Office of Clinical Pharmacology Review

NDA or BLA Number	NDA 022512/S041 [redacted] NDA 214358
Link to EDR	\\CDSESUB1\evsprod\NDA022512\0452 [redacted] \\CDSESUB1\evsprod\NDA214358\0000
Submission Date	9/21/2020
Submission Type	Priority
Brand Name	PRADAXA®
Generic Name	dabigatran etexilate capsules (NDA 022512/S041) [redacted] dabigatran etexilate [redacted] pellets (NDA 214358)
Proposed Dosage Form and Strength	Capsule: 75 mg, 110 mg, or 150 mg [redacted] pellets (pellets) in sachets (packets): 20 mg, 30 mg, 40 mg, 50 mg, 110 mg, or 150 mg [redacted]
Route of Administration	Oral administration
Proposed Indication	• Treatment of venous thromboembolic events (VTE) in pediatric patients [redacted] to <18 y) • Reduction in the risk of recurrence of VTE in pediatric patients [redacted] to <18 y)
Applicant	Boehringer Ingelheim Pharmaceuticals, Inc
Associated IND	IND 063267
OCP Review Team	Peng Zou, PhD; Jihye Ahn, PharmD; Justin Earp, PhD; Sudharshan Hariharan, PhD

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1. EXECUTIVE SUMMARY

Dabigatran etexilate is an oral anticoagulant which is approved under NDA 022512 to reduce the risk of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation, for the treatment of deep venous thrombosis and pulmonary embolism in adult patients who have been treated with a parenteral anticoagulant for 5-10 days and to reduce the risk of recurrence of deep venous thrombosis and pulmonary embolism in adult patients who have been previously treated. For the indications above, the approved dosing regimen is 150 mg twice daily (BID) in patients with creatine clearance >30 mL/min. Dabigatran etexilate has also been developed for the prophylaxis of deep vein thrombosis and pulmonary embolism in adult patients who have undergone hip replacement surgery. The approved dosing regimen is 110 mg taken orally 1-4 hours after surgery and after hemostasis has been achieved, then 220 mg taken once daily for 28-35 days.

To address the Pediatric Research Equity Act requirements and fulfill the FDA's post-marketing requirements, in addition to the approved capsule formulation, the Applicant, Boehringer Ingelheim International GmbH (BI), developed (b) (4) pellets (b) (4) for the treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients. The applications for capsules, (b) (4) and (b) (4) pellets were submitted under NDA 22512/S-41, (b) (4) and NDA 214358, respectively. (b) (4) NDA 214258 for PRADAXA® (dabigatran etexilate) (b) (4) pellets cross reference NDA 022512. All (b) (4) dosage forms together cover children from (b) (4) to less than 18 years. Please see 'Recommendations' below for the dosage forms and their associated age range that are approvable in this review cycle.

In the current NDA submissions (NDA 22512/S-41, (b) (4) and NDA 214358) for pediatric use, the Applicant submitted study reports for 7 clinical studies including two Phase 1 studies (1160.87 and 1160.194), three Phase 2 studies (1160.88, 1160.89, and 1160.105), and two pivotal Phase 3 studies (1160.106 and 1160.108).

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 022512/S041 (capsules) (b) (4) and NDA 214358 ((b) (4) pellets). The OCP review team recommends approval of NDA 022512/S014, PRADAXA capsules, in pediatric patients ≥8 years of age with adjustments to the Applicant proposed doses (b) (4) The OCP review team recommends approval of NDA 214358, PRADAXA (b) (4) pellets, in pediatric patients from 3 months to <12 years of age, with adjustments to the Applicant proposed doses. Key review issues with specific recommendations/ comments are summarized in the table below:

Review Issue	Recommendations and Comments
Supportive evidence of effectiveness	Clinical pharmacology information demonstrated similar exposure-response relationships for clotting time variables (aPTT, ECT and dTT) between pediatric and adult patients with VTE. In addition, the proposed doses in pediatric patients are expected to result in a similar range of steady-state dabigatran trough concentrations ($C_{trough,ss}$) as observed in adults, with certain exceptions as noted in section 3.3.2.
Relative bioavailability between oral solution/coated pellets and tablets	The (b) (4) pellets (b) (4) are not bioequivalent to the capsule dosage form. PRADAXA (b) (4) pellets (b) (4) resulted in 37% (b) (4) higher relative bioavailability (BA) in healthy adult subjects, respectively, compared to PRADAXAcapsules.

