yrs: 10-30 min, 1-2h, 3-5h and 7-8h post
Study 14372 (EINSTEIN Jr): Phase III, OL, active-controlled study to evaluate the efficacy and safety of an age-and body weight-adjusted rivaroxaban regimen compared to SoC in children aged birth to < 18 years with acute VTE. Dosing: Tablets or granules for oral suspension at a	QD/BID regimen[b]: Day 30: 0.5-1.5h, 2.5-4h post, Day 60: 2-8h post, Day 90: 20-24h (QD), 10-16h (BID) after last dose on previous day.

bodyweight-adjusted dose to achieve a similar exposure as that observed in adult DVT patients receiving 20 mg rivaroxaban QD.	TID regimen: Day 2+1: 0.5-3h, 7-8h, Day 30: 0.5-3h, 7-8h, Day 60: 2-6 h (if dosing was continued for CVC-VTE patients)
UNIVERSE[c]: Phase III, OL, active-controlled study to evaluate PK/PD, safety, and efficacy of rivaroxaban for thromboprophylaxis in children from 2 to 8 years of age after the Fontan procedure Dosing: BID oral suspension with target exposure matching to 10 mg QD in adults	Part A: Day 1: 0.5-1.5 h, 1.5-4 h, Day 4: predose, 0.5-1.5 h, 1.5-4h, 6-8h, Month 3: predose, 0.5-1.5h, 2.5-4 h, Month 12: at any time 3h predose to 8 h postdose Part B: Day1: 0.5-1.5h, 1.5-4h, Month 3: predose, 0.5-1.5h, 1.5-4h, 6-8h, Month 12: 3h at any time predose to 8 h postdose
[a]PK sampling scheme changed after amendment 2. Modified schemes after the amendment are presented. [b]Patients with CVC-VTE aged <2 years BID dosing: Day 30: 10-16h after last evening dose on previous day / prior to morning dose, 0.5-1.5h and 2.5-4h post, Day 60: 2-8 h post, if dosing was continued [c]PopPK dataset for the VTE treatment program includes only the preliminary PK data of 12 Fontan-patients; PopPK dataset for the CHD prophylaxis program includes all data from UNIVERSE study.	

Source: Reviewer's summary based on the Applicant's reports. Note that only the relevant information is presented in this table. Refer to the respective CSRs for details of study designs and PK/PD assessment schemes.

4.3.1.1 Applicant's PopPK analysis for VTE treatment program

Reviewer's note: This analysis is referred to as "EINSTEIN Jr. PopPK analysis" in this review.

Data: The PopPK dataset contained PK observations for 524 patients with a total number of 1988 plasma rivaroxaban concentrations. Summary statistics of continuous covariates for data included in the analysis are shown in Table 19. The majority of patients were White (80.3%) and there were 24 (4.6%) Asian and 23 (4.4%) African Americans or Black. A total of 12 (2.3%) patients had Fontan procedures, 16 (3.1%) patients had creatinine greater than upper limit of normal (ULN), and 2 (0.4%) patients had missing creatinine measurement.

Table 19. Summary statistics of continuous covariates for the final PopPK dataset

Covariate	N[a]	Min[b]	P5[c]	Q1[d]	Median	Q3[e]	P95[f]	Max[g]	Mean	SD[h]
AGEM (months)	524	0	6	42	108	181	208	216	109	70.9
WGHTC (kg)	524	2.7	6.2	15.3	29.5	59.4	89.9	194	38.4	28
EGFR (mL/min/1.73m^2)	524	43.8	96.2	127	150	183	245	456	158	47.3
FULN (mg/dL)	524	0.48	1.04	1.35	1.71	2.26	3.66	11.8	1.94	0.96
GFRRHOD (mL/min/1.73m^2)	524	0.00153	2.38	37.2	57.6	81	100	122	57	29.1

Source: Study Report No. 18376. Table 11.1:12 on page 55.

Reviewer's note: The Applicant reported their methodology for handling of missing /erroneous data and observations below the detection limit and no specific concerns were noted. A total of 24 observations below the LLOQ (0.5 µg/L) were not present in the source data. The final PK data did not contain the individual race/ethnicity data.

Starting model: (b) (4),

(b) (4)

Model optimization:

(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Final model: The parameter estimates for the final EINSTEIN Jr PopPK model was presented in Table 20. The final PopPK model for rivaroxaban was a two-compartment model with first-order absorption and first-order elimination. A lower rate of absorption was estimated for undiluted suspension, compared to the other formulations (tablet, granules for oral suspension, and diluted suspension). The dose dependent effect on relative BA was described using Eq. 3, where Fmin is 0.59, Fmax is 1.25, D_{50} equals to 14.4 mg/WGHT. The relative oral BA of 100% was assumed for a dose/weight of 0.12 mg/kg and decreased gradually to 79.1% at 0.30 mg/kg and 68.1% at 0.50 mg/kg (Figure 31). All clearance and volume parameters (CL, Q, Vc and Vp) were allometrically scaled with body weight with a single value estimated for the scaling exponent of Vc and Vp. IIV was included for CL and F1. A proportional error model was used. ETA shrinkages were 23.5% for CL, and 33.2% for F1. The goodness of fit (GOF) plots and the prediction corrected visual predictive check (pcVPC) plots stratified by study are presented in Figure 32 and Figure 33.

Table 20. Parameters estimates for the EINSTEIN Jr PopPK model

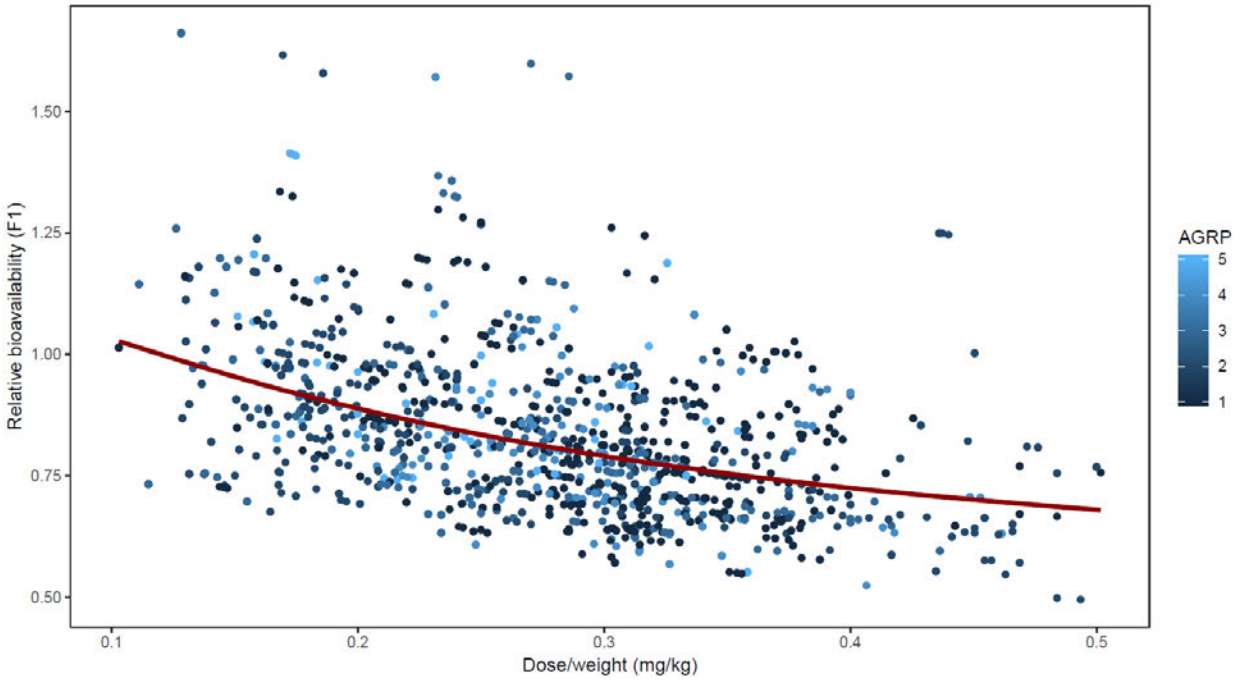
Parameter	Unit	Value[a]	SE[b]	CV (%)[c]	LLCI[d]	ULCI[e]
			Fixed effects			
KA for tablets, granules and diluted suspension	h^{-1}	0.799	0.0736	9.21	0.655	0.944
KA for undiluted suspension	h^{-1}	0.226	0.0365	16.2	0.154	0.297
CL for subject with WGHT of 82.48kg[f]	$L \cdot h^{-1}$	8.02	0.252	3.14	7.53	8.51
Exponent to scale CL on WGHT	-	0.481	0.0238	4.96	0.434	0.527
Vc for subject with WGHT of 82.48kg[f]	L	53.2	3.07	5.77	47.2	59.3
Vp for subject with WGHT of 82.48kg[f]	L	59.1	15.3	25.9	29.1	89.1
Exponent to scale Vc and Vp on WGHT	-	0.821	0.0308	3.75	0.760	0.881
Q for subject with WGHT of 82.48kg[f]	$L \cdot h^{-1}$	2.50	0.414	16.6	1.69	3.31
Exponent to scale Q on WGHT	-	0.761	0.102	13.4	0.561	0.961
			Random effects: Inter-individual variability			
ω^2_{CL} $(exponential)$		0.0705 (27.0%)[g]	0.0128	18.2	0.0453	0.0957
ω^2_{F1} $(exponential)$		0.0612 (25.1%)[g]	0.0105	17.2	0.0407	0.0818
			Random effects: residual error			
σ^2 $(proportional)$		0.220 (46.9%)[h]	0.00918	4.18	0.202	0.238

Source: Study Report No. 18376. Table 7.1:3 on page 40.

[a]Reported by NONMEM; [b]Standard error of parameter estimate; [c]Coefficient of variation, calculated as SE/Value*100%; [d]Lower limit of 95% CI; [e]Upper limit of 95% CI; [f]mean weight of the integrated PK analysis in adults

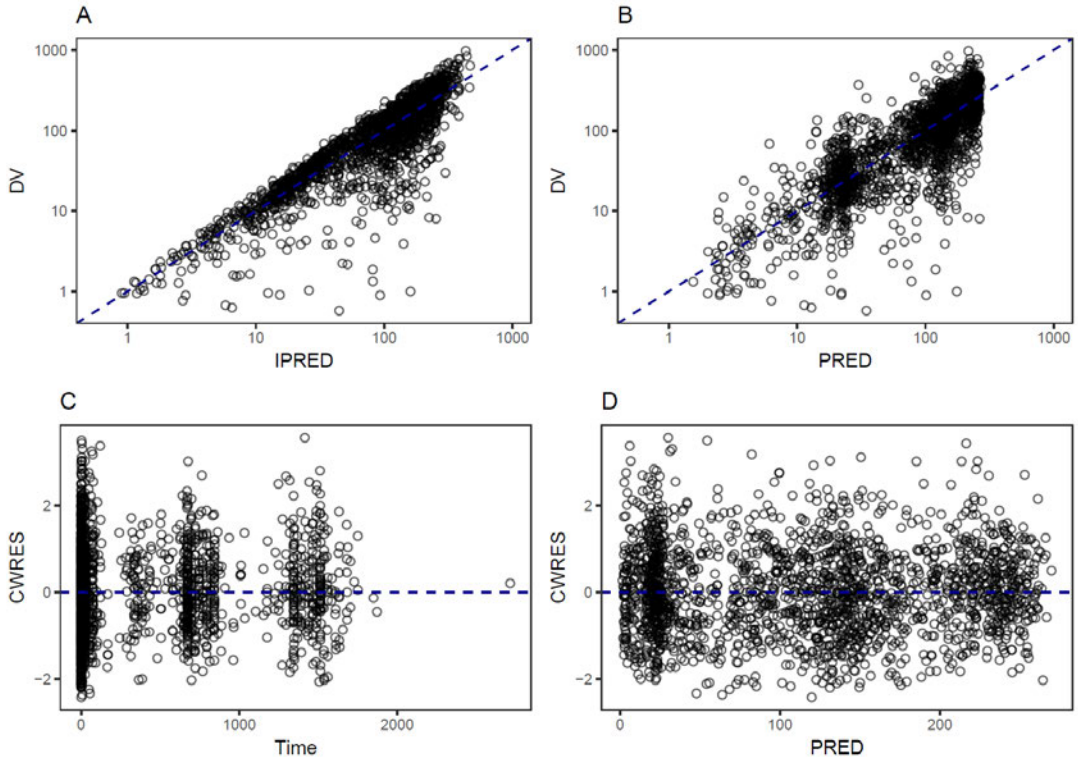
used as reference; [g]The population variation is calculated using sqrt(exp(ω^2)-1) * 100 %; [h]The population variation is calculated by sqrt(σ^2) * 100 (%)

Figure 31. Relationship between F1 and dose/weight ratio (mg/kg)



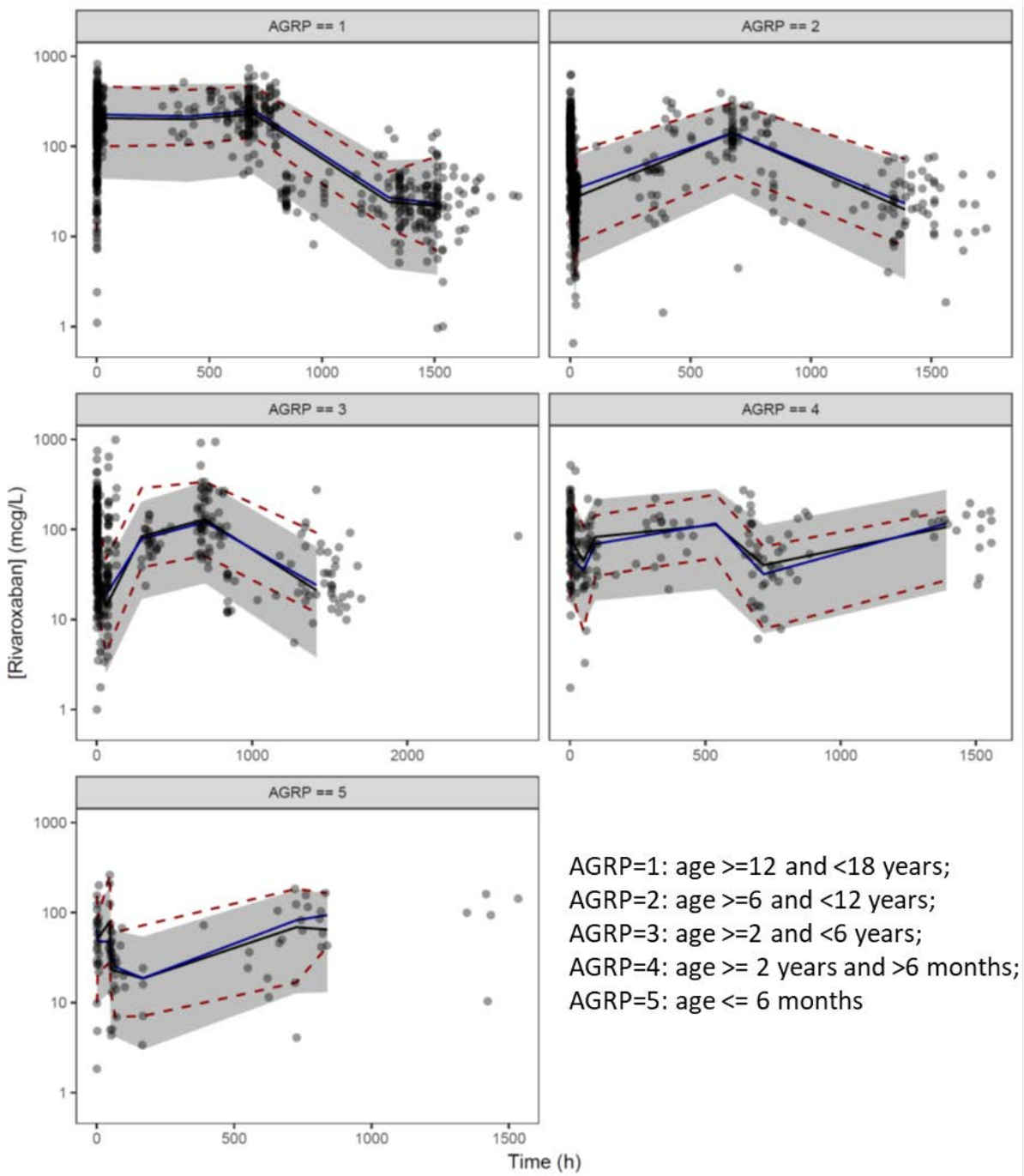
Source: Study Report No. 18376. Figure 7.1:1 on page 39. Symbols (colored by age group): individual F1 estimates; Solid red line: Population prediction of F1 using adult F1 function; AGRP=1: age 12-18 years; AGRP=2: age 6-12 years; AGRP=3: age 2-6 years; AGRP=4: age 0.5-2 years; AGRP=5: age 0-0.5 years

Figure 32 Goodness of fit plots of the EINSTEIN Jr PopPK model



Source: Study Report No. 18376. Figure 7.1:2 on page 39.

Figure 33. Prediction Corrected Visual Predictive Check (pcVPC) of the EINSTEIN Jr PopPK model



Source: Study Report No. 18376. Figure 11.2:37 on page 108. Grey symbols: prediction-corrected observations; blue lines: observed median; black lines: predicted median; red dashed lines: 5th and 95th percentiles of the observations; grey area: 90% prediction interval.

Estimation of individual PK exposures: Individual estimates for the following parameters were estimated using empirical Bayes estimates (EBEs)

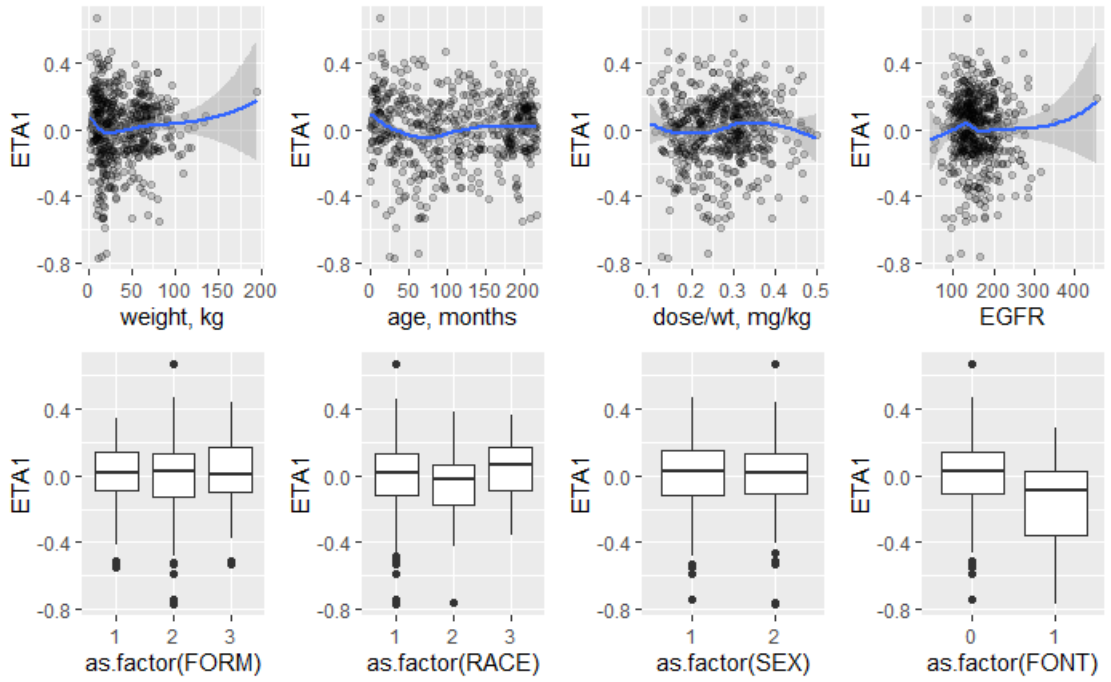
- PK model parameters: CL, Q, Vc, Vp, KA, F1. Vss was calculated as the sum of Vc and Vp and used as the estimate for the volume of distribution (Vd)
- Model-derived exposure metrics: AUC_{inf}, C8, C12, C24, Cmax, tmax, AUC8ss, AUC12ss, AUC24ss, C8ss, C12ss, C24ss, Cmaxss, tmaxss and t1/2.
    - Following a single dose, AUCinf was analytically calculated (AUC_{inf} = Dose*F1/CL)
    - Following multiple dose administrations, AUC (AUC24_ss for QD dosing, AUC12_ss for BID dosing or AUC8_ss for TID dosing) was determined to be AUC at steady state calculated in the same way as AUC_{inf}
    - Rivaroxaban concentrations at steady state after multiple dose administrations (Cmaxss, C8ss, C12ss and C24ss) were derived from dense simulated individual concentration-time profiles

Reviewer's Assessment:

The Applicant's final PopPK model (EINSTEIN Jr PopPK) reasonably described the observed PK data in the pediatric studies for the pediatric VTE program. The parameters for clearances, volumes of distribution, and the allometric exponents, and Ka were estimated with acceptable precisions (%CV<30%). IIVs were estimated with %CV <20%. In general, the model diagnostics (GOF plots and pcVPC) did not indicate unacceptable bias. The GOF plots stratified by studies and formulation did not show any unacceptable bias. The pcVPC plot shows that the model captures the central tendency and observed variability in rivaroxaban concentrations. Based on the model diagnostics and moderate ETA shrinkages for the IIVs for CL and F1, using the EBEs to calculate individual predicted exposures for EINSTEIN Jr. is acceptable. The summary of individual predicted exposure metrics is presented in the main section of review and is discussed in detail to evaluate the Applicant's proposed dosing regimen for VTE treatment for pediatric patients. Refer to Section 3.3 for more information.