	While healthy adult relative BA studies demonstrated higher BA for (b) (4) pellets (b) (4) compared to capsules, the popPK model estimated relative BA between (b) (4) pellets and capsules using pediatric data is 0.62. The inconsistency in relative BA finding between pediatric patients and adults is not well understood. A direct BA comparison between the (b) (4) pellets and capsules in the pediatric population was not feasible because the (b) (4) pellets and capsules were used in different age groups (0 to 1 year, 0 to <12 years, and 8 to <18 years, respectively). The review team's dosing recommendation for (b) (4) pellets takes into account the inconsistency in relative BA estimates and their associated uncertainty in estimated exposures in pediatric patients. See section 4.3.3. for more details.
General dosing instructions	The Applicant proposed body weight- and age-based pediatric dosing regimens (b) (4) (See section 2.2.1) is based on pediatric clinical experience from Studies 106 and 108. The doses for these studies were selected by accounting for maturation and growth of the glomerular filtration rate (GFR) as a function of age and body weight during childhood. PRADAXA (b) (4) capsules can be administered with or without food. PRADAXA (b) (4) pellets are administered either with two teaspoons of soft food or (b) (4) of apple juice.
Dosing recommendations	Capsules: The review team's proposed dosing recommendations for PRADAXA capsules is guided by the exposure-response relationships observed in adult patients with VTE. The FDA recommended doses of PRADAXA capsules to be administered in patients >8 years of age targets dabigatran $C_{trough,ss}$ between 26 to 146 ng/mL. These concentrations correspond to the 10th and 90th percentiles of trough exposures observed in adult patients with VTE from RE-COVER. The geometric mean (gMean) pre-titration $C_{trough,ss}$ in pediatric patients receiving dabigatran capsules was 68% higher than that in adult patients with VTE. Also, in Studies 106 and 108, approximately 15 to 25% of patients receiving PRADAXA capsules had pre-titration $C_{trough,ss}$ higher than 146 ng/mL. Given the known exposure-response relationship for major bleeding in adults and the higher exposures at the proposed doses, the review team proposed up to (b) (4)% reduction of doses for pediatric patients age ≥8 years taking capsules. The revised doses are expected to result in dabigatran $C_{trough,ss}$ below 146 ng/mL in majority of patients (see Figure 3.3.2.3). The Applicant has agreed to the revised dosing regimen for PRADAXA capsules. (b) (4) pellets: The review team's dosing recommendations for PRADAXA (b) (4) pellets targets dabigatran $C_{trough,ss}$ between 50 to 250 ng/mL. Younger pediatric patients with VTE are considered to be more hypercoagulable which introduces uncertainty in assuming that a lower $C_{trough,ss}$ of 26 ng/mL observed in adults will also be efficacious in pediatric patients. Therefore, a lower bound of 50 ng/mL was set

	for deriving dosing recommendations for (b) (4) pellets, similar to how doses in Studies 106 and 108 were titrated to maintain a $C_{trough,ss}$ higher than 50 ng/mL. Owing to the high pharmacokinetic variability of (b) (4) pellets, there is a wider range in the predicted $C_{trough,ss}$ which results in exposures beyond 146 ng/mL, but within the exposure cap of 250 ng/mL set in Studies 106 and 108. In Studies 106 and 108, with the evaluated starting doses, 49% of the patients receiving (b) (4) pellets (b) (4) (b) (4) had pre-titration $C_{trough,ss}$ <50 ng/mL. To address this concern, the Applicant's originally proposed doses for PRADAXA (b) (4) pellets were approximately (b) (4)% higher. However, even with the proposed dose increase, popPK simulations show that (b) (4)% of patients have predicted dabigatran $C_{trough,ss}$ less than 50 ng/mL. In subsequent communications during the review cycle, the Applicant further increased the dose by up to (b) (4)% to maximize the proportion of patients achieving $C_{trough,ss}$ >50 ng/mL without exceeding an upper bound of 250 ng/mL. The doses were also optimized not to exceed the daily intake limit for tartaric acid. Applicant's revised dosing for PRADAXA (b) (4) pellets is acceptable with specific recommendations made by the review team as outlined below: (1) to include dosing information in patients ≥3 months and <4 months of age; (2) reducing the dose from (b) (4) mg BID to 220 mg BID for patients ⩾2 years of age and with body weight ⩾31 kg to <41 kg; and (3) reducing the dose from (b) (4) mg BID to 260 mg BID for patients ⩾2 years of age and with body weight ⩾81 kg. See section 3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought? for details.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Body weight-based starting dosing regimen is required for pediatric patients. • Avoid use of PRADAXA in pediatric patients with eGFR <50 mL/min/1.73 m^2. • Avoid concomitant use with P-gp inducers in pediatric patients.
Labeling	Refer to section 2.4 for the review team's recommendations.

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Absorption: Following oral administration of dabigatran etexilate to pediatric VTE patients, population pharmacokinetic (popPK) analysis showed that 1) the peak plasma concentrations of dabigatran reached approximately at 2.5 hours post dose, 2) dabigatran exhibits dose-proportional pharmacokinetics in pediatric VTE patients, 3) multiple administrations of oral doses of dabigatran etexilate in pediatric patients resulted in drug accumulation of approximately 1.5- to 1.9- fold in the plasma, and 4) the

pharmacokinetic steady state was reached following approximately 2–3 days of dosing in pediatric VTE patients.

Oral absorption of dabigatran etexilate is formulation-dependent. Study 1160.194 in healthy adults showed that at steady state, PRADAXA (b) (4) pellets (b) (4) administered under fasted state resulted in 37% (b) (4) higher relative bioavailability (BA) compared to PRADAXA capsules administered under fasted state. However, in children receiving the (b) (4) pellets in sachets, popPK analysis showed that the apparent relative BA of dabigatran was (b) (4) 0.619 times that for capsules, respectively.

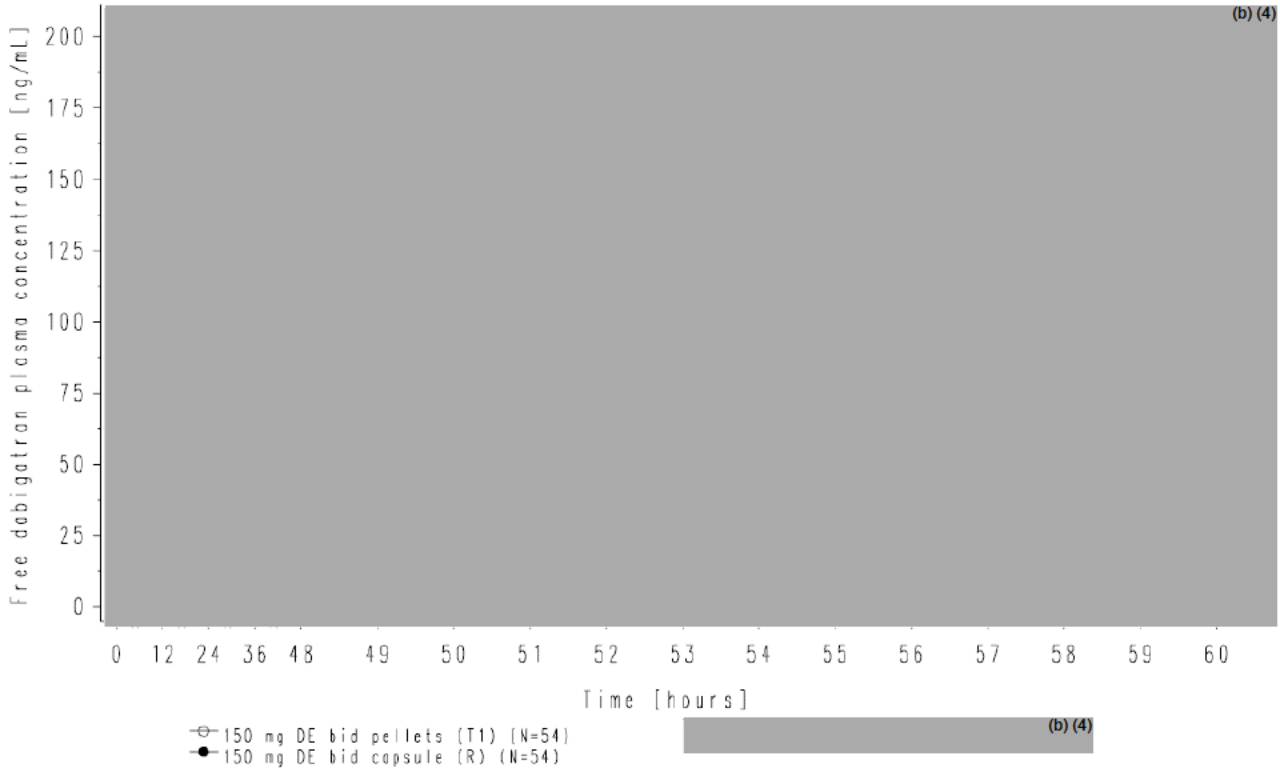
In pediatric patients taking age- and weight-adjusted doses of PRADAXA capsules, (b) (4) pellets (b) (4) in Study 1160-0106, the observed gMean steady-state trough concentration ($C_{trough,ss}$) was 99.9 ng/mL, 57.7 ng/mL (b) (4) respectively.

Based on the results from a food effect study conducted with PRADAXA capsules in adults, a high-fat meal did not affect the AUC or C_{max} of dabigatran. No dedicated food effect study was conducted with (b) (4) pellet formulations. In phase 3 trials, dabigatran etexilate was administered with or without food.

The plasma concentration-time profiles of total dabigatran following oral administration of multiple doses of PRADAXA capsules, (b) (4) pellets (b) (4) 150 mg under the fasted state in healthy adult subjects are shown in

Figure 2.1- ***1***.