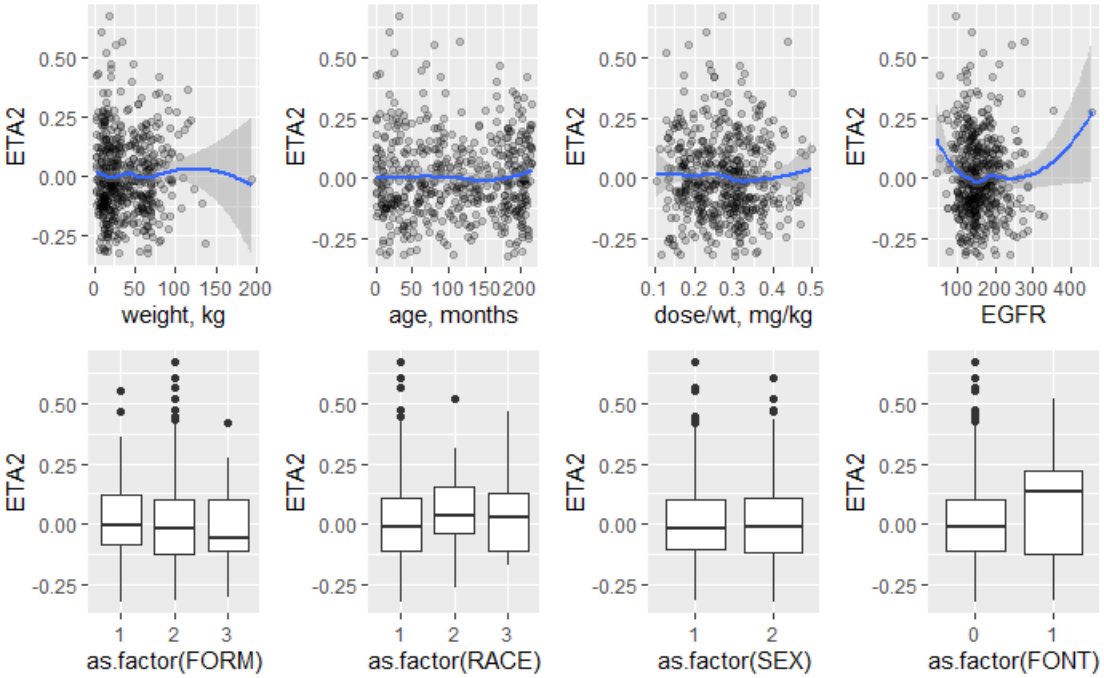
The Applicant's covariate analysis showed that only body weight effect on clearances and volumes of distributions and formulation effect on Ka were included in the model. Once these covariate models were included in the model, ETA-covariate relationship plots do not show any obvious trends with dose/weight, formulations, eGFR, sex, and race (Figure 34 and Figure 35*). Therefore, the Applicant's final covariate model is generally acceptable for the use of deriving individual predicted exposures, and simulating exposures to exploration of alternative dose for pediatric patients with different body weight.*

Figure 34. Relationship between ETA for CL (ETA1) and key covariates in the Applicant's final PopPK model



Source: Reviewer's plot generated based on the Applicant's final model and model output table. ETA1 represents IIV for CL. For race, the data from three races were presented: RACE=1: White; RACE=2 for Black or African Americans; RACE=3 for Asians.

Figure 35. Relationship between ETA for F1 (ETA2) and key covariates in the Applicant's final PopPK model



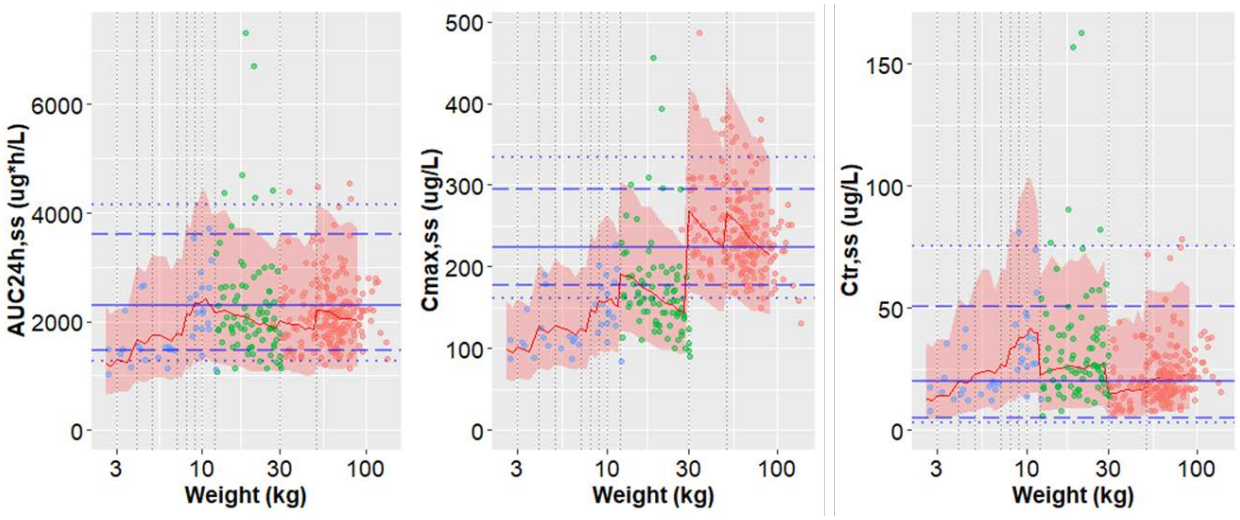
Source: Reviewer's plot generated based on the output table for EINSTEIN Jr PopPK model. For race, the data from three races were presented: RACE=1: White; RACE=2 for Black or African Americans; RACE=3 for Asians.

- *Body weight: Effect of body weight were included as allometric scaling approach with estimated exponents. The low estimate (0.481) for allometric exponent for CL indicates that a higher mg/kg dose would be needed for a patient with lower body weight to achieve similar exposures as a patient with a higher body weight. In the Applicant's propose dosing regimen for VTE treatment program, a pediatric patient weighing 2.6 kg is to receive 0.92 mg/kg/day, while 0.29 mg/kg/day for 70 kg patients taking 20 mg QD.*
- *Dose/kg ratio: The Applicant tested different mathematical functions to describe dose-dependent effect on oral bioavailability (F1). The selected function (Eq.3) reasonably captures the dose-dependent PK: ETAs for both CL and F1 are distributed around of 0 along the observed range of dose/kg ratio (Figure 34,*Figure 35*). Note that this function may be only valid in the observed dose/kg range (0.1 mg/kg to 0.5 mg/kg).*
- *Formulation: In line with the observations from the adult BE studies (Report PH-40127, and PH-40136), the PopPK analysis did not indicate a significant difference in rivaroxaban PK between pediatric patients receiving the IR tablet and the granules-for-oral-suspension.*
- *Renal function: Effect of renal function was assessed using different metrics (eGFR calculated by Schwartz equation, Scr above ULN, Rhodin eGFR). None of these metrics was identified as the significant covariate. It should be noted that the majority of patients in this PopPK analysis dataset had, eGFR >50 mL/min/1.73 m^2 and SCr <ULN, respectively. In the observed range of renal function measures, no significant difference in PK was identified.*

- *Race: Exploratory ETA-covariate relationships for the final model showed similar CL between White and Black or African American, but Asian patients tended to have higher CL. Inclusion of race effect on CL did not improve the model fit based on the objective function values. Out of 24 Asian patients, there were 5 Japanese children, 8 Chinese children and 8 Asian children outside Japan and China. Due to the small sample size for each race, the covariate effect for Japanese vs. Non-Japanese could not be evaluated in the covariate analysis.*
- *Post-Fontan patients: Shown in Figure 34 and Figure 35, there is a trend of lower CL and higher F1 for post-Fontan patients. But this was only based on 12 (2.3%) patients aged 2 years to <5 years. This is further discussed with UNIVERSE PopPK analysis. Refer to Section 4.3.1.2 for more details.*

The reviewer further performed simulations using the EINSTEIN Jr PopPK model at the proposed dose levels across the body weight groups (Figure 36). The simulated exposures generally in line with the central tendency and variability for the individual predicted exposures. The simulations show that the proposed dose for VTE treatment provides rivaroxaban $C_{trough,ss}$ within the adult reference, lower $C_{max,ss}$ for body wieht <30 kg, and lower $AUC_{0\text{-}24h,ss}$ for <10 kg. Refer to Section 3.3.2 for more discussion.

Figure 36. Simulated rivaroxaban exposures with the proposed dose for VTE treatment (without RUV)



Source: Reviewer's analysis. Dots: individual predicted exposures for EINSTEIN Jr patients which were derived using EBEs from EINSTEIN Jr PopPK analysis-blue dots (TID dosing), green dots (BID dosing), red dots (QD dosing); Blue horizontal lines: adult exposures receiving 20 mg QD, 5th, 10th, median (solid lines), 90th, 95th; Red lines and ribbons: median, and 5th-95th percentiles of the reviewer's simulated exposure; Vertical dotted lines represent the weight bands for the proposed dosing regimen.

The EINSTEIN Jr PopPK model developed based on the data from the VTE program was also used to predict exposures for dose extrapolation for CHD patients with Fontan procedure ages 9 to <18 years old receiving thromboprophylaxis dose (equivalent to adult 10 mg QD). Based on the model diagnostics (GOF plots and pcVPC) and the covariate analysis that adequately captures dose dependent F1, this model is

acceptable to be used for simulation for prophylaxis dose extrapolation. See Section 4.3.1.3 for further details.

4.3.1.2 Applicant's PopPK analysis for thromboprophylaxis program for CHD patients

Reviewer's note: This analysis is referred to as "UNIVERSE popPK analysis" in this review.

Data: UNIVERSE study was the only study included in the PopPK analysis for CHD patients with Fontan procedure (as referred to as "post-Fontan patients" in this section of review). UNIVERSE study was a Phase 3, A prospective, open-label, active-controlled study to evaluate the PK, PD, safety and efficacy of rivaroxaban for thromboprophylaxis in pediatric patients 2 to 8 years of age after the Fontan procedure. Patients received body-weight-adjusted, a 10 mg QD-equivalent dosing regimen. All patients received dose as BID regimen. There was a total of 76 patients with 12 patients from Part A and remaining patients from Part B.

- In Part A, PK, and PD data were collected Day 1 postdose 0.5-1.5 h and 1.5-4 h; Day 4 predose, postdose 0.5-1.5 h, 1.5-4 h, and 6-8 h; Month 3 predose, postdose 0.5-1.5 h and 2.5-4 h, and Month 12 at any time 3h predose to 8 h postdose.
- In Part B, PK, and PD data were collected Day 1 postdose 0.5-1.5 h and 1.5-4 h; Month 3 predose, postdose 0.5-1.5 h, 1.5-4 h, and 6.0-8 h; Month 12 3h at any time predose to 8 h postdose.

All 76 patients with 455 PK observations from the UNIVERSE study were included in the PopPK analysis. A total of 42 (55.3%) were male patients. The mean (range) of age and body weight were 3.86 (2, 8) years old, and 15.6 (9.8, 25.3) kg. The majority of patients were White (62%). There were 14 Asians of which 8 were Japanese. Baseline continuous and categorical covariates from the UNIVERSE study are summarized in Table 21 and Table 22, respectively. There were 5 records of BLOQ values per the LLOQ for rivaroxaban (0.5 µg/L) and they were excluded from the PopPK analysis.

Table 21. Summary of baseline continuous covariates UNIVERSE patients

	Rivaroxaban Total Daily Dose (Subject Body Weight)				
	3.2 mg (8 kg to <10 kg)	3.4 mg (10 kg to <12 kg)	4.0 mg (12 kg to <20 kg)	5.0 mg (20 kg to <30 kg)	Total
N	1	12	51	12	76
Age(years)					
Mean (SD)	2.00 (NA)	2.25 (0.622)	3.71 (1.42)	6.25 (1.14)	3.86 (1.73)
Median	2	2	4	6	4
Range	(2.00; 2.00)	(2.00; 4.00)	(2.00; 8.00)	(5.00; 8.00)	(2.00; 8.00)
Weight (kg)					
Mean (SD)	9.80 (NA)	11.2 (0.892)	15.3 (2.09)	21.6 (1.64)	15.6 (3.58)
Median	9.8	11.2	15.1	21.4	15
Range	(9.80; 9.80)	(9.80; 12.8)	(12.3; 20.1)	(19.6; 25.3)	(9.80; 25.3)
Height (cm)					
Mean (SD)	78.0 (NA)	85.7 (6.26)	98.6 (8.22)	119 (6.59)	99.5 (12.5)
Median	78	84	98.3	120	98.7
Range	(78.0; 78.0)	(78.0; 103)	(82.0; 118)	(109; 133)	(78.0; 133)
Body mass index (kg/m^2)					
Mean (SD)	16.1 (NA)	15.3 (1.85)	15.8 (1.79)	15.3 (1.48)	15.6 (1.74)
Median	16.1	15.6	15.5	14.7	15.5
Range	(16.1; 16.1)	(10.8; 17.4)	(11.8; 20.6)	(13.5; 18.7)	(10.8; 20.6)
Creatinine clearance, calculated (mL/min)					
Mean (SD)	55.0 (NA)	57.5 (11.7)	79.4 (20.3)	88.3 (25.2)	77.0 (21.9)
Median	55	56.3	76	83.3	74
Range	(55.0; 55.0)	(37.4; 81.5)	(44.1; 146)	(60.2; 149)	(37.4; 149)

Source: Applicant's report PopPK-CHD3001, Table 3, page 21.

Table 22. Summary of baseline categorical covariates for UNIVERSE patients

	Rivaroxaban Total Daily Dose (Subject Body Weight)				
	3.2 mg (8 kg to <10 kg)	3.4 mg (10 kg to <12 kg)	4.0 mg (12 kg to <20 kg)	5.0 mg (20 kg to <30 kg)	Total
N	1	12	51	12	76
Race/Ethnicity, n (%)					
White, Not Hispanic or Latino	0 (0)	5 (41.7)	19 (37.3)	2 (16.7)	26 (34.2)
Black, of African heritage or African American	0 (0)	2 (16.7)	7 (13.7)	2 (16.7)	11 (14.5)
White, Hispanic or Latino	0 (0)	1 (8.3)	14 (27.5)	6 (50)	21 (27.6)
Asian	1 (100)	3 (25)	9 (17.6)	1 (8.3)	14 (18.4)
Other	0 (0)	1 (8.3)	2 (3.9)	1 (8.3)	4 (5.3)
Sex, n (%)					
Male	0 (0)	5 (41.7)	31 (60.8)	6 (50)	42 (55.3)
Female	1 (100)	7 (58.3)	20 (39.2)	6 (50)	34 (44.7)
Japanese, n (%)					
Non-Japanese	1 (100)	10 (83.3)	46 (90.2)	11 (91.7)	68 (89.5)
Japanese	0 (0)	2 (16.7)	5 (9.8)	1 (8.3)	8 (10.5)

Source: Applicant's report PopPK-CHD3001, Table 4, page 22.

UNIVERSE PopPK analysis: A model structure similar to EINSTEIN Jr PopPK model for the VTE program was used to fit the plasma concentration-time data of rivaroxaban in patients from the UNIVERSE study. The UNIVERSE PopPK model was described by a linear two-compartment model with first-order absorption and first-order elimination from the central compartment with the absorption rate constant (KA). CL and Vc were exponentially scaled with body weight. IIV was applied to F1 and CL. Residual error

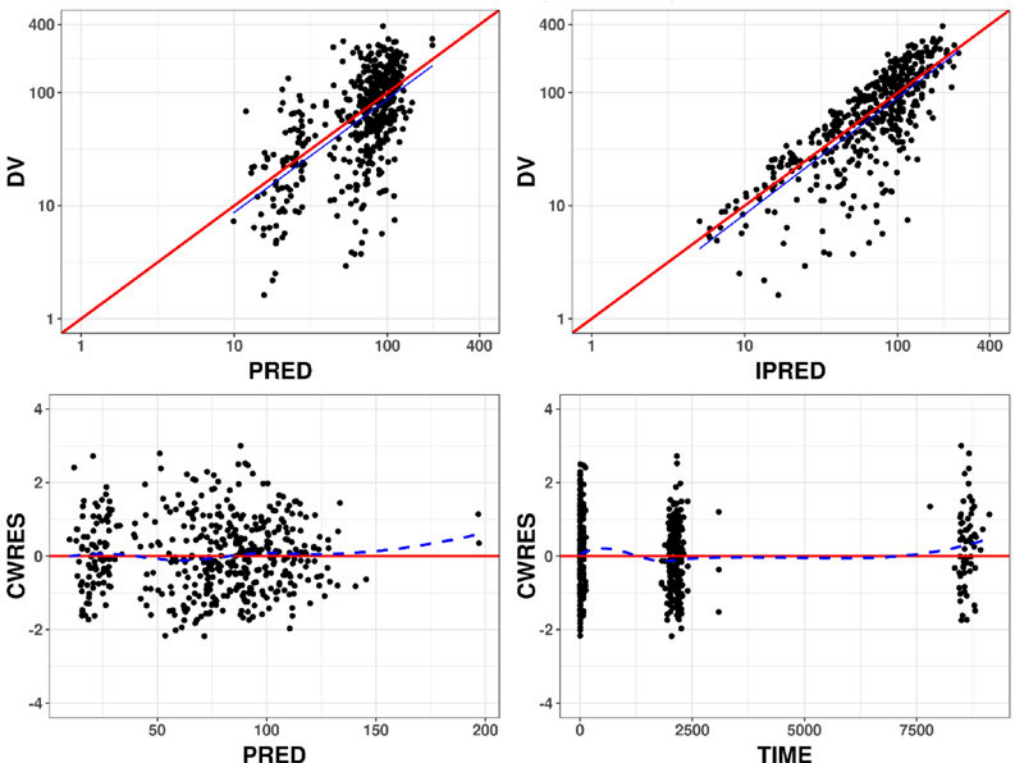
was described by a proportional error model. The same function for relative F1 used in EINSTEIN Jr PopPK model was used. Parameter estimates for UNIVERSE PopPK model are presented in Table 23. GOF plots and pcVPC plots are presented in Figure 37 and Figure 38, respectively.

Table 23. Parameter Estimates of UNIVERSE PopPK analysis

Parameter	Unit	Estimate	RSE (%)	Shrinkage (%)
		Fixed effects		
KA	1/h	1.12	19	-
CL	L/h	3.3	7.01	-
Vc	L	17.6	12.6	-
Exponent to scale CL and Q on WGHT	-	1.01	23.6	-
Exponent to scale Vc and Vp on WGHT	-	1.2	20.9	-
Q	L/h	1.09	38.5	-
Vp	L	33.4	61.9	-
		Random effects: Interindividual variability		
ω^2_{CL} (exponential)	-	0.0905	37	24.7
ω^2_{F1} (exponential)	-	0.164	25.2	13.1
		Random effects: residual error		
σ^2 (proportional)	-	0.274	9.27	7.22

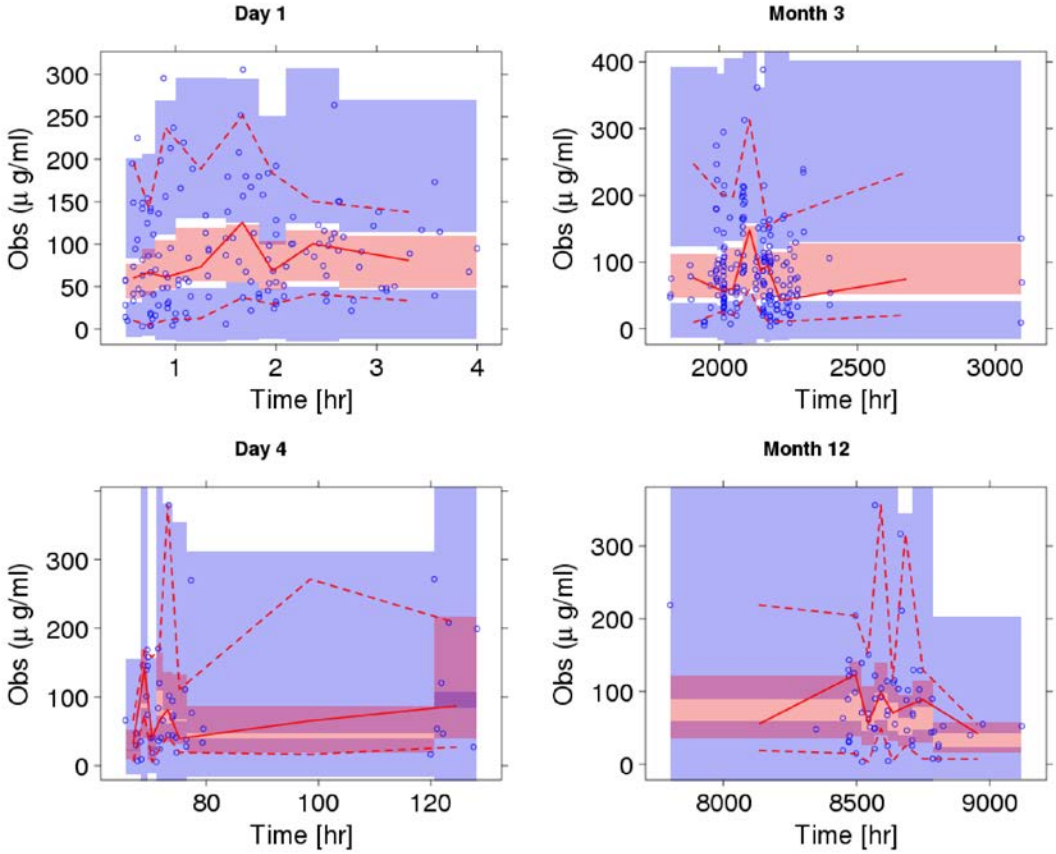
Source: Applicant's report PopPK-CHD3001, Table 5, page 28.

Figure 37. GOF plots of the UNIVERSE PopPK analysis



Source: Applicant's report PopPK-CHD3001, Figure 2, page 29.

Figure 38. pcVPC Plots of UNIVERSE PopPK analysis by time of PK assessment



Source: Applicant's report PopPK-CHD3001, Figure 3, page 30.

Estimation of individual PK exposures: Exposure metrics (including AUC24h,ss, Ctrough,ss, and Cmax,ss) were derived for pediatric patients in the UNIVERSE study from simulation of rivaroxaban PK profiles using EBEs for individual PK parameters based on the UNIVERSE PopPK model. The individual exposures for the post-Fontan patients from UNIVERSE estimated by the UNIVERSE PopPK model (triangles) were overlaid with the adult reference exposures and the simulated exposures for post-Fontan patients using EINSTEIN Jr PopPK model at the proposed prophylaxis dosing regimen. The individual predicted exposures in post-Fontan patients largely overlap with these simulations, with underprediction at the lower body weight range, which was further discussed in Section 4.3.1.3.

Reviewer's Assessment:

The GOF plots did not show unacceptable bias, and the pcVPC presented by the time after the first dose generally captures the central tendency of the observed data. The ETA shrinkages are acceptable (<25%). Therefore, the Applicant's UNIVERSE PopPK model could be used for the purpose of deriving the individual predicted exposure metrics for post-Fontan patients in UNIVERSE study to support the proposed dosing regimen at an age range of 2-8 years and a body weight range of 9.8 to 25.3 kg.

However, the reviewer does not recommend using this model for any simulations for the studied population nor extrapolation of PK exposures beyond the studied pediatric population, because the

model parameters from UNIVERSE PopPK analysis were estimated by fitting the UNIVERSE data without parameter optimization steps and covariate analyses. Also, the model was developed based on the dataset consisting of sparse PK samples collected from a small sample size (76 post-Fontan patients) with the narrow ranges of key covariates (age range 2-8 years and a body weight range of 9.8 to 25.3 kg).

Given the limitation of UNIVESE PopPK analysis, the reviewer conducted a sensitivity analysis to assess the reliability of the individual predicted exposure metrics derived from the UNIVERSE model. The UNIVERSE dataset was combined with the dataset used for EINSTEIN Jr PopPK analysis. The EINSTEIN Jr PopPK model was then fitted to the combined dataset and all parameters were re-estimated. Including UNIVERSE data did not notably change the population parameter estimates compared to those estimated from the EINSTEIN Jr PopPK model. The GOF plots for all data did not show any unacceptable bias. ETA shrinkages were similar to those reported in EINSTEIN Jr PopPK analysis. The GOF plot (CWRES vs. PRED) generated based on only Fontan patient data showed misspecifications at population levels. However, there was no obvious bias in the plot of IPRED vs. DV. Further, the individual predicted concentrations (IPRED) were nearly identical to those predicted by UNIVERSE PopPK model with small variation with unbiased trend around the unity line.

4.3.1.3. Dose extrapolation for post-Fontan patients

Dosing regimen for post-Fontan patients 7 to <8 kg

The Applicant proposed dosing regimen of rivaroxaban for thromboprophylaxis for CHD patients with Fontan procedures aged 2 to 18 years and weighing 7 kg and above. The patients enrolled in Study UNIVERSE were only 2 to 8 years old with a body weight range of 9.8 kg to 25.3 kg. The proposed dose for the body weight range 7 to <8 kg (1.1 mg BID) was not clinically tested in UNIVERSE study.

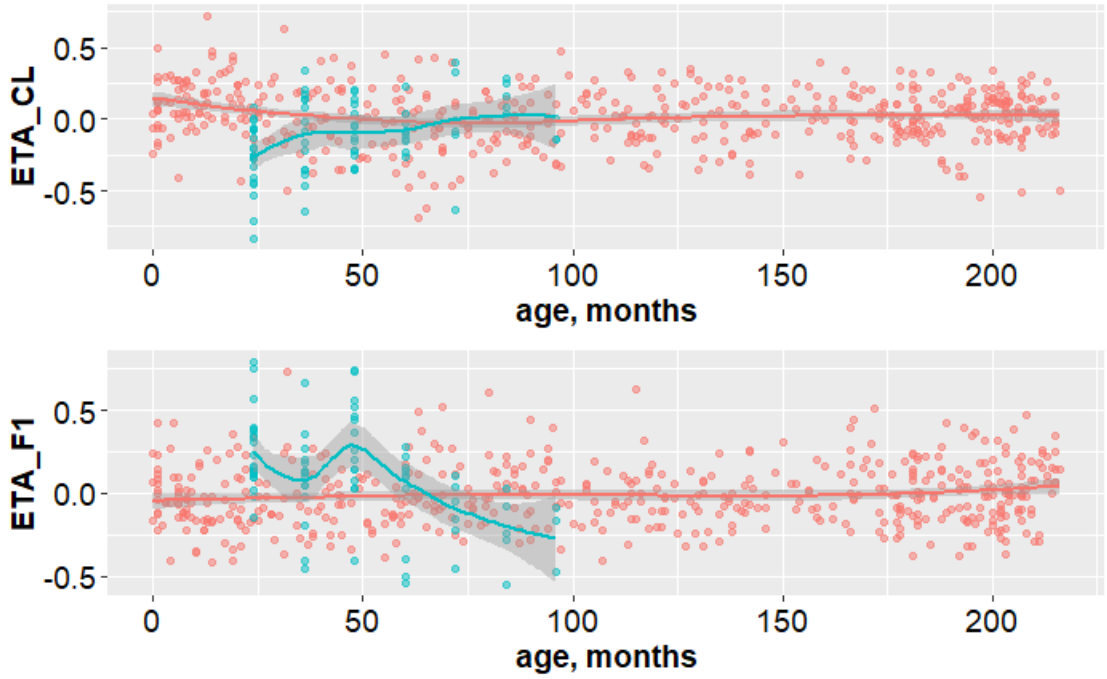
The Applicant did not provide supporting analyses or rationales for the dosing regimen for post-Fontan patients weighing 7 to <8 kg, noting limitations of the current PopPK analysis and PBPK analysis. The Applicant noted that the proposal for the daily dose of 2.2 mg (1.1 mg BID) for post-Fontan patients weighing 7 to <8 kg originated from the post-Fontan PBPK model. However, the current post-Fontan PBPK model is not considered qualified to predict exposure in patients weighing 7 to <8 kg as the retrospective qualification of this PBPK model using the PK data observed in the UNIVERSE study revealed a tendency towards underestimation of the rivaroxaban exposure in post-Fontan patients 2 to <5 years of age by this PBPK model. The Applicant also noted that the UNIVERSE PopPK study is limited to be used for simulations for the weight range below 9.8 kg.

Reviewer's Assessment:

The limitations of the UNIVERSE PopPK analysis negate the use of this model in any extrapolation. An optimal strategy could be developing an integrated PopPK model based on the combined data from post-Fontan patients and VTE patients, so that the PK of post-Fontan patients can be characterized as a covariate in context of the well characterized pediatric PK model (i.e., EINSTEIN Jr. PopPK model). However, the reviewer recognized challenges to conduct such analysis, due to the difficulty in

characterizing covariate effect of post-Fontan patients with a typical covariate analysis for a categorical covariate (Fontan vs. non-Fontan patients). Particularly, the reviewer's sensitivity analysis (the combined model fit) showed that the effect of Fontan procedure on PK parameters do not appear to be uni-directional, rather the direction/magnitude of the effect appears to vary depending on age of post-Fontan patients (Figure 39).

Figure 39. Relationship between ETA for CL and F1 and age for PK parameters – EINSTEIN Jr. model fitted to the combined dataset



Source: Reviewer's figures. Generated based on the reviewer's sensitivity analysis of model fitting based on the pooled dataset combining EINSTEIN Jr. data and UNIVERSE data. Red dots represent EINSTEIN Jr PopPK data; Blue dots represents UNIVERSE PopPK data.

To adequately implement the observed covariate effect, an option could be applying the different covariate effect (directions) based on age group in the model. This adjustment may improve model fit in capturing the covariate effect of post-Fontan patients and the predictive performance for the "studied" population. However, this adjustment is not expected to overcome the limitation of the model to be used for extrapolation to the unstudied population (i.e., Fontan patients <9.8 kg). Without any physiologically plausible justification, the reviewer recognizes a uncertainty in extrapolating the model-forced covariate effect to the unstudied population. The Applicant provided analyses and discussion regarding the limitations of UNIVERSE PopPK analysis in the reports (R-13636, and PopPK for CHD3001) and the IR response (received on 10/15/2021), which is generally in line with the reviewer's assessment.

<u>Dosing regimen for post-Fontan patients aged 9 to 18 years</u>

The Applicant proposed the model-informed bridging to extrapolate the dose-exposure relationship of rivaroxaban to pediatric post-Fontan patients aged 9 to <18 years using PopPK modeling and simulations. Table below summarizes the proposed dosing regimen for thromboprophylaxis dose for

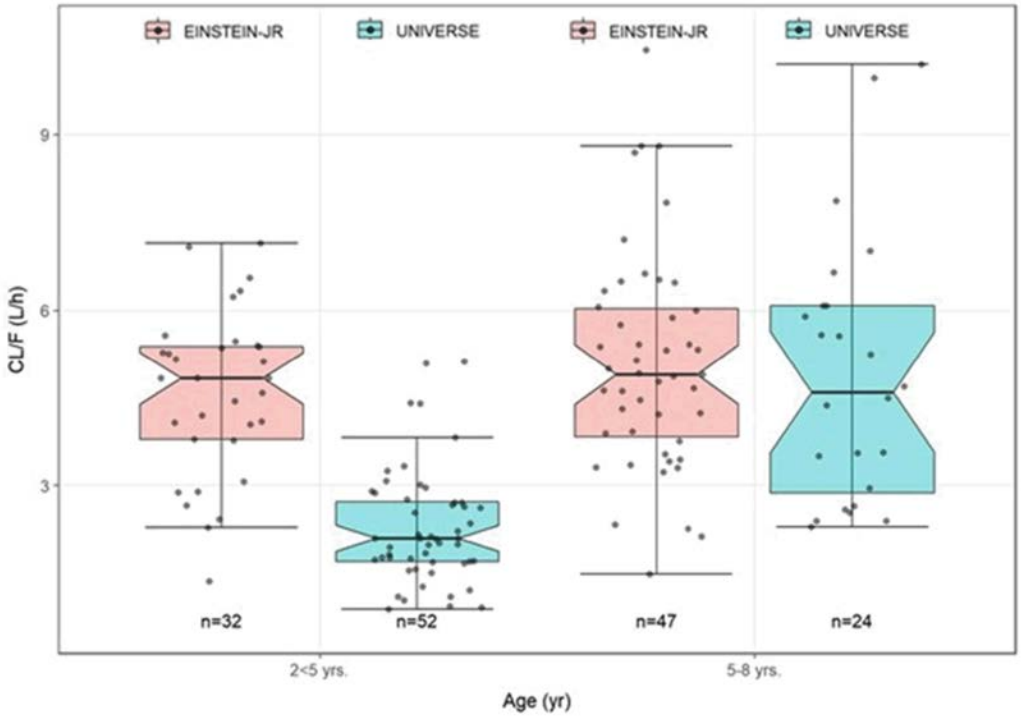
post-Fontan patients (right column) at a 10 mg QD-equivalent regimen. The proposed dosing regimen for prophylaxis for post-Fontan patients aged weighing 30 kg and above is a half of the VTE treatment dosing regimen for the same weight groups.

Body weight	EINSTEIN Jr doses (matching 20 mg once daily in adults)	Proposed Doses for Pediatric Post-Fontan Subjects (targeting 10 mg once daily in adults)
30 kg to <50 kg	15 mg once daily	7.5 mg once daily
≥50 kg	20 mg once daily[a]	10 mg once daily

[a] 15 mg in Japan

The Applicant considered the EINSTEIN Jr PopPK model adequate to simulate rivaroxaban exposures to support the proposed prophylaxis dosing regimen in pediatric post-Fontan patients ≥30 kg. In comparison of the PK parameters obtained using the UNIVERSE PopPK and the EINSTEIN Jr PopPK models (Figure 40), rivaroxaban exposure in post-Fontan patients aged ≥5 years can be described by the EINSTEIN Jr PopPK model as the oral clearance (CL/F) and, thus, $AUC_{24h,ss}$ were similar for UNIVERSE and EINSTEIN Jr patients between 5 and 8 years of age. However, for UNIVERSE patients aged 2 to <5 years, the median CL/F was 56.7% lower compared to EINSTEIN Jr patients (2.09 vs. 4.83 L/h), which can be partly attributed to the lower doses, on average, and, thus, higher oral BA (F1) in UNIVERSE patients receiving a 10 mg QD-equivalent dose compared to EINSTEIN Jr patients receiving 20 mg QD-equivalent dose. When the difference in F1 due to the lower doses in UNIVERSE compared to EINSTEIN Jr is factored in, median CL of UNIVERSE patients between 2 and 5 years of age was reduced by approximately 28.4% compared to EINSTEIN Jr patients (2.52 vs. 3.51 L/h).

Figure 40. Comparison of apparent CL (CL/F) between UNIVERSE patients and EINSTEIN Jr. patients by age groups

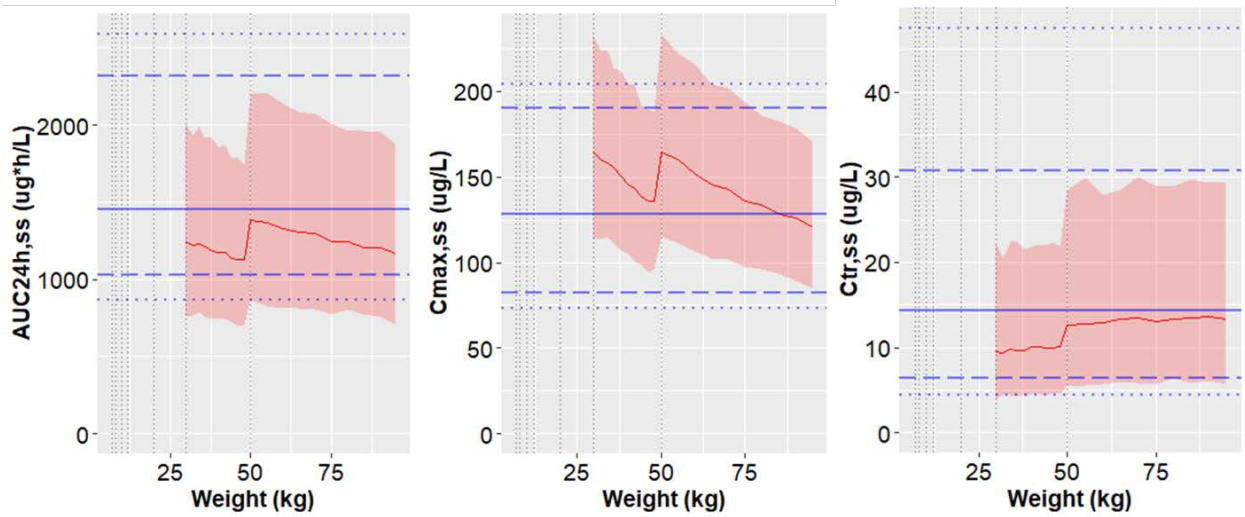


Source: Applicant's Summary of Clinical Pharmacology Studies-CHD3001, Figure 23, page 35.

Reviewer's Assessment:

Given the similar estimates for apparent clearance (CL/F) between post-Fontan patients and VTE patients aged 5 to 8 years old, the use of EINSTEIN Jr model to project rivaroxaban exposures for the dose extrapolation for patients ages 9 to 18 years appears to be a reasonable approach. The reviewer conducted confirmatory simulations to project the exposures to assess the proposed dosing regimen for post-Fontan patients aged 9 to 18 years (body weight ranging 30 to <120 kg) using EINSTEIN Jr. PopPK model and was able to obtain the similar results as those performed by the Applicant (Figure 41). The summary of the Applicant's simulated rivaroxaban exposures is presented in the main section of review and is discussed in detail to discuss the Applicant's proposed dosing regimen for post-Fontan patients weighing ≥30 kg (See Section 3.3.2).

Figure 41. Reviewer's simulations of exposures for post-Fontan patients weighing ≥30 kg using EINSTEIN Jr PopPK model at the proposed prophylaxis dose regimen



Source: Reviewer's analysis. Red lines represent the median values for simulated exposures. Red ribbon represents 5th - 95th percentiles of the simulated exposures. Blue lines represent the adult reference exposures ranges (5th, 10th, 50th, 90th, 95th) from adult VTE prevention program.

4.3.2 Population PK-PD analysis

4.3.2.1 Applicant's Exploratory PK-PD analysis for VTE treatment program

Data: A total of 1828 PT observations and 1776 aPTT measurements were included in the analysis from 510 and 507 patients, respectively. These patients were from studies 12892, 14372, 14373, 14374, 17992, 17618, and preliminary data of the first part of the UNIVERSE study. After initial evaluation of the PD models on data from the PT and aPTT dataset, observations with |CWRES|>3 were identified as potential outliers. These observations were excluded from the analysis if deemed necessary after assessing their influence on the overall modeling results. This was done by running the same model on two different datasets, namely: 1) a dataset containing all data including the outliers and 2) a dataset in which the potential outliers were excluded.

Prothrombin time (PT)

The relationship between measured PT and observed rivaroxaban concentrations (Figure 42) was described by a modulated power model (Eq.4), where PD is a PT value (in sec), BSL is a baseline PT (in sec), SLP is a slope parameter, CP (µg/L) is the measured rivaroxaban concentration, and FAC is a model parameter (L/ug). The term EXP approaches 1 for small rivaroxaban concentrations, and <1 for large concentrations depending on the model parameter FAC. The exclusion of potential outliers (observations with |CWRES|>3) did not have a large impact on the model fit based on the GOF plots and were therefore kept in the analysis.

$$PD = BSL + SLP \cdot CP^{\mathrm{EXP}} \; where \; EXP = 1 - FAC \cdot CP \quad \text{(Eq. 4)}$$

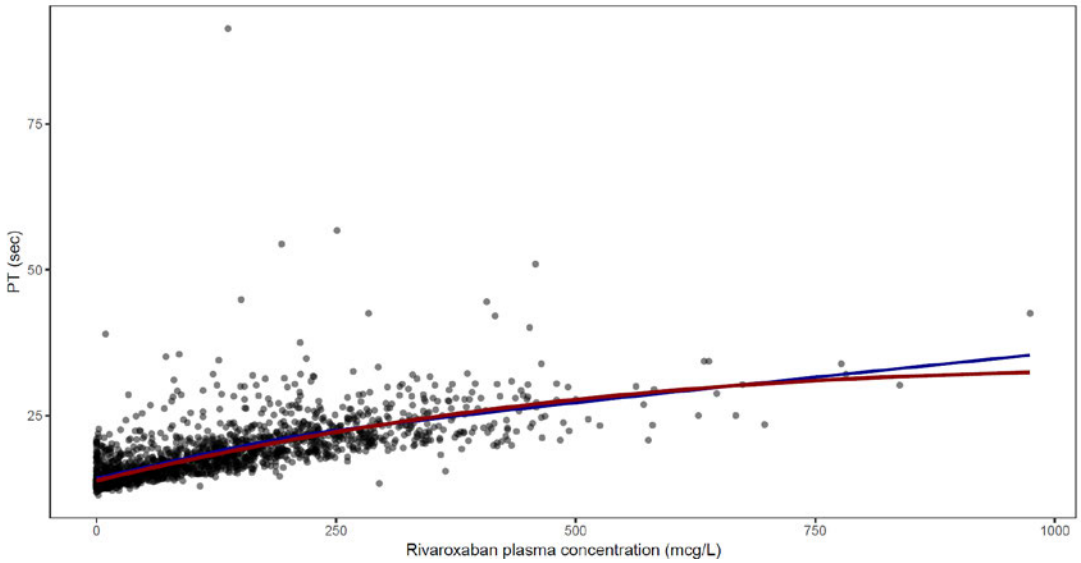
Final parameter estimates for this model are presented in Table 24. GOF plots and pcVPC are provided in Figure 43 and Figure 44, respectively. IIV was included for both BSL and SLP. There were no correlations between ETAs for baseline and slope and age. A proportional residual error model was used. All parameters were estimated with precision of CV <21%. The ETA shrinkage was 21.5% for the baseline and 20.2% for the slope. The ETA-shrinkage for the residual error was 19.2%.

Table 24. Parameter estimates with the final PK-PT model (VTE treatment program)

Parameter	Unit	Value[a]	SE[b]	CV (%)[c]	LLCI[d]	ULCI[e]
		Fixed effects				
BSL (PT baseline)	sec	13.9	0.0815	0.587	13.7	14.0
SLP (slope)	sec/μg · L	0.0384	0.00126	3.28	0.0360	0.0409
FAC parameter from Equation (6.2-20))	L/μg	0.000105	0.0000183	17.5	0.0000690	0.000141
		Random effects: Inter-individual variability				
ω^2_{BSL} $(exponential)$		0.0108 (10.4%)[f]	0.00188	17.3	0.00717	0.0145
ω^2_{SLP} $(exponential)$		0.163 (42.1%)[f]	0.0330	20.3	0.0980	0.227
		Random effects: residual error				
σ^2 $(proportional)$		0.00711 (8.43%)[g]	0.000858	12.1	0.00542	0.00879

Source: Applicant's Report 18376. Table 7.2:6, page 43.