Figure 2.1- **1**. Mean (+SD) Plasma Concentration-Time Profiles of Total Dabigatran Following Oral Administration of Multiple Doses of Dabigatran Etexilate Capsules, Pellets (b) (4) 150 mg Under Fasted State



Source: Figure 15.6.5.3:1 in Study 1160-194 report, page 281.

Distribution: Based on popPK model in pediatric patients, volume of distribution increased with body weight in accordance with allometric scaling.

Elimination: The elimination half-life in pediatric patients was approximately 10–14 hours.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

Dabigatran is excreted predominantly unchanged in urine, and, consequently, renal clearance is responsible for the majority of dabigatran elimination. The age- and body weight-based pediatric dosing was designed using Hayton equation (Hayton WL. AAPS PharmSci 2000;2(1): 22-28) that describes maturation and growth of the glomerular filtration rate (GFR) as a function of age and body weight during childhood.

PRADAXA (b) (4) capsules are administered with or without food. PRADAXA (b) (4) pellets are administered either with two teaspoons of soft food or (b) (4) of apple juice. (b) (4) formulations are administered twice daily. The OCP review team recommends adjustments of the doses for capsules and (b) (4) pellets. (b) (4) The Applicant-proposed and the FDA-recommended dosing algorithms for capsules and (b) (4) pellets are listed below.

Applicant-proposed dosing table for PRADAXA capsules (mg) for patients aged ≥ 8 years and <18 years:

(b) (4)

(b) (4)

FDA-proposed dosing table for PRADAXA capsules (mg) for patients aged ≥8 years and <18 years:

Actual Weight (kg)	Dose (mg)	Number of Capsules Needed
11 kg to less than 16 kg	75 mg twice daily	one 75 mg capsule twice daily
16 kg to less than 26 kg	110 mg twice daily	one 110 mg capsule twice daily
26 kg to less than 41 kg	150 mg twice daily	one 150 mg capsule twice daily or two 75 mg capsules twice daily
41 kg to less than 61 kg	185 mg twice daily	one 110 mg capsule plus one 75 mg capsule twice daily
61 kg to less than 81 kg	220 mg twice daily	two 110 mg capsule twice daily
81 kg or greater	260 mg twice daily	one 150 mg capsule plus one 110 mg capsule twice daily or one 110 mg capsule plus two 75 capsules twice daily

Applicant's initially proposed dosing table for PRADAXA (b) (4) pellets for patients aged < (b) (4) years:

(b) (4)

(b) (4)

Applicant's initially proposed dosing table for PRADAXA (b) (4) pellets for patients aged ≥ (b) (4) and <12 years:

(b) (4)

(b) (4)

(b) (4)

FDA-proposed dosing table for PRADAXA (b) (4) pellets for patients aged 3 months to <2 years:

Weight [kg]	Age in months								Age in years	
	3 to <4	4 to <5	5 to <6	6 to <8	8 to <9	9 to <10	10 to <11	11 to <12	1 to < 1.5	1.5 to <2
21 to <26										180
16 to <21									140	140
13 to <16							100	140	140	140
11 to <13					100	100	100	100	100	110
9 to <11			60	80	80	80	80	90	90	90
7 to <9	50	60	60	60	60	70	70	70	70	70
5 to <7	40	40	50	50	50	50	50	50	50	50
4 to <5	40	40	40	40	40	40				
3 to <4	30	30	30							

FDA-proposed dosing table for PRADAXA (b) (4) pelletsfor patients aged ≥2 and <12 years:

Actual Weight (kg)	Dose (mg)	Number of Packets Needed
7 kg to less than 9 kg	70 mg twice daily	one 30 mg packet plus one 40 mg packet twice daily
9 kg to less than 11 kg	90 mg twice daily	one 40 mg packet plus one 50 mg packet twice daily
11 kg to less than 13 kg	110 mg twice daily	one 110 mg packet twice daily
13 kg to less than 16 kg	140 mg twice daily	one 30 mg packet plus one 110 mg packet twice daily
16 kg to less than 21 kg	170 mg twice daily	one 20 mg packet plus one 150 mg packet twice daily
21 kg to less than 41 kg	220 mg twice daily	two 110 mg packets twice daily
41 kg or greater	260 mg twice daily	one 110 mg packet plus one 150 mg packet twice daily

2.2.2 Therapeutic individualization

Body Weight and Age:
Based on the popPK model, CL/F and V_d/F of dabigatran in pediatric patients increased with increasing body weight in accordance with allometric scaling. Body weight-based starting doses are required for pediatric patients. The apparent clearance increased with age in infants. Age- and body weight-based dosing regimen is required for patients aged <2 years.

Renal Impairment: Dabigatran is eliminated primarily by renal excretion and exposure to dabigatran increases with severity of renal function impairment. For pediatric patients with eGFR ≥50 mL/min/1.73 m^2, no dose adjustment is needed. Due to lack of data in pediatric patients with eGFR <50 mL/min/1.73 m^2 and the risk of increased exposure, avoid use of PRADAXA in these patients.