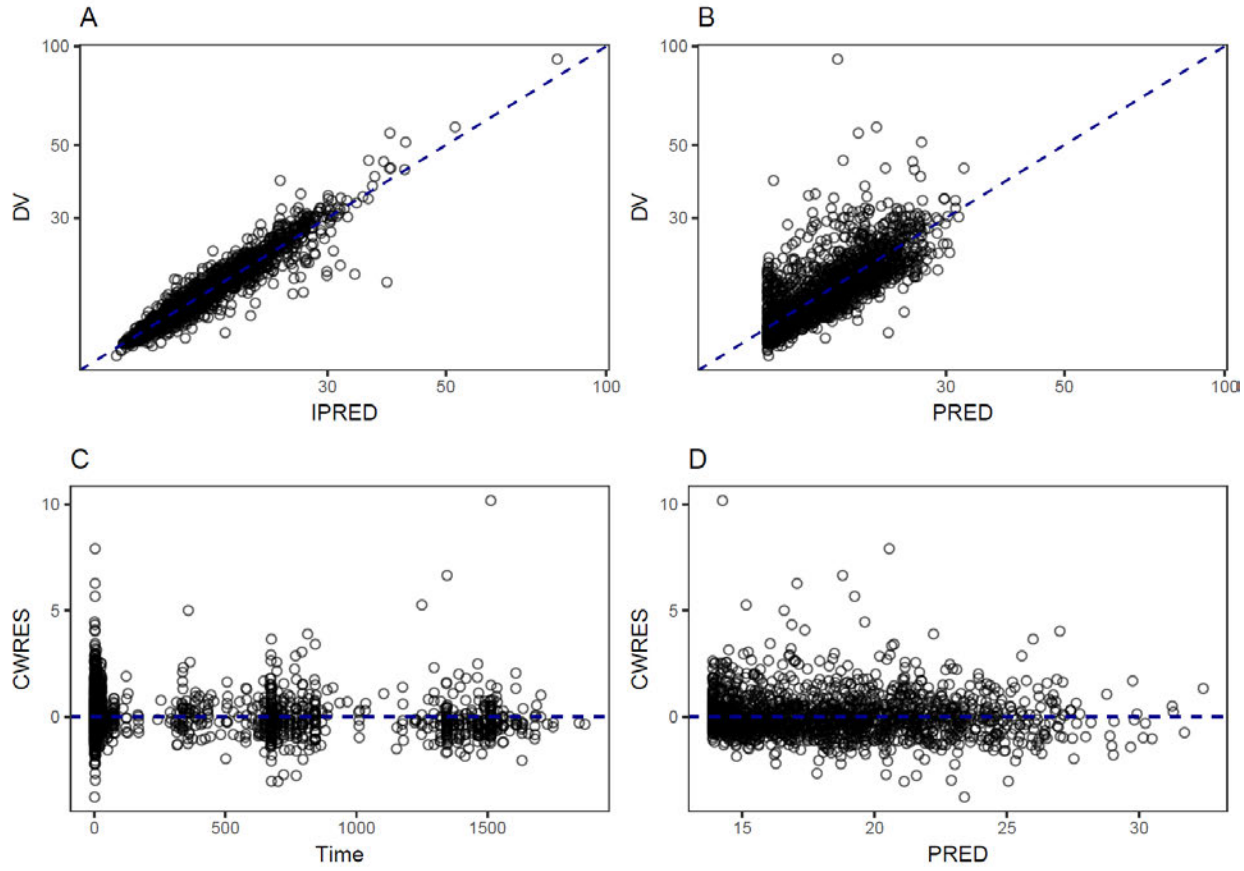
Figure 42. Relationship between PT and rivaroxaban concentrations predicted by the modulated power model (VTE treatment program)



Source: Applicant's Report 18376. Table 7.2:4, page 42.

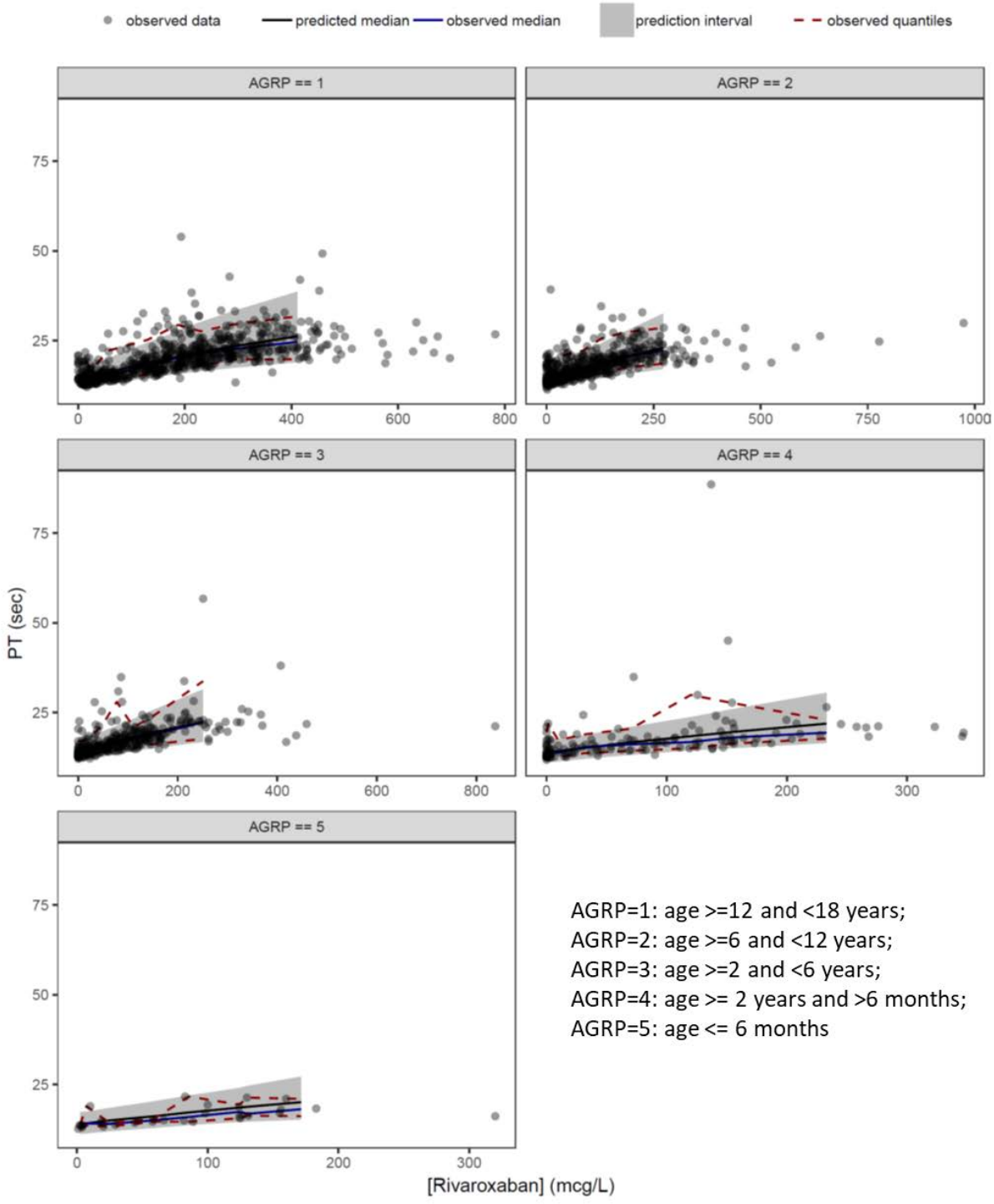
Scatter: observations; Red solid line: population predictions; Blue solid line: spline through data

Figure 43. GOF plots for the final PK-PT model



Source: Applicant's Report 18376. Figure 7.2:5, page 43.

Figure 44. pcVPC of final PK-PT model stratified by age group (VTE treatment program)



Source: Applicant's Report 18376. Figure 11.2:45, page 43.

Activated partial thromboplastin time (aPTT)

The initial evaluation based on all aPTT data showed the best description of data with the power model without a flattening of the PD effect with increasing rivaroxaban concentrations. When excluding 24

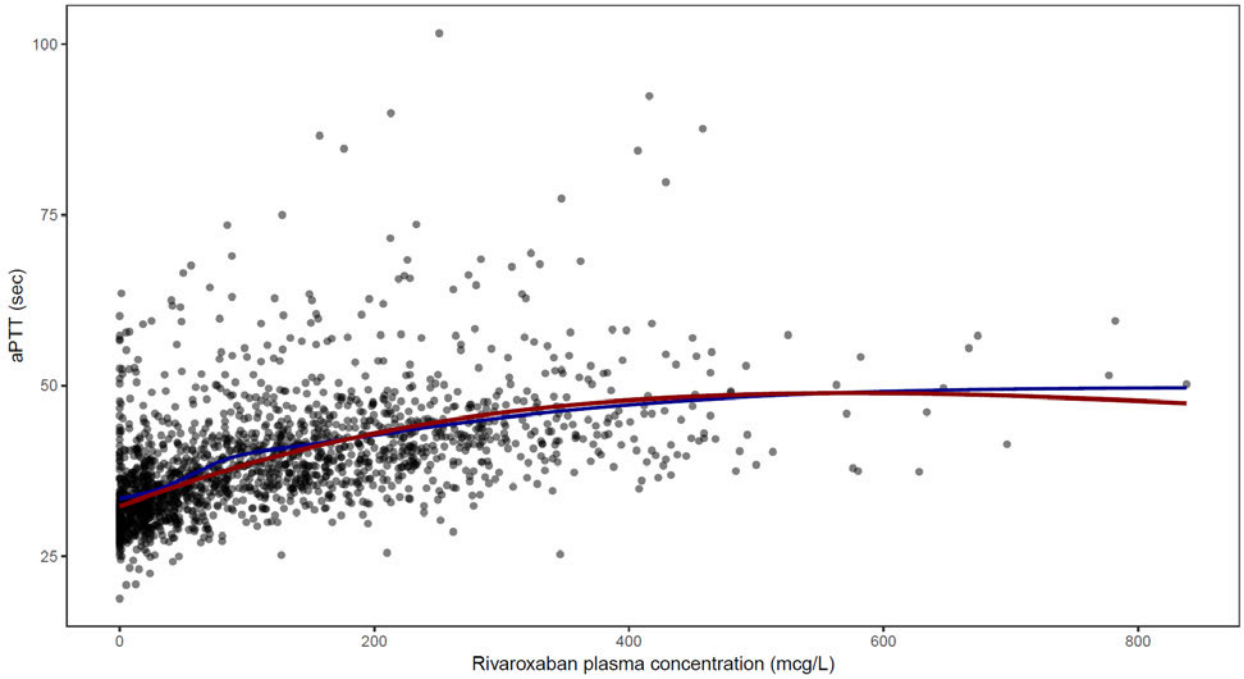
observations (~ 1% of all data) with |CWRES|>3 observed in the aPTT data, the Applicant noted that fitting with a modulated power model resulted in improvement of the model fit as indicated by the GOF plots.. Hence, a modulated power model (Eq.4) was chosen as the final model to describe the relationship between aPTT and measured rivaroxaban concentrations: PD is an aPTT value (in sec), BSL is a baseline aPTT (in sec), SLP is a slope parameter, CP (µg/L) is the measured rivaroxaban concentration, and FAC is a model parameter (L/ug) for exponent for the modulated power model. The parameter estimates for the final PK-aPTT model are presented in Table 25. The GOF plots by all data and pcVPC plots stratified by age group are presented in Figure 46 and Figure 47.

Table 25.Parameter estimates with the final PK-aPTT model (VTE treatment program)

Parameter	Unit	Value[a]	SE[b]	CV (%)[c]	LLCI[d]	ULCI[e]
			Fixed effects			
BSL (aPTT baseline)	sec	32.3	0.244	0.753	31.9	32.8
SLP (slope)	sec/$\mu g \cdot L$	0.0685	0.00294	4.30	0.0627	0.0742
FAC parameter from Equation (6.2-20))	L/μg	0.000237	0.0000228	9.62	0.000192	0.000281
			Random effects: Inter-individual variability			
$\omega^2_{BSL}\ (exponential)$		0.0193 (14.0%)[f]	0.00258	13.4	0.0143	0.0244
$\omega^2_{SLP}\ (exponential)$		0.189 (45.6%)[f]	0.0292	15.4	0.132	0.246
			Random effects: residual error			
$\sigma^2\ (proportional)$		0.00692 (8.32%)[g]	0.000524	7.56	0.00590	0.00795

Source: Applicant's Report 18376. Table 7.2:8, page 46.

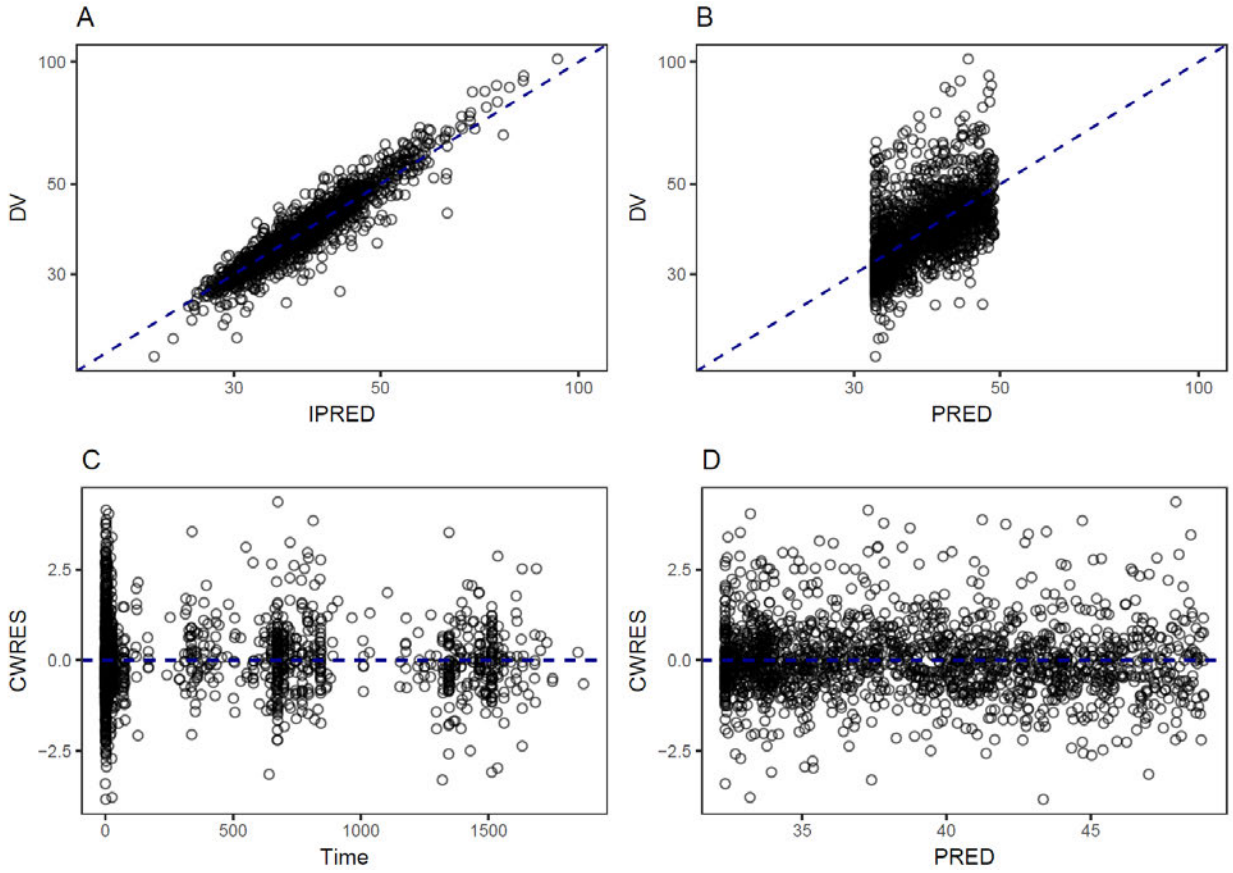
Figure 45. Relationship between aPTT and measured plasma concentrations of rivaroxaban with the final model (VTE treatment program)



Source: Applicant's Report 18376. Figure 7.2:6, page 45.

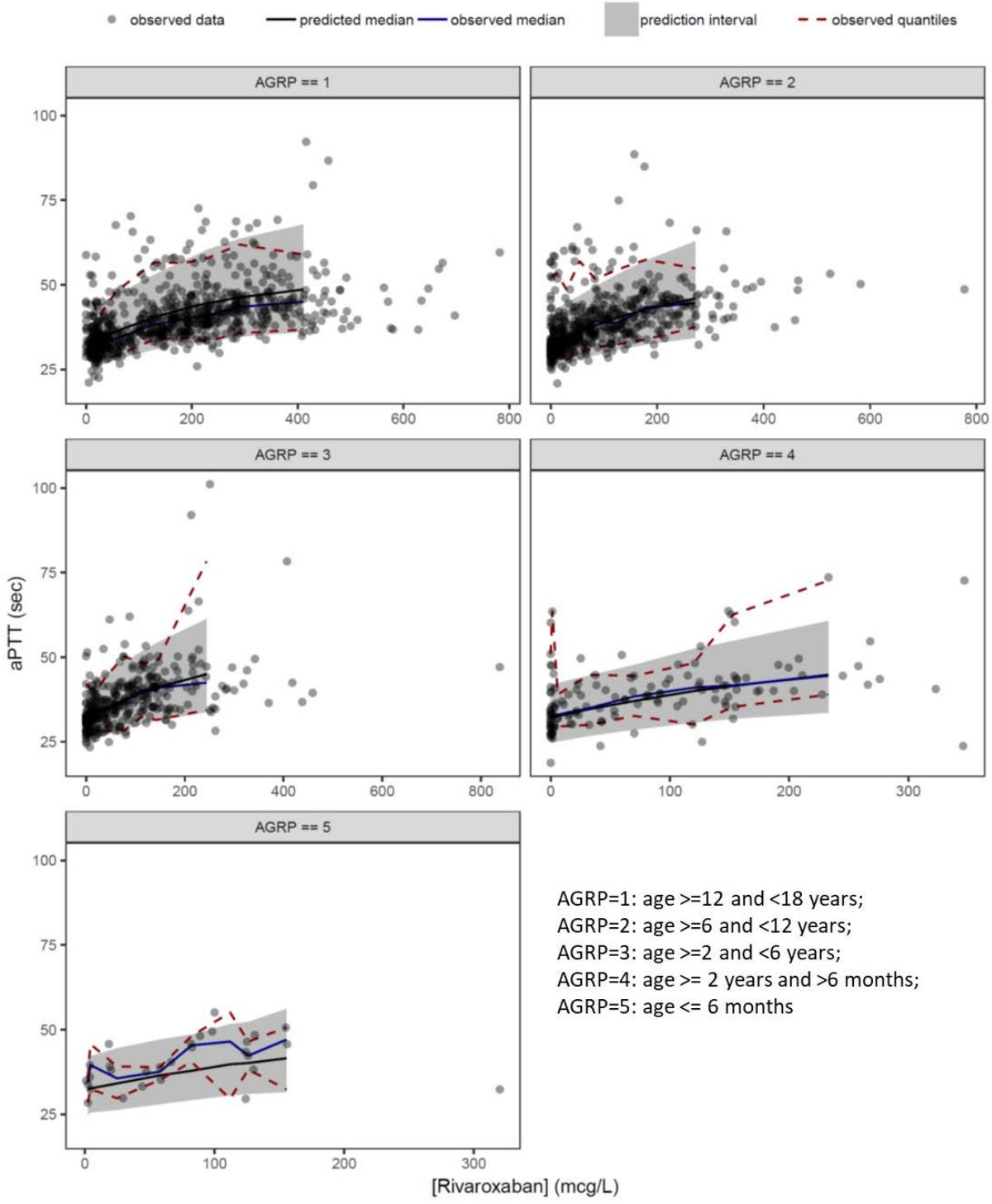
Scatter: observations; Red solid line: population predictions; Blue solid line: spline through data

Figure 46. GOF plots for the final PK-aPPT model (VTE treatment program)



Source: Applicant's Report 18376. Figure 7.2:7, page 46.

Figure 47. pcVPC of final PK-aPTT model stratified by age group (VTE treatment program)



Source: Applicant's Report 18376. Figure 11.2:53, page 146.

4.3.2.2 Applicant's PK-PD analysis for thromboprophylaxis program for Fontan-patients

Prothrombin time (PT)

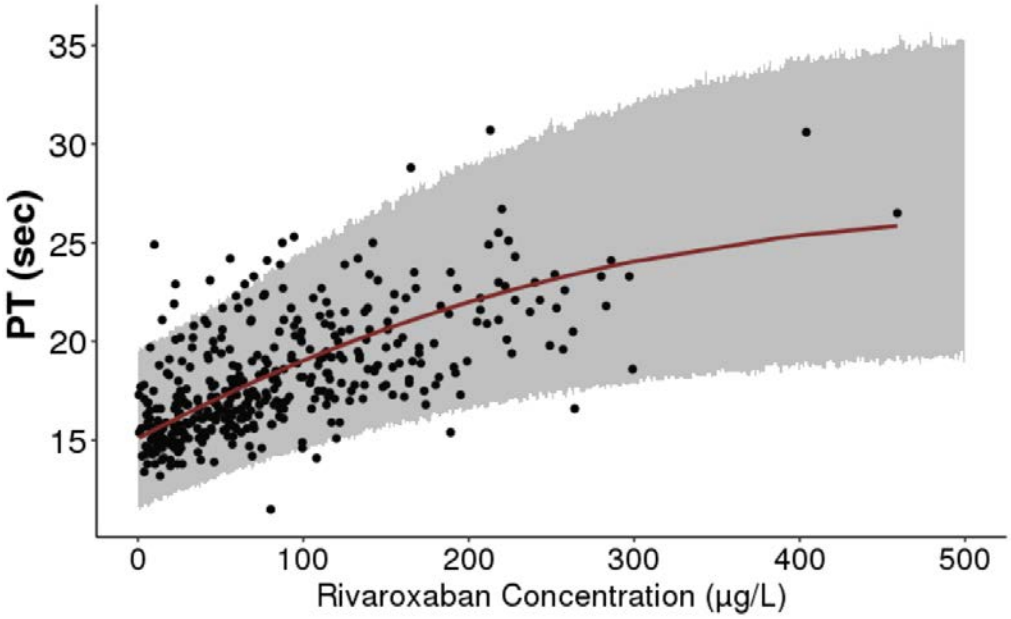
The relationship between observed rivaroxaban concentrations and PT was described by the modulated power model (Table 26). Model predicted PK-PT relationship is presented overlaid with the observed data in Figure 48. The parameter estimates for the rivaroxaban concentration and PT model in the UNIVERSE study were similar to the parameters estimated in the adult reference in Study 10944 (also referred to as ODIXa-HIP2) and 10945 (also referred to as ODIXa-KNEE) with BSL=13.0 sec, SLOP=0.0401 sec/µg·L, and FAC= 0.000153 L/µg.

Table 26. Parameter estimates with a modulated power PK-PT model (UNIVERSE Study)

Parameter	Unit	Estimate	RSE (%)
BSL	sec	15.1	1.59
SLOP	sec/µg·L	0.0435	10.4
FAC	L/µg	0.00022	37.4
ω^2BSL (random effect)		0.00803	29.8
ω^2SLP (random effect)		0.0597	48.2
Sigma (residual error^2)		0.00876	15.7

Source: Applicant's report PopPK-CHD3001, Table 7, page 35.

Figure 48. PK-PT relationship predicted by the modulated power model (UNIVERSE study)



Source: Adapted from Applicant's report PopPK-CHD3001, Figure 6, page 34.
Black dots: observed data; Brown solid line in bottom plot: model predicted population median; Gray shaded area in bottom plot: model predicted 90% CI.

Activated partial thromboplastin time (aPTT)

The relationship between observed rivaroxaban concentrations and aPTT was described by the modulated power model (Table 27). Model predicted PK-aPTT relationship is presented overlaid with the observed data in Figure 49. The parameter estimates for the rivaroxaban concentration and aPTT model in the UNIVERSE study showed a shallower relationship with rivaroxaban concentration

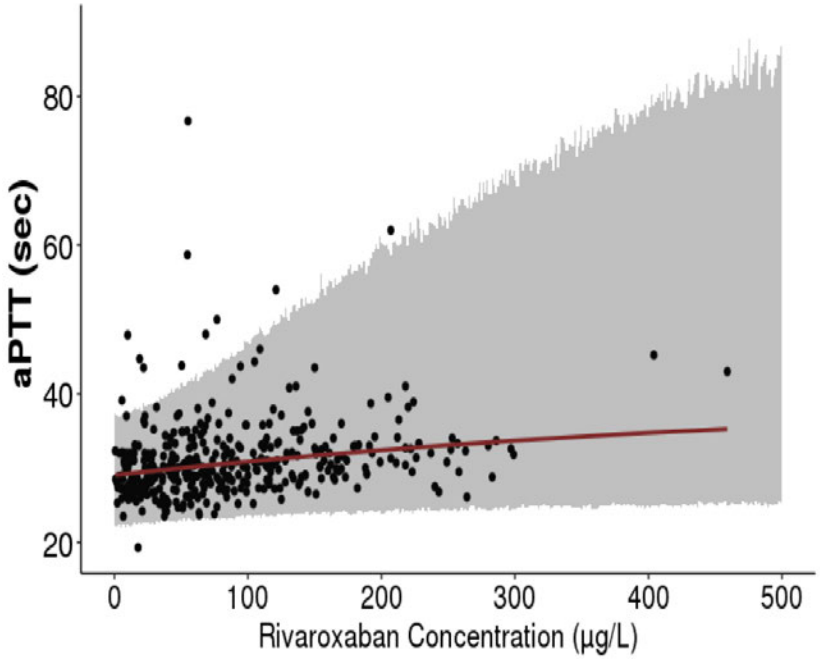
than what was observed in the adult reference in Study 10944 and 10945 (BSL=50.5 sec, SLOP=0.137 sec/µg·L and FAC=0.000276 L/µg) or the EINSTEIN Jr program: (BSL=32.3 sec, SLOP=0.0685 sec/µg·L and FAC=0.000237 L/µg). The Applicant noted that this may be due to the low sensitivity of aPTT assays and its known large variability between studies due to sensitivity to reagents and experimental condition.

Table 27. Parameters estimated with modulated power PK-aPTT model (UNIVERSE Study)

Parameter	Unit	Estimate	RSE%
BSL	sec	29.1	1.81
SLOP	sec/µg·L	0.0190	35.9
FAC	L/µg	0.000122	107
ω^2BSL (random effect)		0.00493	36.6
ω^2SLP (random effect)		1.22	40.6
Sigma (residual error^2)		0.0115	19.1

Key: BSL = baseline; FAC = coefficient; RSE = relative standard error; SLOP = slope.
Source: Applicant's report PopPK-CHD3001, Table 8, page 37.

Figure 49. PK-aPTT relationship predicted by the modulated power model (UNIVERSE study)



Source: Adapted from Applicant's report PopPK-CHD3001, Figure 7, page 36.
Black dots: observed data; Brown solid line in bottom plot: model predicted population median; Gray shaded area in bottom plot: model predicted 90% CI.

Reviewer's note: The submitted population PK-PD models are considered exploratory and descriptive and briefly summarized in this section. Comparisons of PK-PD relationships between pediatric and adult patients to support efficacy extrapolation are further discussed based on visual inspection (Section 3.3.1). No formal statistical comparison was conducted.

4.4 Physiologically based Pharmacokinetic Analysis

The objective of this review is providing an overview of the application of physiologically based pharmacokinetic (PBPK) analysis to support the pediatric program of rivaroxaban.

Background

The Applicant seeks approval of XARELTO® (rivaroxaban) for two pediatric indications: (1) treatment of venous thromboembolism (VTE) and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years and (2) thromboprophylaxis in pediatric patients aged 2 years and older with congenital heart disease (CHD) who had the Fontan procedure.

The overall objective of the clinical pharmacology program was to identify body weight-adjusted rivaroxaban dosage for children that would yield the target adult exposure. For the VTE indication, the rivaroxaban dosage in adults corresponding to targeted exposure was 20 mg once daily (Table 28); for the CHD thromboprophylaxis indication, the dosage in adults was 10 mg once daily (Table 29).

Table 28. Proposed Dosage in Pediatric Patients Birth to less than 18 Years for Treatment of VTE

Dosage Form	Body weight	Dosage			Total daily dose‡
		Once a day	2 times a day	3 times a day	
Oral Suspension (1 mg XARELTO = 1 mL suspension)	2.6 to <3 kg			0.8 mg	2.4 mg
	3 to <4 kg			0.9 mg	2.7 mg
	4 to <5 kg			1.4 mg	4.2 mg
	5 to <7 kg			1.6 mg	4.8 mg
	7 to <8 kg			1.8 mg	5.4 mg
	8 to <9 kg			2.4 mg	7.2 mg
	9 to <10 kg			2.8 mg	8.4 mg
	10 to <12 kg			3.0 mg	9 mg
	12 to <30 kg		5 mg		10 mg
Oral Suspension or Tablets	30 to <50 kg	15 mg			15 mg
	≥50 kg	20 mg			20 mg

†Patients <6 months of age should meet the following criteria: at birth were at least 37 weeks of gestation, have had at least 10 days of oral feeding, and weigh ≥2.6 kg at the time of dosing. ‡ All doses should be taken with food.

Table 29. Proposed Dosage for Thromboprophylaxis in Pediatric Patients with CHD

Dosage Form	Body weight	Dosage		Total daily dose*
Oral Suspension (1 mg XARELTO = 1 mL suspension)	7 to <8 kg		1.1 mg BID	2.2 mg
	8 to <10 kg		1.6 mg BID	3.2 mg
	10 to <12 kg		1.7 mg BID	3.4 mg
	12 to <20 kg		2.0 mg BID	4.0 mg
	20 to <30 kg		2.5 mg BID	5.0 mg
	30 to <50 kg	7.5 mg QD		7.5 mg
Oral Suspension or Tablets	≥50 kg	10 mg QD		10 mg

*Patients ≥2 years. All doses can be taken with or without food

The clinical pharmacology of rivaroxaban has been established in adults [NDA 202439 supplemental S-0125, NDA 022406 supplemental S-0088]. Briefly, the absolute bioavailability of rivaroxaban tablets is

dose dependent. For the 2.5 mg and 10 mg dose, it is estimated to be 80% to 100%, and not affected by food. For the 20 mg dose, the absolute bioavailability was approximately 66%, in the fasted state, while coadministration in the fed state increased its bioavailability (mean AUC and C_{max} increased by 39% and 76% respectively). XARELTO 2.5 mg and 10 mg tablets can be taken with or without food, while 15 mg and 20 mg tablets should be taken with food. Rivaroxaban is mainly metabolized by CYP3A4/5 and CYP2J2, and hydrolysis. Unchanged rivaroxaban was the predominant moiety in plasma with no major or active circulating metabolites. Unchanged drug was excreted into urine (36%), mainly via active tubular secretion and to a lesser extent via glomerular filtration (approximate 5:1 ratio). Rivaroxaban is a substrate of the efflux transporter P-gp and BCRP. Rivaroxaban clearance was around 10 L/h in healthy volunteers following intravenous administration. The terminal elimination half-life was 5 to 9 hours. Protein binding of rivaroxaban in human plasma was approximately 92% to 95%.

XARELTO film-coated, immediate-release (IR) tablets for oral administration in dose strengths of 2.5, 10, 15, and 20 mg are approved and marketed in several adult indications. In the pediatric development program, rivaroxaban was administered as tablets in dose strengths of 5, 7.5, 10, 15, and 20 mg or as an age-appropriate liquid formulation for oral use. XARELTO granules-for- oral-suspension will be a new market presentation, with 1 mg of rivaroxaban per mL, after reconstitution. This formulation was characterized in 6 phase 1 studies in healthy adults. The results of these studies demonstrated that the granules-for-oral-suspension formulation was similar to the marketed IR tablet formulation in terms of the rate and extent of absorption at a 10 mg dose in fasted state as well as at a 20 mg dose in fed state [Summary of Biopharmaceutic Studies-EINSTEIN Jr]. In pediatrics, the rate and extent of absorption were similar between the marketed IR tablet and granules-for-oral-suspension, based on population PK analysis of sparse sampling of children from birth to <18 years [M&S Study 18376, Report R-12947].

PBPK Analysis in the VTE Indication Program

To support the VTE pediatric indication six clinical studies, namely phase 1 studies 12892 and 17992, phase 1/2 study 17618, phase 2 studies 14373 and 14374, and phase 3 study 14372, were conducted in the EINSTEIN Jr program. Children were enrolled following an age-staggered, stepwise approach, starting with adolescents to term neonates. PBPK and population PK (PPK) analyses were applied throughout the EINSTEIN Jr program to identify body weight-adjusted dosage in pediatric population that would yield similar exposures as in adults with deep vein thrombosis (DVT) who were treated with rivaroxaban 20 mg QD.

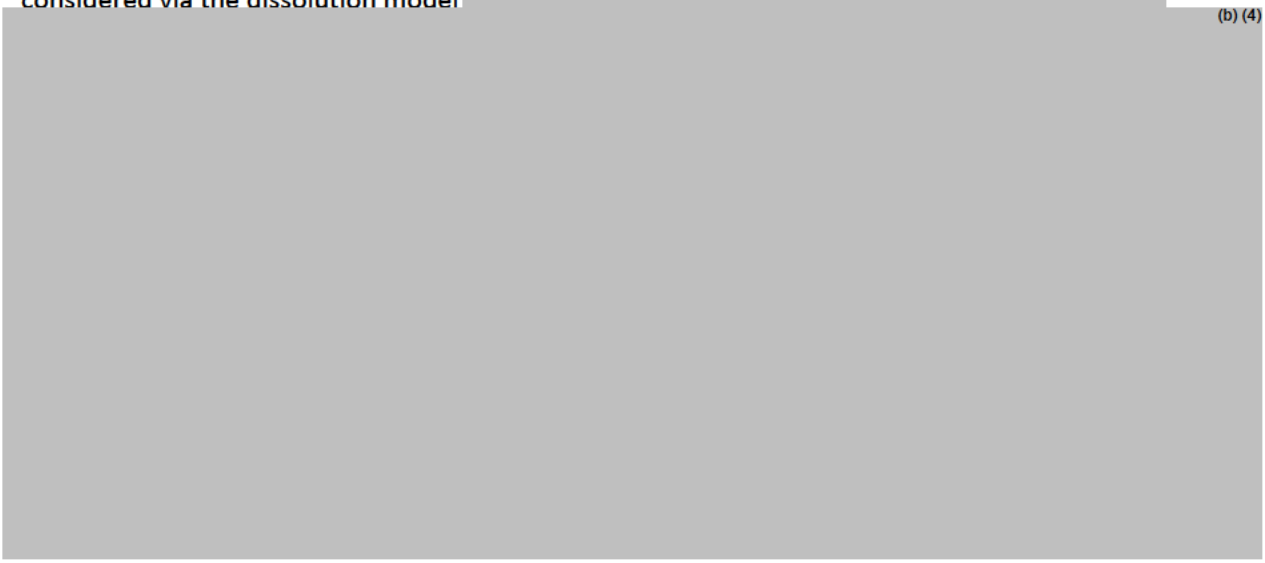
Rivaroxaban PBPK Model Development and Validation:

The PBPK model development process followed a generic workflow beginning with validation of the PBPK model of rivaroxaban in adults (M&S Study 13148, Report PH-35614 and M&S Study 15802, Report PH-37113).

The adult PBPK model of rivaroxaban for oral administration was parameterized considering the fractional contributions of renal glomerular filtration (6%), renal tubular secretion (30%), hepatic CYP3A4 (18%) and CYP2J2 (14%) metabolism, hydrolysis (14%), fecal excretion (7%), and unaccounted (11%) to the total clearance of rivaroxaban, based on mass balance, absolute bioavailability, and in vitro

data. For IV administration, fecal excretion was disregarded, and all other processes were proportionally re-adjusted to 100%. The unaccounted part was assumed to be due to hepatic clearance processes and proportionally re-distributed across the three hepatic processes.

A compartmental GI tract model [Thelen K et al 2011 and Thelen K et al 2012] was used to describe rivaroxaban absorption. The dissolution behavior of rivaroxaban immediate release formulation was considered via the dissolution model (b) (4)



The adequacy of the model to predict rivaroxaban exposure in adult population was assessed by comparing predicted PK to corresponding observed data after intravenous (IV 1 mg [Study 11273]) and oral administration (IR tablets 10 and 20 mg fasted and fed states [Studies 10846 /10989, 11937/11938]; and oral suspension 10 and 20 mg fasted state and 20 mg fed state [Study 14022]) (Figure 50).

Additional comments: The adequacy of the fractional clearance contributions of rivaroxaban implemented in the model was partially validated by comparing predicted and observed increases of rivaroxaban exposure when co-administered with CYP3A4 and P-gp inhibitors (ketoconazole, ritonavir and clarithromycin). The predicted increases in AUC and Cmax values were comparable to the corresponding clinical drug interaction data, although the predicted increase in Cmax was mostly underestimated [Willmann et al 2021]. It was acknowledged that the main source of information for parameterizing the hepatic and renal contributions was the human ADME study (n=4 healthy subjects, single dose, total recovery of radioactivity of 93.7%) and in vitro data. A parameter sensitivity analysis showed that, in general, parameters that are related to rivaroxaban elimination are among the most sensitive model parameters affecting AUC and Cmax predictions. However, as most sensitive clearance-related parameters, the volumes of liver and kidney and their fractional contributions of cells, vascular, and interstitial space, as well as kidney blood flow were identified; but not the fractional contributions of hepatic or renal processes to the total rivaroxaban clearance [Willmann et al 2021].

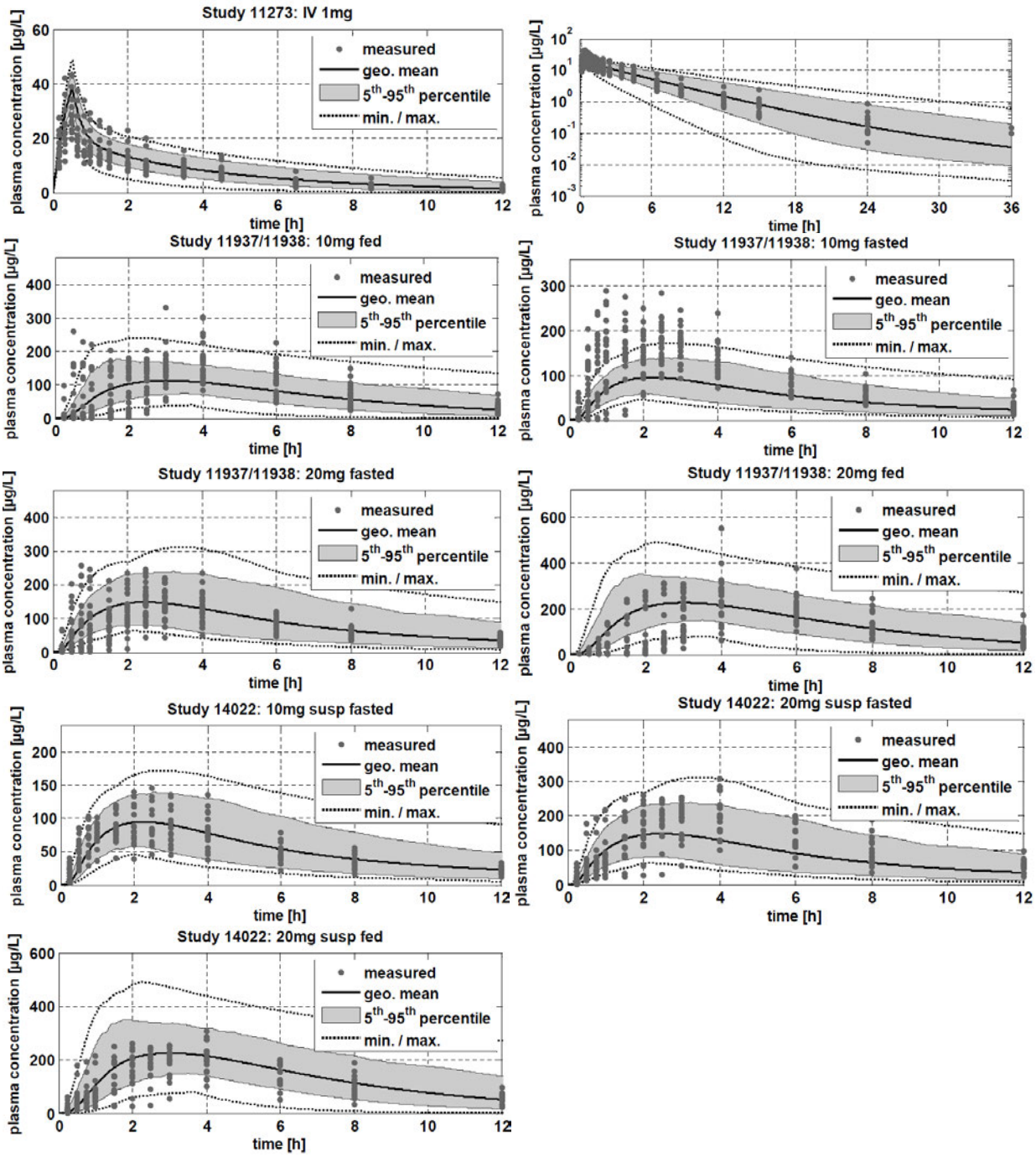


Figure 50. Comparison of observed vs PBPK predicted plasma concentration-time profiles of rivaroxaban in adults.

Solid black line: geomean of predicted PK using the adult PBPK model; shaded grey area: 5th-95th percentile of predicted values. Circles: individual observed data following a 30 min IV infusion of 1 mg in healthy adults; 10 mg or 20 mg IR oral tablet under fasted and fed states; 10 mg or 20 mg oral suspension under fasted state; 20 mg oral suspension under fed state. (Source: Report PH-37113, Figures 12-2, and 12-7 to 12-17).

Rivaroxaban Pediatric PBPK Model Development:

The pediatric PBPK model of rivaroxaban [Willmann et al 2014] was developed (in PK-Sim Version 4.2) by considering prior knowledge about age-dependent changes in anthropometric (height, weight),

physiology (e.g., blood flow rates, organ volumes, binding protein concentrations, hematocrit, cardiac output) [Edginton et al 2006], and relevant clearance processes. Notably, the ontogeny of human serum albumin concentration in plasma was used to scale the unbound fraction of rivaroxaban in children [Edginton et al 2006]. The clearance pathways, as defined and quantified in the adult PBPK model, were scaled by age with the ontogenies being process specific. In brief, CYP3A activity in term neonates was 20% of adult activity, climbed to 130% of adult activity by the age of 1 and reached adult activity by the age of 4 [Edginton et al 2006]. The activity of CYP2J2 was assumed to be at 100% of adult activity for all ages. The hydrolysis, mediated via unknown enzymes, was scaled to children only physiologically (i.e., same activity per gram tissue weight as in adults). This considered the effects of growth but not maturity. The glomerular filtration was scaled by age based on adaptation from the maturation process model of Rhodin et al (2009). The net tubular secretion of rivaroxaban was assumed to be mediated by P-glycoprotein. The ontogeny of this transporter has not been explicitly studied in humans. Available digoxin renal clearance in neonates to 18 years was used as a surrogate to quantify P-gp ontogeny in the kidney. The adult activity for net secretion via P-gp was reached around 6 months of age.

For the absorption parameters, age dependent differences in intestinal surface area and large intestinal transit time (scaling factor of (b) (4) across all sections of the GI tract for the ages of 0 to 7 years) were considered in the pediatric model. Intestinal permeability and small intestinal transit times were not implemented as age-dependent parameter, based on prior literature data. The GET was considered similar between children and adults based on literature data. The GET functions under fasted and fed state conditions for adults were used for all age groups.

Rivaroxaban was orally administered to children as tablet or suspension formulations. (b) (4) the kinetics of rivaroxaban absorption was expected to be identical for both formulations. Thus, the PBPK model did not distinguish between tablet and oral suspension formulation [Report PH-38803].

For modeling purposes, rivaroxaban was assumed to be administered either in the fasted stated (with water) or fed stated after ingestion of an intermediate-to-high calorie meal. The fasted (half of virtual children population) and fed (half of virtual children population) states were simulated separately, and the results were then merged to represent the expected intermediate feeding state, or range of feeding states, of the children in the clinical setting.