Drug Interactions: Dabigatran is a substrate of P-gp transporter. Concomitant use of PRADAXA with P-gp inhibitors has not been studied in pediatric patients and may increase exposure to dabigatran. However, as use of P-gp inhibitors is allowed in adults with eGFR >50 mL/min, no changes to dosing instructions are needed with P-gp inhibitor use in pediatric patients. Concomitant use of PRADAXA with P-gp inducers has not been studied in pediatric patients and may decrease exposure to dabigatran. Avoid concomitant use of P-gp inducers and dabigatran etexilate.

2.3 Outstanding Issues

(b) (4)

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology has following major labeling recommendations:

- Section 2: Revised the proposed doses for PRADAXA capsules (patients ⩾8 years of age) and (b) (4) pellets (patients ⩾3 months and <12 years of age).
- Section 12.3: Updated pediatric PK data.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Dabigatran etexilate is the oral pro-drug of the active moiety of dabigatran. The pro-drug, dabigatran etexilate, is administered in its salt form, dabigatran etexilate mesylate, which is converted into its active form, dabigatran, in-vivo via esterases. The clinical pharmacology study program of dabigatran in pediatric patients is comprised of three Phase 2 trials: 1160.105 (birth to <1 year old), 1160.89 (1 to <12 years old), and 1160.88 (12 to <18 years old). PK and pharmacodynamic (PD) data were also collected in two Phase IIb/III trials: 1160.106 (birth to <18 years old) and 1160.108 (birth to <18 years old). The dosage forms, strengths, target populations and dose ranges proposed by the applicant are summarized in *Table 3.1- 1*.

Table 3.1- 1 The NDAs, strengths, target population and dose ranges for [redacted] dosage forms of dabigatran etexilate

NDA	Dosage Form	Strength	Target VTE Patients	Age- and Weight-based Daily Dose
022512/ S-41	Capsules	75, 110 and 150 mg	≥8 and <18 years	75 – 300 mg twice daily
[redacted]				
214358	[redacted] Pellets	20, 30, 40, 50, 110, 150 mg per packet	<12 years	70 – [redacted] mg twice daily

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of Action	Dabigatran and its acyl-glucuronides are competitive, direct thrombin inhibitors. Because thrombin (serine protease) enables the conversion of fibrinogen into fibrin during the coagulation cascade, its inhibition prevents the development of a thrombus. Both free and clot-bound thrombin, and thrombin-induced platelet aggregation are inhibited by the active moieties.
Active Moieties	Dabigatran
QT Prolongation	No prolongation of the QTc interval was observed with dabigatran etexilate in adults at doses up to 600 mg.
General Information	
Bioanalysis	LC-MS/MS methods were used to measure plasma and urine non-conjugated and total dabigatran as well as dabigatran etexilate and intermediate metabolites of dabigatran etexilate .
Healthy vs. Patients	N.A.
Trough concentrations at steady state (Mean ± SD)	Capsules: 106 ± 37 ng/mL; Pellets: 65.4 ± 31.7 ng/mL; [redacted]
Range of effective dose or exposure	• Steady-state trough exposure ($C_{trough,ss}$) range observed in adult VTE patients: 26 to 146 ng/mL • Target range of $C_{trough,ss}$ used by the Applicant to guide pediatric trials: 50 to 250 ng/mL
Maximally tolerated dose or exposure	Healthy adults: 900 mg (single dose); 400 mg TID X 7 days (multiple dose) Pediatric VTE patients: 300 mg BID X 12 months
Pharmacodynamics	As in adults, there is a correlation between plasma dabigatran concentrations and the degree of its anticoagulant effect in pediatric patients with venous thromboembolism. The parameters dTT and ecarin clotting time (ECT) increased in direct linear proportion to the plasma concentration of dabigatran, whereas activated partial thromboplastin time (aPTT) prolongation increases in a nonlinear fashion with dabigatran plasma concentrations. Similar PK/PD relationships for aPTT, ECT, and dTT were observed across age groups of pediatric patients (ages 26 days to <18 years) and between pediatric and adult patients with venous thromboembolism.
Dose Proportionality	PopPK analysis showed that dabigatran exhibits dose-proportional pharmacokinetics in pediatric VTE patients.