Rivaroxaban Pediatric PBPK Model Application:

The pediatric PBPK model was used to predict rivaroxaban exposure in children following oral administration to guide the dosage for the first pediatric study. PBPK predictions were the starting points for the dosage (b) (4) initially proposed for the phase 1 study 12892. Simulations showed that (b) (4) doses (b) (4) would not achieve plasma exposure compared to the adult reference population. Thus, a

pediatric dosage considering both age and body weight was proposed (Table 30), as it yielded simulated plasma exposure for all age groups within the ranges of the adult reference populations. However, lower than the adult target exposures were expected particularly in children weighing < 30kg (Figure 51). Due to uncertainties in model predictions, a cautious dosing approach was employed in this first study in healthy children, permitting individual exposure values to be below the adult reference range and acknowledging that dosing optimization steps would be needed in later phases of the clinical development program [SCP Einstein Jr].

Table 30. Initial rivaroxaban proposed dosage scheme based on age, body weight and target exposure

Age group	Body weight [kg]		High dose group (20 mg equivalent)	Low dose group (10 mg equivalent)
	Min	Max	simulated doses	
≥6 months to <6 years	2	<3	0.8 mg	0.4 mg
	3	<4	1.2 mg	0.6 mg
	4	<5	1.8 mg	0.8 mg
	5	<6	2.2 mg	1.2 mg
	6	<7	2.8 mg	1.4 mg
	7	<8	3.2 mg	1.6 mg
	8	<9	3.8 mg	1.8 mg
	9	<10	4.2 mg	2.2 mg
	10	<12	4.8 mg	2.4 mg
	12	<14	5.0 mg	2.5 mg
6 to <18 years	14	<16	5 mg	2.5 mg
	16	<18	5 mg	2.5 mg
	18	<20	5 mg	2.5 mg
	20	<25	7.5 mg	3.75 mg
	25	<30	7.5 mg	3.75 mg
	30	<35	10 mg	5 mg
	35	<40	10 mg	5 mg
	40	<50	15 mg	7.5 mg
Pediatric subjects with a body weight comparable to adults	50	<60	20 mg	10 mg
	60	<70	20 mg	10 mg
	70	<80	20 mg	10 mg
	80	<90	20 mg	10 mg
	90	<100	20 mg	10 mg
	≥100		20 mg	10 mg

(Source: Report PH-37113, Table 5-1)

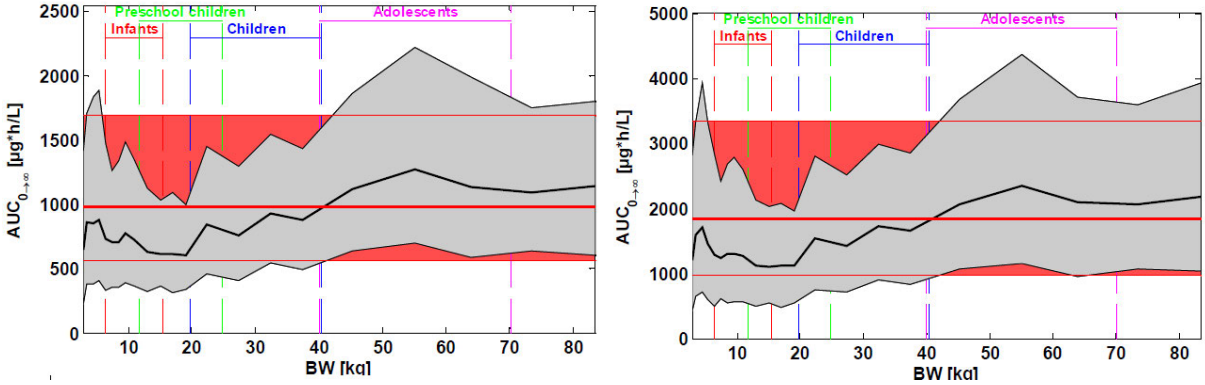


Figure 51. Body weight dependence of AUC predicted by the PBPK model for 10 mg-equivalent dose (left) and 20 mg-equivalent dose (right).

Black line: geomean in virtual pediatric population; shaded gray area: 5th-95th percentile of the predicted range. Red line: geomean in virtual healthy adult population dosed 10 mg or 20 mg; shaded red area: 90th percentile confidence interval first-in-man red dashed line: infants, green dashed line: preschool children, blue dashed line: children, purple dashed line: adolescents (Source: Report PH-37113, Figure 12-18 to 12-21).

As the first-in-children PK data become available from the single dose study 12892, an initial evaluation of the predictive performance of the pediatric PBPK model for rivaroxaban was conducted [M&S Study 18585, Report PH-38803]. In children aged 6 to <18 years, the observed PK profiles, for 10 mg- or 20 mg-

equivalent doses, were well contained in the expected range predicted by the model (Figure 52). Of note, besides the 90% prediction range (5th and 95th percentiles), an enlarged expected concentration range (0.5 and 1.5 times for 5th and 95th percentile, respectively) was introduced due to uncertainties in the estimation of some physiological parameters that may affect bioavailability and clearance since these parameters were not sufficiently described in the available literature. It was noted, however, for children aged 6 to <12 years receiving the undiluted suspension compared to the tablet tested in the same age cohort, maximum rivaroxaban plasma concentrations were reached at later time points and located at the lower end of the PBPK prediction range (Figure 52, red symbols), suggesting a delay in absorption (refer to Item (1) below).

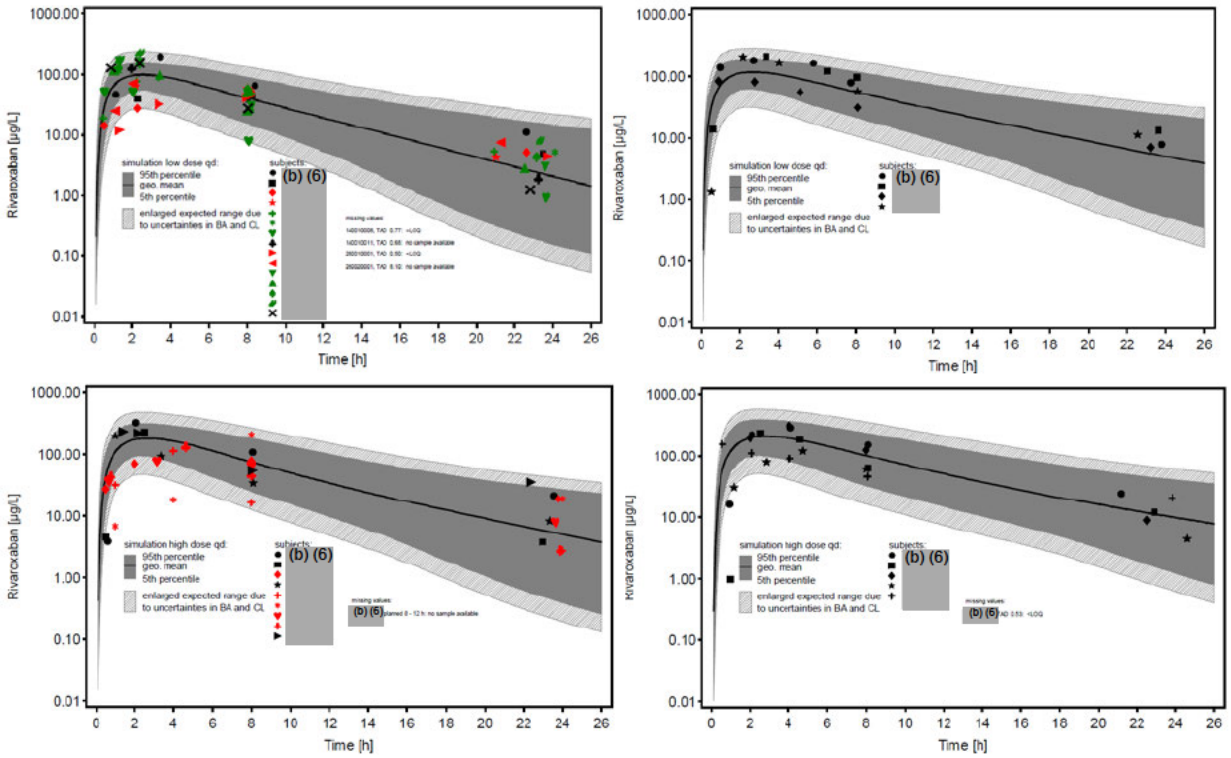


Figure 52. Comparison of PBPK predictions and observed rivaroxaban PK profile for subjects aged 6-<12 years (left) and 12-<18 years (right) in Study 12892. Black line: geomean in virtual pediatric population; shaded grey area: 5th-95th percentile of predicted values; shaded dashed area: enlarged expected range (0.5 x 5th-1.5 x 95th percentile). Symbols: individual data from subjects receiving a single 10 mg- or 20 mg- equivalent dose as either tablet (black), undiluted suspension (red) or diluted suspension (green) in Study 12892. Source: Report PH-38803 Appendix 1- Figures 1 to 4).

The observed PK data (measured trough values and PPK estimates of AUC and Cmax) were fairly contained in the predicted range for children aged 6 months to 18 years receiving 10 mg- or 20 mg-equivalent doses in tablet or oral suspension formulations (Figure 53). As expected from PBPK predictions, a tendency towards lower exposures than the targe adult exposure was confirmed in children weighing <40 kg.

Consequently, an increased individual dose of the diluted ready-to-use suspension in children weighing <40 kg was proposed, to achieve the target exposure of 20 mg-equivalent dose in adults, for the suspension cohorts in the study 14373 [Report PH-38995] and in children aged 0.5 to <6 years in the

study 14374 [Report PH-39333]. Additionally, in view of the possible trend towards lower Ctrough values with decreasing age/body weight, a switch to BID regimen was implemented for the oral suspension cohorts in these phase 2 studies (see item (2) below).

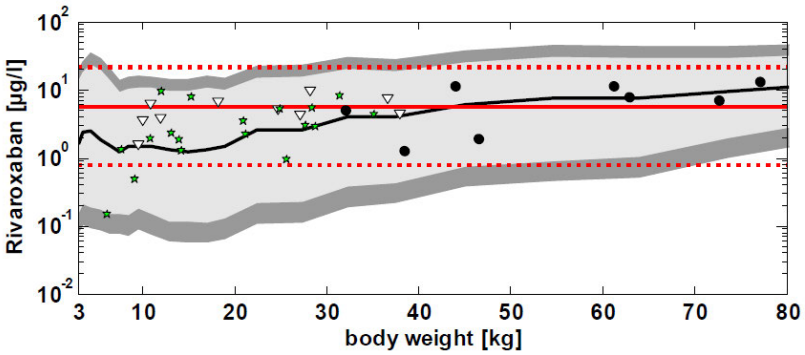


Figure 53. Comparison of PBPK predicted and observed rivaroxaban plasma concentration in the time interval of 20-24 h, as a function of body weight, for subjects aged 6 months to <18 years in Study 12892.

Symbols: individual data from subjects receiving a single 10 mg-equivalent dose as either tablet (circles) or oral suspension (undiluted=triangles; diluted=stars) in Study 12892. Black line: geomean in virtual pediatric population; shaded areas: light gray: 5th-95th percentile and dark gray: enlarged expected range (0.5 x 5th-1.5 x 95th percentile). Red line: geomean in virtual adult population (10 mg); dashed red line: 5th-95th percentile (Source: Report PH-38803 Figures 8-2).

The PK data from phase 2 studies showed that measured steady state plasma exposure (Ctrough) and PPK estimates were in good agreement with the PBPK predictions in children weighing >40 kg (Figure 54). For children weighing ≥30 kg, the observed values for Ctrough,ss and AUC24,ss were mostly within the targeted adult exposure. However, for children weighing <30 kg, receiving rivaroxaban tablet once daily, AUC24,ss values were generally lower than the targeted adult exposure. Accordingly, for children weighing between 30 to <40 kg, a dose increase from 10 mg to 15 mg QD was implemented to achieve the targeted exposure of 20 mg QD in adults. No adjustments in individual QD doses for children weighing >40 kg was considered necessary for the phase 3 study.

In children weighing <20 kg, and prominently for children weighing <12 kg, most individual AUC,ss, Cmax,ss and Ctrough,ss values were in the lower range or below the adult reference range (Figure 55). This observation supported an additional increase of the individual dose from 4 mg to 5 mg, administered in BID regimen, for children weighing 12 to <20 kg.

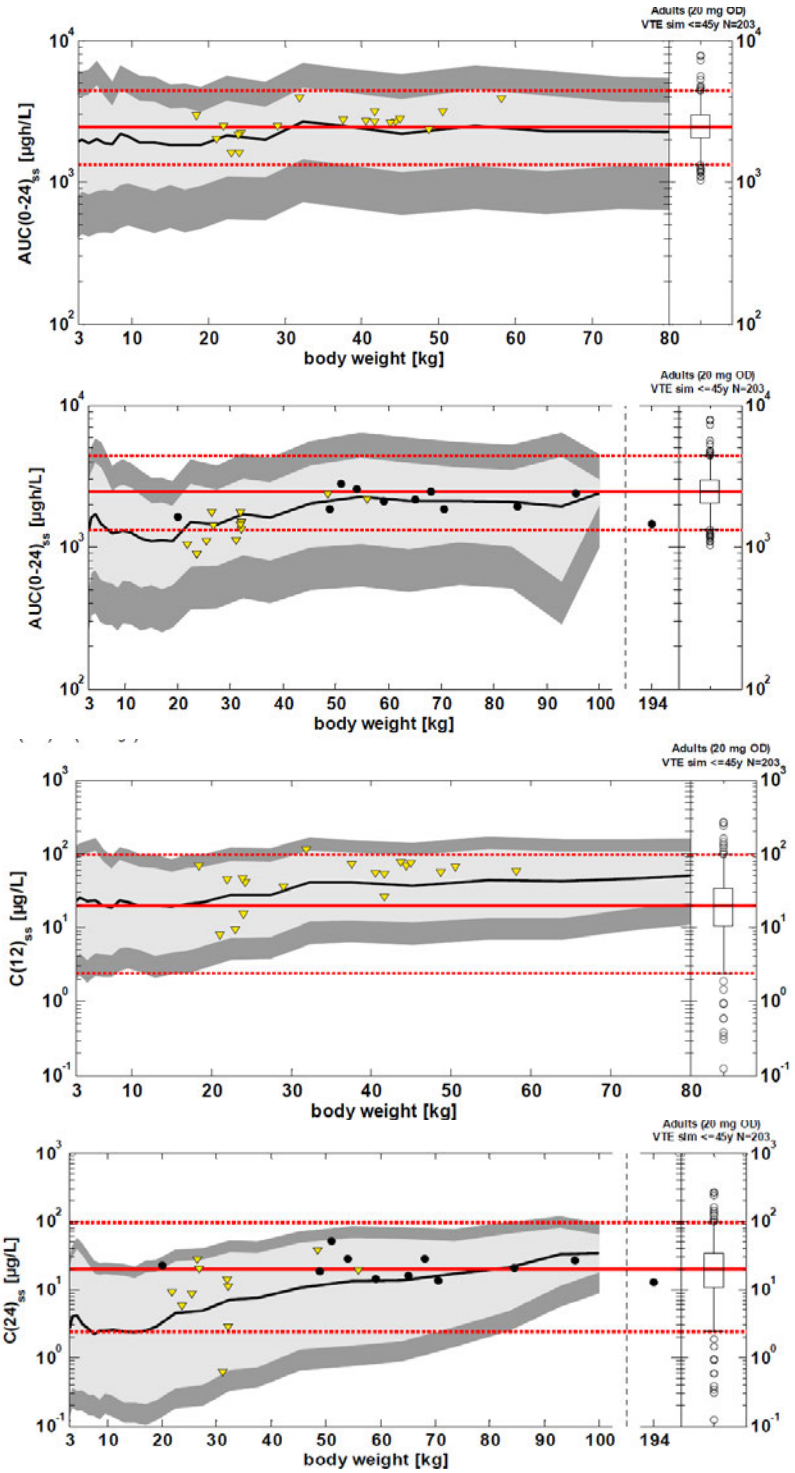


Figure 54. Comparison of PBPK predictions to PPK estimates of AUC24ss and measured Ctrough,ss for subjects aged 6-<12 years receiving rivaroxaban 10 mg-equivalent dose BID and 6-<18 years receiving rivaroxaban 20 mg-equivalent dose QD.

Symbols: Study 14373- At the top: PPK estimates of AUC24,ss and measured C12,ss for children (aged, 6-<12 years, n=19) receiving rivaroxaban 10 mg-equivalent dose BID as oral suspension. At the bottom: PPK estimates of AUC24,ss measured C24,ss for children (aged, 6-<18 years, n=23) receiving rivaroxaban 20 mg-equivalent dose QD as tablet. Solid black line: geomean of PBPK predictions for virtual pediatric population; grey shaded area: 5^{th}-95^{th} percentiles of predicted values and enlarged expected range ($0.5x5^{th}$ -$1.5x95^{th}$ percentile). Solid red line: median of PPK estimates of adult DVT patient exposure

(20 mg QD); dashed red line: 5th-95th percentile of adult exposure. ("VTE sim", box-whisker plot: percentiles 5, 25, 50, 75, and 95; open circles: individual values beyond the 5th-95th percentile range) (Source: Report PH-38995 (14373), Figure 11-26 to Figure 11-29).

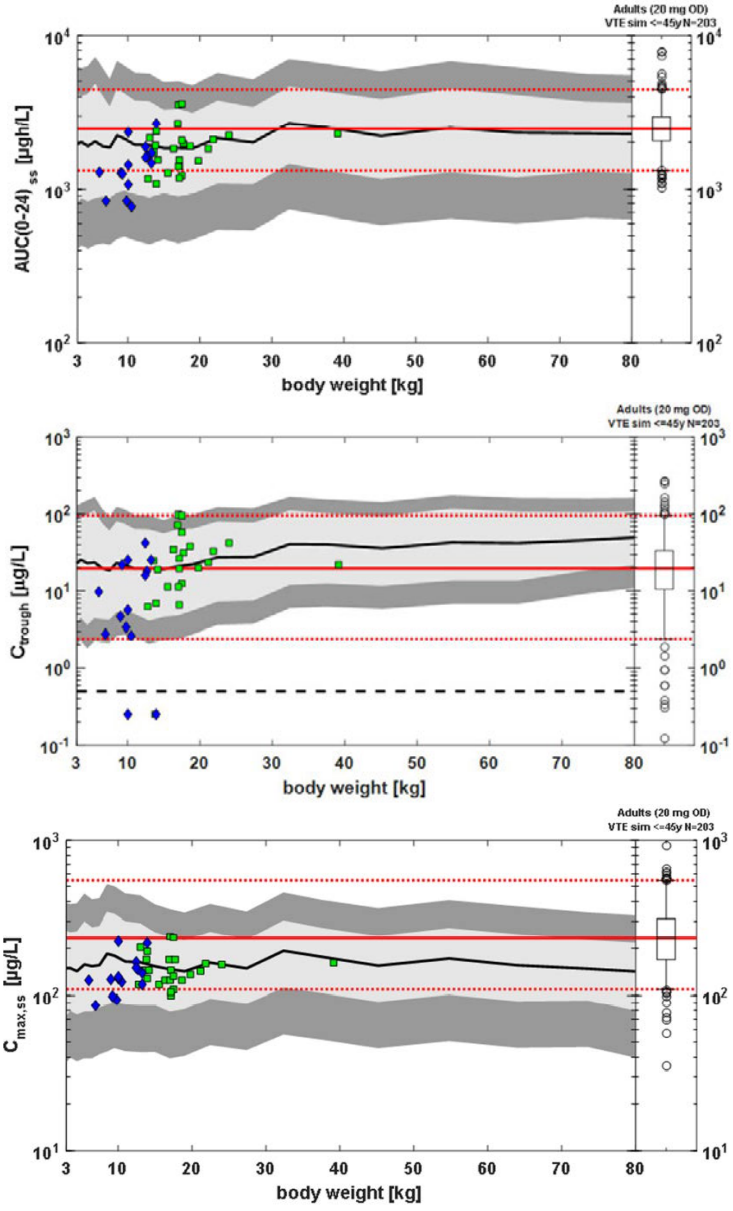


Figure 55. Comparison of PBPK predictions to PPK estimates of AUC24ss, Cmax,ss and measured Ctrough (10-16 hours) for subjects aged 6 months and <6 years receiving rivaroxaban BID as oral suspension.

Symbols: Study 14374-PPK estimates for children receiving rivaroxaban 10 mg-equivalent dose BID in; green circles: 2-6 years of age (n=25); blue diamonds: 6 months to 2 years (n=15). Solid black line: geomean of PBPK predictions for virtual pediatric population (10 mg equivalent dose BID); grey shaded area: 5th-95th percentiles of predicted values and enlarged expected range (0.5x5th -1.5x95th percentile). Solid red line: median of PPK estimates of adult DVT patient exposure (20 mg QD); dashed red line: 5th-95th percentile of adult exposure. (box-whisker plot: percentiles 5, 25, 50, 75, and 95; open circles: individual values beyond the 5th-95th percentile range). Black dashed line: LLOQ, measurements below LLOQ were set to LLOQ/2. (Source: Report PH-39333 (14374), Figure 11-17 to Figure 11-19).

In the neonate study 17618, rivaroxaban was initially administered to children from birth (term neonates) to <0.5 years as the diluted ready-to-use suspension in BID regimen. Given it was the first time to enroll children aged <0.5 years as well as the uncertainty in PBPK predictions regarding the rate and extent of absorption, a cautious dosing approach was selected for this study. Intermediate individual oral doses (in mg/kg body weight) between those already tested in children aged > 0.5 years (=minimum body weight of 6 kg) in studies 12892 and 14374 were selected for this neonate study.

Available PK data from studies 176181 and 14374 in children aged <0.5 years indicated lower AUC24,ss and Ctrough,ss values than initially expected based on the PBPK predictions. It was noted that Ctrough in children weighing ≤12 kg was consistently at the lower end of the prediction range. Therefore, the pediatric PBPK model was considered reliable to predict rivaroxaban PK only in children weighing >12 kg. (b) (4) For children weighing <12 kg, PK data from the study 17618 would serve to support the dosing recommendation for the phase 3 study.

Thereafter, all available PK data in children aged <2 years, corresponding to a body weight of around 12 kg, was analyzed using a PPK model specific to children aged <2 years [M&S Study 19397, Report PH-39769]. The results were used to propose a (b) (4) TID, (b) (4) Thus, a 50% increase of the total daily dose aimed to increase the daily exposure, targeting the lower 30% of the adult exposure range. The shortening of the dosing interval aimed to increase the Ctrough,ss values. As all individual estimates of AUC24,ss values were still found below the 5th percentile of the adult reference, particularly in children weighing ≤5 kg, the individual doses were further increased. The body-weight-adjusted rivaroxaban dosing schedule for children from birth to <18 years of age used in phase 3 study 14372 is listed in Table 28. Refer to the pharmacometrics review for the evaluation of dosing adequacy for treatment of VTE in pediatrics.

In summary, the pediatric PBPK model was considered helpful, by the Applicant, to derive the body-weigh-adjusted doses achieving the target exposure (i.e., adult exposure range for 20 mg QD). A good agreement between the observed plasma concentrations and the PBPK predictions was observed in the single dose study 12892 in children and adolescents. However, during multiple dosing studies 14374 and 17618, it became apparent that in children aged <2 years, and particularly in those weighing <12 kg, the majority of observed Ctrough values were below the geometric mean of the PBPK predictions. No reason in terms of physiological changes or maturation of processes affecting rivaroxaban PK could be identified to support adjustment of the model (b) (4) .

The pediatric PBPK model of rivaroxaban was considered reasonable to predict rivaroxaban PK for children weighing >12 kg in the EINSTEIN Jr program. Predictions of rivaroxaban PK following the administration of multiple 20 mg-equivalent dose in children yielded Cmax,ss and AUC24,ss values comparable to PPK estimates from study 14372 (Table 31, PBPK-combined).

Likewise, for children aged >2 years, the PBPK predictions of rivaroxaban clearance as a function of age were consistent with PPK estimates, including the predicted vs observed range of interindividual variability. For children aged <2 years, the predicted clearance was, on average, lower than PPK estimates (Figure 56).

Table 31. Summary of rivaroxaban PK parameters predicted by PBPK stratified by fasted and fed state and PPK estimates (OBS) by body weight group

Body weight/ Dosing regimen	<12 kg /TID	12-<30 kg /BID	30-<50 kg /QD	≥50 kg /QD
AUC24h,ss (µg.h/L)				
OBS	1790 (1130-3413)	2001 (1183-4391)	2049 (1352-3488)	2098 (1391-3192)
PBPK - combined	3308 (1419-7593)	2212 (1085-3930)	2247 (1029-4100)	2287 (1043-4109)
PBPK - fed	3738 (1737-8213)	2459 (1322-4232)	2568 (1416-4433)	2600 (1414-4440)
PBPK - fasted	2921 (1247-6796)	1975 (961.5-3530)	1919 (887.9-3577)	1953 (881.1-3641)
Cmax,ss (µg/L)				
OBS	126 (87.9-201)	161 (104-298)	246 (189-382)	230 (173-335)
PBPK - combined	202 (97.0-400)	170 (93.7-293)	264 (135-469)	255 (125-428)
PBPK- fed	233 (116-434)	195 (109-326)	327 (182-506)	310 (179-460)
PBPK- fasted	175 (86.2-344)	151 (86.1-237)	214 (120-344)	205 (110-324)
Ctrough,ss (µg/L)				
OBS	25.3 (12.1-68.6)	26.1 (12.6-78.7)	18.1 (7.87-38.8)	21 (10.2-43.5)
PBPK - combined	73.4 (20.5-230)	28.8 (6.65-78)	13.4 (1.27-48)	16.8 (1.68-55.5)
PBPK - fed	83.5 (20.1-253)	26.5 (4.75-84.4)	6.61 (0.744-38.8)	9.39 (0.998-47.6)
PBPK - fasted	66.0 (20.6-204)	30.2 (10.4-72.9)	20.3 (5.82-53)	23.3 (7.62-61.7)

PK data are median (5^{th}- 95^{th} percentile) values. Population PK estimates using the EINSTEIN Jr PPK model, data from Study 14372, pooled for regimen and formulation (Source: Applicant's Response to Clinical Pharmacology IR-015)

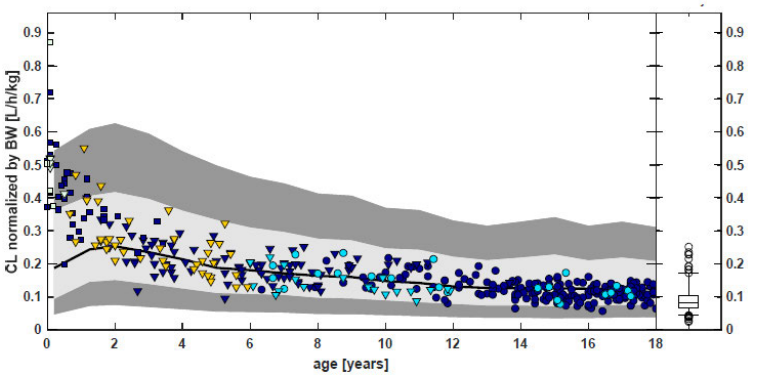


Figure 56. Comparison of PBPK predictions to PPK analysis estimates of CL normalized by body weight, as a function of age.

Symbols individual estimates by PPK analysis from children in the EINSTEIN Jr program (M&S Study 18736). Black line: geomean of PBPK predictions of CL for a virtual pediatric population; Gray-shaded areas: 5^{th}-95^{th} percentile for a virtual pediatric population and enlarged expected range (0.5 x 5^{th}-1.5 x 95^{th} percentile). On the right, box whisker plot: PPK results of the adult VTE (20 mg QD) (Source: Report PH- 40947, Figure 6).

Regarding the PBPK model overprediction of Ctrough (and consequently AUC) in children weighing <12 kg (Table 31), the underlying mechanism for the lower trough concentrations than anticipated by the model is unknown. However, the Applicant suggested it is likely related to a more rapid elimination of

rivaroxaban in young children rather than slower absorption. This was supported by PPK results indicating that rivaroxaban absorption is almost complete in children, as was predicted by the PBPK model. However, in the absence of IV data in children, it cannot be entirely excluded that an overprediction of absorption from more distal segments, driven by solubility-limited absorption, also contributed to the model misprediction.

For the VTE indication (and in the EINSTEIN Jr program), rivaroxaban is recommended to be administer with food, in line with adult PK following 20 mg rivaroxaban administration. Retrospective verification of PBPK predictions under fasted and fed state compared to PPK estimates from study 14372 were conducted (Table 31). PBPK predicted AUC and Cmax values were slightly higher in fed state compared to fasted. However, the differences were within the predicted inter-individual variability (largely overlapping distributions, particularly for AUC). In agreement with different food effect for rivaroxaban doses of 10 and 20 mg in adults, the impact of feeding conditions is more pronounced for children receiving rivaroxaban QD dosing compared to BID and TID. For Ctrough, predicted distributions are similar under fasting and fed state conditions in children receiving rivaroxaban BID or TID, whereas for QD dosing the model predicted higher Ctrough values in fasted state compared to fed. This agreed with the anticipated flip-flop kinetics in adults, leading to slightly longer apparent terminal half-life at higher doses in fasted state [NDA 022406]. A decrease in relative bioavailability for increasing doses (in mg/kg body weight) was also observed in children, even under fed conditions. This agrees with the observation in adults of no further increase in exposure was reached at a dose of 50 mg rivaroxaban in the fed state (i.e., ceiling effect) [Applicant's Response to IR-015].

The pediatric PBPK model of rivaroxaban was also used to support the following:

(1) PBPK analysis [M&S Study 1858 Report PH-38803] was used to evaluate the observation that children aged 6 to 12 years who initially received the undiluted ready-to-use suspension showed a delayed absorption of rivaroxaban [Study 12892, Report PH-38444]. The Cmax decreased; C_{24h} slightly increased; AUC was unchanged. This finding was attributed (b) (4) to a lower rate of absorption) for the undiluted suspension compared to the tablet or diluted suspension. (b) (4) The observed concentrations after administration of the diluted suspension matched the predicted range (b) (4) corresponding to the tablet formulation (Figure 57). (b) (4)

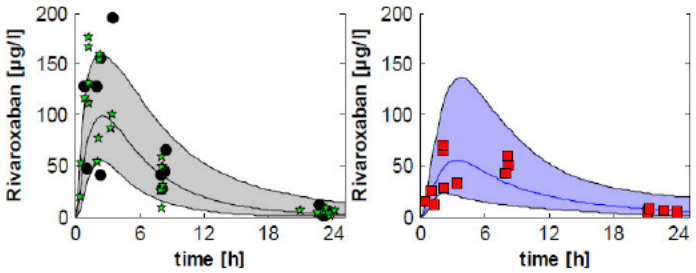


Figure 57. Plasma PK profile observed after administration of diluted suspension (green stars), tablet (black circles), or undiluted suspension (red squares) to children (aged 6 to 12 years) receiving 10 mg equivalent dose compared to expected PK ranges simulated with the [redacted] (b) (4) rate (left) or [redacted] (b) (4) rate (right). Solid lines: geomean in virtual pediatric population; shaded areas: 5th-95th percentile (Source: Report PH-38803, Figure 8-16).

(2) PBPK analysis [M&S Study 18807, Report PH-39027] was used to derive a body weight limit for the [redacted] (b) (4) BID dosing regimen of rivaroxaban. Simulations of subjects from 6 months to 18 years binned into bodyweight categories (binning width of 1 kg [up to 16 kg], 2 kg [16 kg up to 34 kg], and 2 or 3 kg [34 kg and above]) and receiving the same daily dose of rivaroxaban either QD or BID were conducted. The fraction of individuals outside the target PK boundaries for a 20 mg-equivalent dose QD and a 10 mg-equivalent dose BID was calculated. The fraction of children with Ctrough,ss values below the 5th percentile of Ctrough,ss in a simulated adult population (receiving 20 mg QD) could be reduced if children weighing < 30 kg would receive BID dosing instead of QD. The fraction of children with Cmax,ss above the 95th percentile of Cmax,ss in a simulated adult population was also considered in the evaluation.

(3) PBPK analysis was used to address how a delayed dosing event would affect plasma concentrations of rivaroxaban [M&S Study 18806 Report PH-39023]. Specifically, the potential increase in Cmax was investigated for a dose with a shorter administration interval than determined per protocol due to a preceding delayed dosing event. A delay in dosing was deemed acceptable, i.e., predicted to be 7 hours for BID and 17 hours for QD dosing, if the resulting median Cmax of the follow-up dose was exceeding Cmax in the steady state by a maximum of 30% (based on the typical interindividual variability in rivaroxaban PK of 30%). These results were used to support recommendations for missed rivaroxaban doses for the multiple-dose studies in children.

PBPK Analysis in the CHD Thromboprophylaxis Indication Program

The UNIVERSE study [Study 18226, Report R-13703] investigated the use of rivaroxaban for thromboprophylaxis in children aged 2 to 8 years with CHD who had the Fontan procedure.

PBPK analysis was used to assess whether children with a Fontan circulation (pediatric post-Fontan population) have a different rivaroxaban dose-exposure relation compared to healthy children [M&S Study 20096, Report PH-38483]. The pediatric PBPK model of rivaroxaban was re-parameterized to reflect changes in the physiology of this pediatric post-Fontan population. The initial modeling analysis indicated that altered physiology of post-Fontan children with normal liver function would not influence the dose-exposure relationship of rivaroxaban in comparison to healthy children, and a similar plasma

exposure of rivaroxaban in post-Fontan children would be expected when using the same body weight-based dosing regimen as in healthy children. The proposed rivaroxaban dosing scheme for pediatric post-Fontan subjects aged 2 to 8 years (weighing 7 to <30 kg) was derived by the Fontan-PBPK model designed to yield a target exposure matching 10 mg total daily dose in adults (i.e., 10 mg QD exposure observed in the VTE prevention Study 11527 [M&S Study CPMX 50089, Report R-13747]).

In the UNIVERSE study, children aged 2 to 8 years with single-ventricle physiology who had the Fontan procedure up to 1 year before rivaroxaban administration received XARELTO in oral suspension, according to a body weight-based BID dosing regimen (Table 29). No clinical data was available for post Fontan patients ≥9 years. To extrapolate the dose-exposure relationship to post-Fontan patients aged ≥9 to 18 years, a model-informed bridging approach using PPK analyses was used. Refer to the pharmacometrics review for the details of the PPK analysis and evaluation of dosing adequacy for thromboprophylaxis indication in pediatric population.

Pediatric Fontan-PBPK Model Development

The Fontan-PBPK model was applied using the Open Systems Pharmacology Suite (OSPS) version 7.2. For the extension of the pediatric PBPK model of rivaroxaban [M&S Study 13148, Report PH-35614, and M&S Study 15802, Report PH-37113] to post-Fontan patients, the population model was updated to include altered physiology reported in pediatric post-Fontan patients and healthy population. Data regarding physiology in children with CHD who had the Fontan procedure in the age range 2 to 8 years was collected and analyzed by the Applicant. It has been noted that these patients have lower body weights at a given age and reduced cardiac output compared to healthy children (Figure 58) [M&S Study 20096, Report PH-38483].

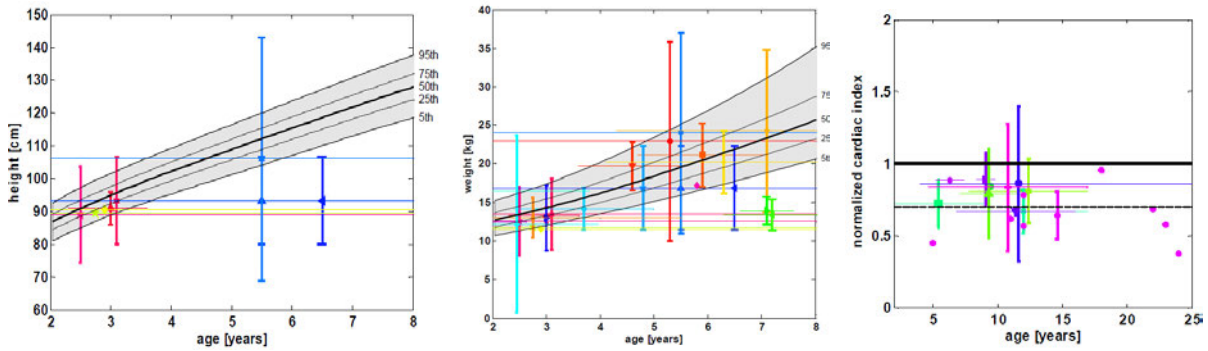


Figure 58. Comparison of the body height and weight distribution, and normalized cardiac index in the post-Fontan population from literature sources with the respective 5%-95% distribution range of the age-matched reference population. Each data set is represented by a mean value, a specific age range (horizontal bar) and a specific height range (vertical bar) of the same color. Normalization of cardiac index was done by dividing cardiac output by the body surface area. The mean normalized cardiac index in the reference population is 1 (horizontal black line) compared to the post-Fontan population of 0.7 (dashed black line). (Source: Report PH-38483, Figures 7-1, 7-3 and 7-6).

In the pediatric PBPK model, the body weight and height distribution of the reference population was shifted by 0 to -0.7 times the standard deviation of the respective age-specific mean to represent the pediatric post-Fontan population. The cardiac output (and cardiac index which is cardiac output related to body surface area) in the post-Fontan population was implemented to be 70% compared to the

reference population. This cardiac output reduction was distributed across all organs, except brain (Figure 59) [M&S Study 20096, Report PH-38483].

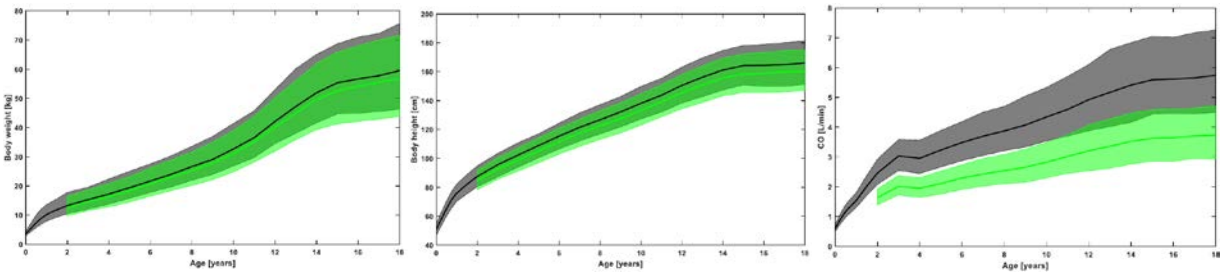


Figure 59. Age dependence of body weight (left), body height (center) and cardiac output (right) for predicted post-Fontan population compared to predicted reference population. Green line: geomean in virtual pediatric post-Fontan Population; shaded green area: 5-95% confidence interval. Black line: geomean in virtual pediatric reference population; shaded gray area: 5-95% confidence interval (Source: Addendum to Report PH-38483, Figures 1, 2 and 4).

Regarding the clearance processes relevant for rivaroxaban PK in the post-Fontan population, liver and kidney functions in post-Fontan patients were mostly not impaired in the first year after surgery, based on Applicant's assessment. Some older studies reported acute liver dysfunction in the early post-operative period, which were associated with difficult postoperative course, acute renal failure and clinically apparent hepatic disease or preoperative liver impairment. Although, there were case reports on abnormal liver function tests in early follow up examinations (up to 1 year). To assess a severe case of an undetected (developing) but clinically relevant liver dysfunction in a post-Fontan patient, the Applicant simulated a scenario in which CYP-dependent hepatic clearance of rivaroxaban was set to zero to represent a severe liver impairment. To best of knowledge, there were no reports on kidney dysfunction after successful Fontan procedure in children matching the study population. After a follow-up of at least 2 years after Fontan completion, 43% of 15 (±8.8) years old patients had elevated microalbumin/creatinine ratios, but normal GFR (glomerular filtration rate). Therefore, kidney clearance in the post-Fontan population was assumed to be similar to healthy children.

Other assumptions were made when transferring the pediatric PBPK model from healthy children to ones with Fontan circulation: (1) gastrointestinal physiology was not altered compared to healthy children; (2) liver function was normal before drug administration, specifically, it was not impaired by the reduced cardiac index before and after completion of the Fontan procedure; and (3) possibly altered coagulation did not impact organ blood flows.

Pediatric Fontan-PBPK model Validation:

The adequacy of assumptions made in the pediatric Fontan-PBPK model as well as a comparison of PBPK predictions of rivaroxaban exposure with observations in the UNIVERSE study in post-Fontan patients aged 2 to 8 years (n=76, Study 18226) was used to retrospectively validate the model.

The reported anthropometric differences between post-Fontan and healthy children were implemented in the Fontan-PBPK model. It was considered that Fontan-patients have lower body weights at a given age and reduced cardiac output compared to reference pediatric subjects (Figure 59). The on average

lower body weight of pediatric post-Fontan patients (body weight distributions of UNIVERSE study) relative to pediatric healthy subjects (body weight distributions of EINSTEN-JR study) of the same age is shown in Figure 60.

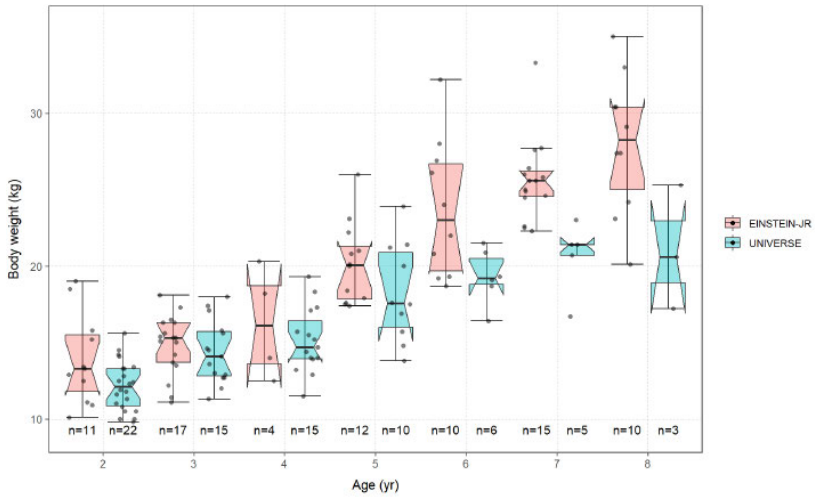


Figure 60. Comparison of body weight distribution per age in the UNIVERSE and EINSTEIN-JR studies.
Pink: Empirical Bayesian estimates for subjects in the EINSTEIN-JR study according to the EINSTEIN-JR PPK model [Report R-12947]. Green: Empirical Bayesian Estimates for post-Fontan patients in the UNIVERSE study according to the UNIVERSE PPK model [Report R-13646]. Box: lower and upper quartile range; whiskers: 5th-95th range of parameter value; Black horizontal line: median; notches: 95% confidence interval of the median; grey dots: individual parameter values. (Source: Report R-13646, Figure 10.1:7).

The body weight distribution per age group for the virtual post-Fontan population aged 2 to 8 years was comparable with individual observations in the UNIVERSE study (at baseline) (Figure 61). These findings supported that the differences in body weight over age relationship for post-Fontan patients aged 2 to 8 years implemented in the model were reasonable.