Accumulation	PopPK simulation showed that multiple administrations of oral doses of dabigatran etexilate in pediatric patients resulted in drug accumulation of approximately 1.5- to 1.9- fold in the plasma.			
Variability	Between-subject CV in $C_{trough,ss}$: capsules 34.5%; (b) (4) pellets 58.6%; (b) (4) (b) (4)			
Absorption				
Bioavailability	3 - 7% in adults			
Fasted T_{max} (Median and Range)	2.0 hour (1.0 – 4.0 hour) (Study 1160.89)			
Food Effect Following a High-Fat Meal (Fed/fasted) [90% CI]	**Drug component**	**$AUC_{0-\infty}$**	**C_{max}**	**T_{max} (Median, hour)**
	dabigatran	118% (90% - 153%)	96% (72% - 129%)	Fed: 4.0, Fasted: 2.0
Distribution				
Volume of Distribution	Vd/F: 271 L (6-month infants) – 1520 L (18-year adolescents)			
Plasma Protein Binding	35%			
Substrate transporter systems	Dabigatran etexilate is a substrate of P-gp, but dabigatran is not a substrate of P-gp.			
Elimination				
Terminal Elimination half-life	10 – 11 hours in 6-month infants and 13 – 14 hours in 18-year adolescents			
CL/F	20 – 22 L/hour in 6-month infants and 95 – 106 L/hour in 18-year adolescents			
Metabolism				
Fraction metabolized (% dose)	<20% following intravenous administration			
Primary metabolic pathway(s)	glucuronidation			
Excretion				
Primary excretion pathways (% dose) ±SD	feces: 86% radioactivity following oral administration urine: 7% radioactivity following oral administration			
In vitro interaction liability (as a perpetrator)				
Inhibition/Induction of metabolism	Not an inhibitor or inducer of CYP enzymes			
Inhibition/Induction of transporter systems	Dabigatran etexilate or dabigatran is not an inhibitor of P-gp. The induction of P-gp by dabigatran etexilate or dabigatran was not determined. It is unknow if dabigatran etexilate or dabigatran is an inducer or inhibitor of other transporters.			

3.3 Clinical Pharmacology Review Questions

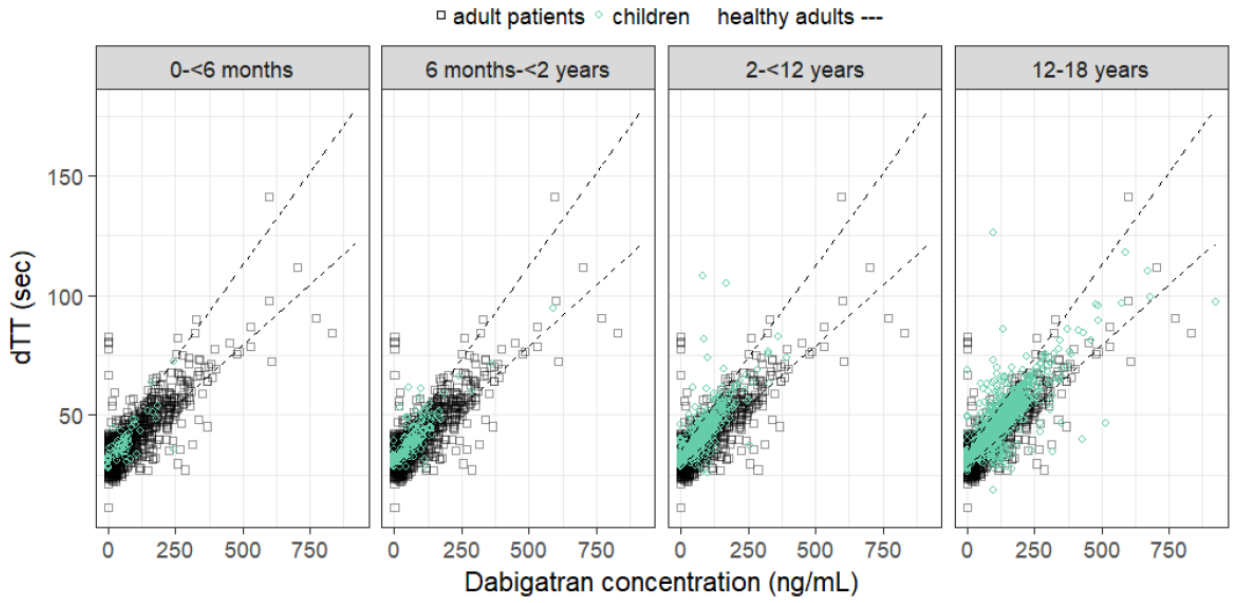
3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?

The clinical pharmacology information provides supportive evidence of effectiveness in the similarity in PK-PD relationships and range of steady-state C_{trough} values between pediatric and adult patients with VTE. Doses for the pivotal pediatric trial (Study 106) were selected with an intent to achieve dabigatran exposures comparable to that achieved in the adult trial, RE-COVER. A total of 267 pediatric patients were randomized in Study 106 and 253 patients completed the study. Results for PK-PD relationship- and dabigatran concentration- comparisons between adults and children are described in the following sections.