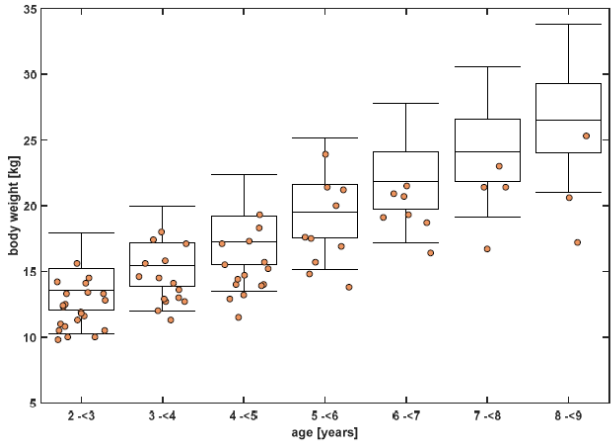


Figure 61. Body weight distribution per age for virtual post-Fontan children using the Fontan-PBPK model compared to individual data of UNIVERSE study.
Box: lower and upper quartile range for predicted post-Fontan subjects; whiskers: 5th and 95th range for predicted values. Dots: individual data from UNIVERSE study (Study 18226, Report R-13703) (Source: Report PH-41912, Figure 5-1).

Rivaroxaban plasma concentrations (on Day 1 and at steady state) observed in the UNIVERSE study were compared with predictions by the Fontan-PBPK model (Figure 62). The PBPK predictions for AUC24,ss in post-Fontan patients were also compared with the individual AUC24,ss estimates obtained from the UNIVERSE PPK Model [M&S Study CPMX 50089, Report R-13747]. Around 80% (19 of 24) of post-Fontan patients aged ≥5 years had an observed AUC24h,ss within the 90% prediction interval of the Fontan-PBPK model (Figure 63).

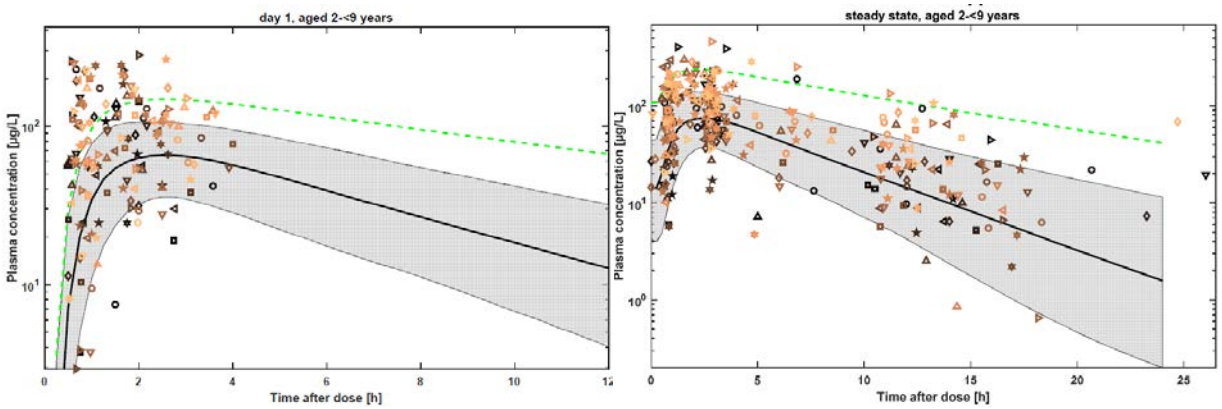


Figure 62. Comparison of predictions and observed rivaroxaban plasma concentration-time profile for post-Fontan patients aged 2- <9 years in the UNIVERSE study.

Black line: geomean of predicted rivaroxaban PK profile on Day 1 (left) and at steady state (right). N=7949 children were simulated, semi-log scale; grey area: predicted 5th - 95th percentile; green dashed line: simulated post-Fontan pediatric subjects with severe hepatic impairment- 95th percentile; symbols: individual data from UNIVERSE (one symbol per subject). (Source: Report PH-41912 Figures 8-2 and 8-10).

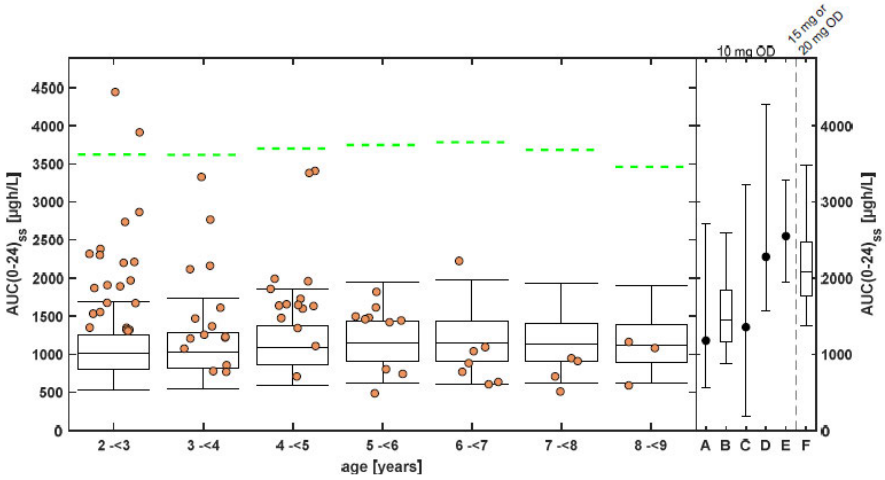


Figure 63. Comparison of PBPK predictions of rivaroxaban steady-state AUC with individual estimates of PPK analysis by age.

Box: lower and upper quartile range for predicted post-Fontan pediatric patients; whiskers: 5th and 95th range for parameter value. Dots: individual estimates from UNIVERSE study using UNIVERSE PPK model (M&S Study CPMX 50089, Report R-13747). Green dashed line: simulated post-Fontan pediatric subjects with severe hepatic impairment- 95th percentile. Reference data are displayed as box whisker plot (B,F), which indicates the percentiles 5, 25, 50, 75, and 95 or geometric mean + range (A,C,D,E). (A) healthy adults (M&S Study 14588, 10 mg OD, N = 263); (B) adult VTE-P patients (Study 11527, 10 mg OD, N = 140); (C) Medical ill (Study 12839, 10 mg OD, N = 35); (D) Chronic stable severe CHF (Study 12980, 10 mg OD, N = 12); (E) Acute decomp. CHF (Study 12980, 10 mg OD, N = 3); (F) EINSTEIN-JR (Study 14372, patients with BW ≥ 30 kg; 15mg OD (BW 30-<50 kg) and 20mg OD (≥ 50 kg), N = 201) (Source: Report PH-41912 Figure 5-4).

This retrospective analysis indicated that the model, however, underestimated rivaroxaban concentrations in younger post-Fontan patients. The exposure in patients aged 2 to <5 years was higher than predicted by the model: around 42% (22 of 52) of subjects had an AUC24h,ss above the 95% prediction interval of the model, and 50% (26 of 52) of subjects were within the 50% to 95% prediction interval (Figure 63).The Applicant reasoned that the discrepancy between predicted and observed rivaroxaban exposure in post-Fontan patients aged 2 to <5 years could be attributed to an overestimation of the rivaroxaban clearance in the model.

A comparison of observed rivaroxaban plasma concentrations at steady-state to PBPK predictions showed a tendency for underestimation of both near-Cmax and near-Ctrough exposure in post-Fontan patients aged 2 to 5 years. This indicated a potential for lower clearance in these patients than predicted by the model (Figure 64). To quantify the extent by which, on average, rivaroxaban clearance was underestimated by the model, the total plasma hepatic clearance was iteratively reduced to match the observed data in the age range between 2 and <5 years. A reasonable agreement between the predictions and observed PK was achieved when the hepatic clearance of the initial Fontan-PBPK model was reduced by a factor of 0.53, 0.64, and 0.45 in the age groups of 4-<5, 3-<4, and 2-<3 years, respectively (Figure 65).

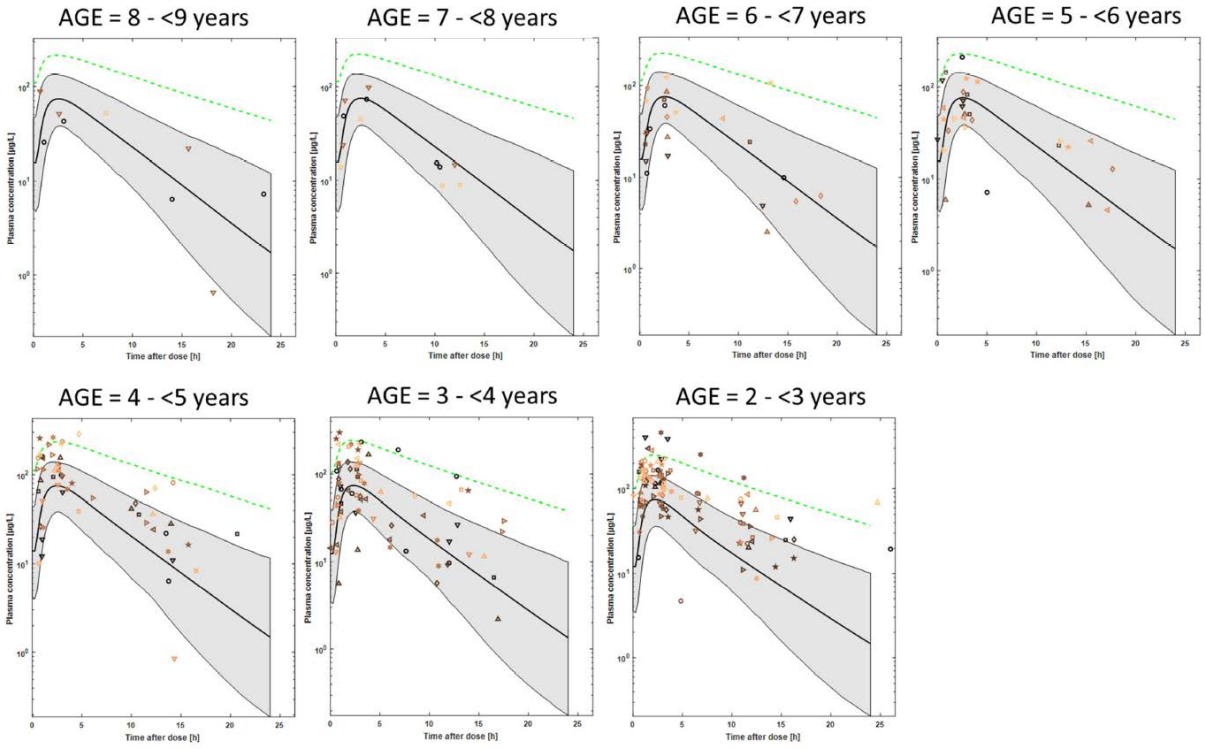


Figure 64. Comparison of predictions and observed rivaroxaban PK profile at steady-state for post-Fontan patients by age.

Black line: geomean of predicted rivaroxaban plasma concentration time profile in post-Fontan pediatric subjects, semi-log scale; grey area: predicted 5th-95th percentile; dashed line: green dashed line: simulated post-Fontan pediatric subjects with severe hepatic impairment- 95th percentile; symbols: individual data from UNIVERSE (one symbol per subject). (Source: Report PH-41912 Figure 5-5).

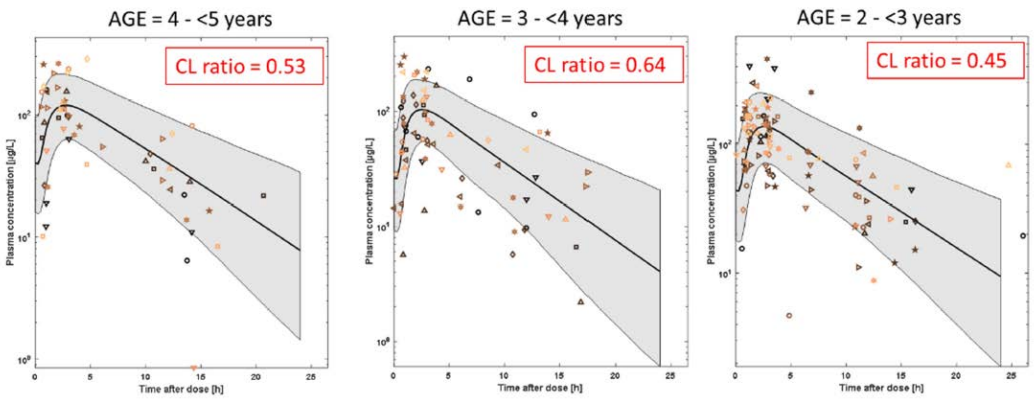


Figure 65. Comparison of predictions and observed rivaroxaban concentrations at steady state for post-Fontan patients aged 2 - <5 years, stratified by age.

Black line: geomean of predicted exposure for post-Fontan pediatric subjects; grey area: 5th-95th percentile; symbols: individual observed data from UNIVERSE study (one symbol per subject). In the simulations, clearance was reduced by factors of 0.53, 0.64 and 0.45 for children aged 4- <5, 3- <4 and 2- <3 years, respectively, relative to the original Fontan-PBPK model (Source: Report PH-41912 Figure 5-6).

This finding was consistent with the results of PPK analysis. A comparative assessment of PPK estimates obtained using the PPK models UNIVERSE and EINSTEIN Jr demonstrated that rivaroxaban exposure in post-Fontan patients aged ≥5 years could be described by the EINSTEIN Jr PPK model [M&S Study CPMX 50070, Report-R13646]; the apparent clearance and AUC24h,ss were similar between children aged 5 to 8 years in the UNIVERSE and EINSTEIN Jr studies (Figure 66). For children aged 2 to <5 years in the UNIVERSE study, the median reduction of apparent clearance was 56.7% compared to the ones in EINSTEIN Jr (2.09 vs. 4.83 L/h).

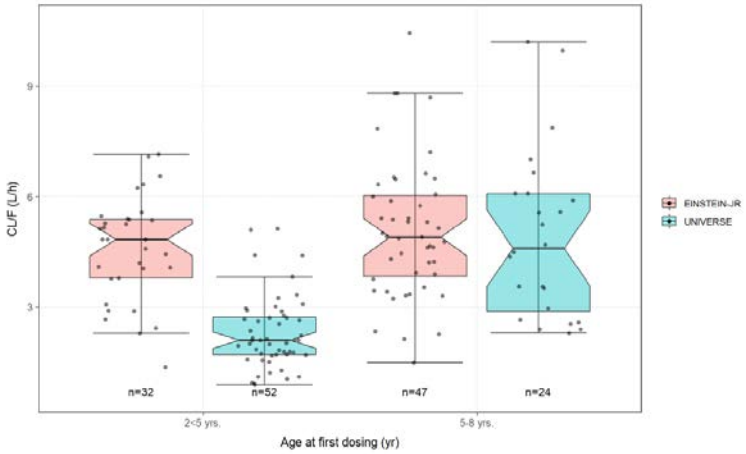


Figure 66. Comparison of rivaroxaban apparent clearance for subjects aged 2- <5 years and 5-8 years in the UNIVERSE and EINSTEIN Jr studies.

Pink: empirical Bayesian estimates for subjects in the EINSTEIN Jr study according to the EINSTEIN Jr PPK model [M&S Study 15802, Report PH -37113]. Green: empirical Bayesian estimates for post-Fontan patients in the UNIVERSE study according to the adapted PPK model [M&S Study CPMX 50070, Report R-13646]. Box: lower and upper quartile range; whiskers: 5^{th}-95^{th} range of parameter value; black horizontal line: median; notches: 95% confidence interval of the median; dots: individual parameter values. (Source: Report R-13646, Figure: 7.2:3).

The Applicant suggested this decrease in apparent clearance can be attributed to, on average, the lower doses yielding higher oral bioavailability (F) in children in the UNIVERSE study compared to the ones in the EINSTEIN Jr program. Rivaroxaban (as a BCS class 2 drug) have a decreasing relative F with increasing dose (or dose per body weight in children) [Report PH-39250]. When the difference in F due to the lower doses in the UNIVERSE study compared to EINSTEIN Jr was factored in, median clearance of children aged 2 to <5 years in the UNIVERSE study was reduced by approximately 28.4% compared to EINSTEIN Jr (2.52 vs. 3.51 L/h) [Report R-13646]. For comparison, the hepatic clearance in the Fontan-PBPK model was decreased by 35% to 54% in this age group compared to the original pediatric model.

Selected covariates, such as Japanese vs. non-Japanese, and the duration between the end of the Fontan-procedure and the start of rivaroxaban, that could explain the lower clearance and corresponding high exposure in some of the UNIVERSE patients aged 2 to <5 years were also explored by the Applicant. None of the tested covariates were related to this finding. The correlation between eGFR, as a measure of renal function, and exposure was also explored. Values of eGFR at baseline of the UNIVERSE patients were in the normal range and not related to AUCss of rivaroxaban.

It should be noted the tendency of the Fontan-PBPK model to underestimate exposure in post-Fontan patients aged 2 to <5 years contrasted with the tendency of the pediatric PBPK model to overpredict the exposure in children weighing <12 kg (corresponding to an approximately ≤2 years of age) in the EINSTEIN-JR program [M&S Study 19397, Report PH-39769]. Currently, no (patho-)physiological or mechanistic explanation was identified for the apparent mispredictions of the pediatric PBPK model compared to the observed PK in either pediatric population.

We noted that the PBPK modeling proposed dose for post-Fontan patients aged >2 years weighing 7 to <8 kg was not clinically tested in the UNIVERSE study. The Fontan-PBPK model; however, was not considered adequate to support the dose-exposure relationship in patients weighing 7 to <8 kg in absence of data, because the model underestimation of the rivaroxaban exposure in post-Fontan patients aged 2 to <5 years.

For the CHD thromboprophylaxis indication, rivaroxaban can be administered without regard to food. The PBPK model predicted minor effects of the feeding conditions on rivaroxaban PK in pediatric post-Fontan patients in relation to the predicted inter-individual variability. The PBPK model assumed slightly faster initial absorption under fed conditions, whereas absorption was prolonged in the fasted state due to a shift towards absorption from more distal regions of the GI tract. This is qualitatively consistent with observations in adults at higher doses. The slow absorption rate seen with higher doses in adults in the fasted state, leading to lower amount of drug being absorbed in the lower GI tract, was also responsible for the slightly longer apparent terminal half-life in adults (i.e., flip-flop PK).

The AUC24h,ss and Cmax,ss were predicted to be independent of the feeding conditions in children administered BID doses of rivaroxaban (<30 kg). Cmax,ss was predicted to be slightly higher in pediatric post-Fontan patients administered once-daily doses of rivaroxaban (>30 Kg) under fed state compared to fasted. For Ctrough,ss, the model predicted a trend towards higher values in the fasted state

compared to the fed state, in agreement with the flip-flop kinetics of rivaroxaban observed in adults at higher doses in the fasted state. This tendency was more pronounced for the QD dosing regimen (= higher individual dose) than the BID dosing regimen (= lower individual dose) [Applicant's Response to Clinical Pharmacology IR-015].

Exploratory Analysis of Potential for PK-based DDI in Pediatrics

In adults, the use of rivaroxaban is not recommended with concomitant use of dual P-gp and strong CYP3A4 inhibitors or P-gp and strong CYP3A inducers due to the potential changes in rivaroxaban plasma concentrations to a clinically relevant degree. Concomitant use of P-gp and strong CYP3A4 inhibitors, as well as strong CYP3A4 inducers were excluded per protocol in all pediatric studies. Comedication data showed that a small number of patients were reported to receive CYP3A4 inducers with narrow scope (n=16 patients, n=36 PK observations), weak CYP3A4 inhibitors (41 patients, 123 PK observations) or moderate CYP3A4 inhibitors (18 patients, 50 PK observations) concomitantly to rivaroxaban [Report R-12947].

Exploratory comparisons were made using the individual values for rivaroxaban PK parameters (AUC24,ss, Cmax,ss and Ctrough,ss) of all multiple-dose studies in children (studies 14373, 14374, 17618, and 14372), derived using the comprehensive PPK model for children. For the subjects receiving moderate or weak CYP3A4 inhibitors, no general trend towards higher exposures was evident. For children receiving CYP3A4 inducers of narrow scope concomitantly to rivaroxaban, the individual PK parameters follow the general trend for bodyweight and dosing regimen of the overall pediatric population. This exploratory visual analysis of individual PK data did not indicate a new drug-drug interaction potential for pediatrics [SCP-Einstein Jr].

Conclusions

- The pediatric rivaroxaban PBPK model had a trend of overestimating the exposure in children < 12 kg (VTE population).
- The Fontan PBPK model had a trend of underestimating the exposure in children < 30 kg (or 2-5 years of age).

References

- *Willmann S, Becker C, Burghaus R, et al.* Development of a paediatric population-based model of the pharmacokinetics of rivaroxaban. Clin Pharmacokinet. 2014; 53(1):89-102
- *Willmann S, Coboeken K, Kapsa S.* Applications of Physiologically Based Pharmacokinetic Modeling of Rivaroxaban -Renal and Hepatic Impairment and Drug-Drug Interaction Potential. J Clin Pharm 2021; 61(5):656–665
- *Edginton AN, Schmitt W, Voith B, Willmann* S. A mechanistic approach for the scaling of clearance in children. Clin Pharmacokinet 2006; 45(7):683-704.
- *Thelen K, Coboeken K, Willmann S, et al.* Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part 1: oral solutions. J Pharm Sci. 2011; 100:5324-45.
- *Thelen K, Coboeken K, Willmann S, et al.* Evolution of a detailed physiological model to simulate the gastrointestinal transit and absorption process in humans, part II: extension to describe performance of solid dosage forms. J Pharm Sci. 2012; 101:1267-80.

- (b) (4)
- *Rhodin MM, Anderson BJ, Peters AM, et al*. Human renal function maturation: a quantitative description using weight and postmenstrual age. Pediatr Nephrol. 2009; 24(1):67-76.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HARISUDHAN THANUKRISHNAN
12/12/2021 04:55:19 PM

JIHYE AHN
12/13/2021 07:38:25 AM

XINYUAN ZHANG on behalf of MANUELA GRIMSTEIN
12/13/2021 08:14:08 AM
On behalf of Dr. Manuela Grimstein

XINYUAN ZHANG
12/13/2021 08:15:52 AM

LIANG LI
12/13/2021 09:58:13 AM

SUDHARSHAN HARIHARAN
12/13/2021 10:01:59 AM