Similar PK-PD relationships for dTT, aPTT and ECT between pediatrics and adults:
The Applicant conducted pooled PK/PD relationship analysis for clotting time variables (activated partial thromboplastin time [aPTT], diluted thrombin time [dTT], and ecarin clotting time [ECT]) in pediatric VTE patients and compared with the PK/PD relationships observed in adult VTE patients and healthy adults (Figures 3.3.1-1, 3.3.1-2, and 3.3.1-3).

The dTT increased linearly with increasing dabigatran concentration, in proportion to baseline (**Figure 3.3.1-*1***). The PK/PD relationship for dTT in children was similar to adults across all pediatric age groups. No age-related differences were detected for the baseline or the slope parameters of the PK/PD relationship. The PK/PD relationships for dTT in pediatric patients were similar to that in adult patients, based on visual inspection.

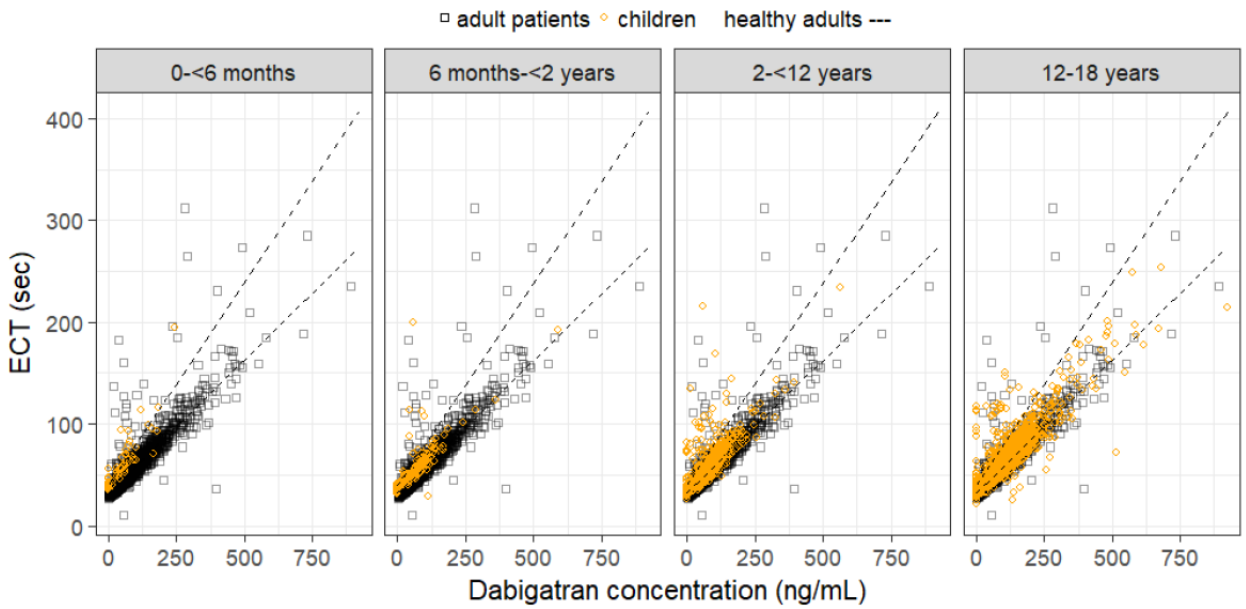
Figure 3.3.1- 1 Observed dTT versus dabigatran plasma concentrations, stratified by age group



Source: Summary of Clinical Pharmacology Studies, Figure 2.2.4: 2

ECT increased linearly with increasing dabigatran concentration, in proportion to baseline (**Figure 3.3.1- *2***). For ECT, there was a trend towards more samples outside of the upper healthy adult reference range in the youngest children aged 0-6 months. The baseline of ECT was on average estimated to be higher in children <6 months of age than in the other children (40 versus 36 seconds). The PK/PD relationships for ECT in pediatric patients >6 months were similar to that in adult patients, based on visual inspection.

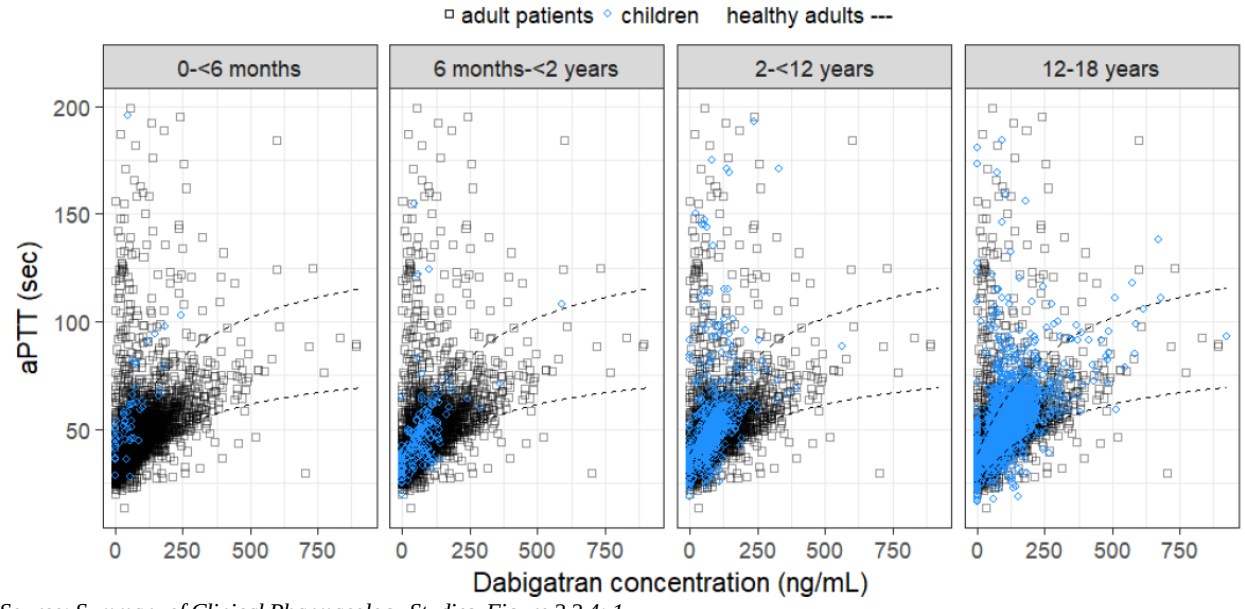
Figure 3.3.1- 2 Observed ECT versus dabigatran plasma concentrations, stratified by age group



Source: Summary of Clinical Pharmacology Studies, Figure 2.2.4: 3

The aPTT increased non-linearly with increasing dabigatran concentration (E_{max} relationship), in proportion to baseline (**Figure 3.3.1- *3***). For aPTT, there was a trend towards more samples outside of the upper healthy adult reference range in the youngest children aged 0-6 months. The baseline of aPTT was on average higher in children below 6 months of age than in the other children (45 versus 36 seconds). The PK/PD relationships for ECT in pediatric patients >6 months were similar to that in adult patients, based on visual inspection.

Figure 3.3.1- 3 Observed aPTT versus dabigatran plasma concentrations, stratified by age group.



Source: Summary of Clinical Pharmacology Studies, Figure 2.2.4: 1

Overall, 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 $C_{trough,ss}$ between pediatric and adult patients:
Based on the 10th to 90th percentile of observed dabigatran trough concentrations in adult VTE patients in Study RE-COVER (26 to 146 ng/mL) and in adult patients with risk of stroke and systemic embolism in non-valvular atrial fibrillation in Study RE-LY (23 to 238 ng/mL), the Applicant used 50 to 250 ng/mL as the target steady-state trough exposure in pediatric VTE patients to guide the design of starting dose and titration plan in Studies 106 and 108. The Applicant selected the lower boundary of trough plasma concentration at 50 ng/mL due to the lack of a quantitative coagulation-based assay that reliably measured dabigatran below 50 ng/mL and the upper boundary based on the exposure-response relationship for major bleeding events (MBE) in RE-COVER and RE-LY.

In Studies 106 and 108, to ensure plasma dabigatran concentrations fall within a 50 to <250 ng/mL window, the Applicant allowed one dose titration. At Visit 3 (after at least 6 consecutive dabigatran etexilate doses), plasma dabigatran concentration was estimated by dTT assay initially, but later directly measured by LC-MS/MS due to low precision in the correlation between values estimated by dTT and directly measured by LC-MS/MS, as noted by the Applicant. If plasma dabigatran concentration was within 50 to 250 ng/mL, the subject continued to receive the same dose. If plasma dabigatran concentration was <50 ng/mL, dose was increased by 10 to 100% (up-titration) and the maximal allowed dose was 330 mg BID. If plasma dabigatran concentration was ≥250 ng/mL, dose was reduced by 25 to 50% (down-titration). If a patient did not reach $C_{trough,ss}$ between 50 and <250 ng/mL after one dose adjustment, the patient had to discontinue trial medication. The observed $C_{trough,ss}$ values in Study 106 and Study 108 were pooled and presented by age groups (**Table 3.3.1- *1***) and formulations (**Table 3.3.1- *2***). Both the pre-titration (Visit 3) and overall (all visits) $C_{trough,ss}$ by age groups and formulations were largely between the 10th and 90th percentile (26 to 146 ng/mL) of the observed dabigatran plasma exposure of the adult VTE patients. However, the pre-titration gMean $C_{trough,ss}$ value for dabigatran capsules (100 ng/mL) was 68% higher than that (59.7 ng/mL) in adult patients taking capsules 150 mg BID. The 90th percentile of pre-titration $C_{trough,ss}$ (180 ng/mL) in pediatric patients taking dabigatran capsules was higher than 146 ng/mL, indicating that the doses for dabigatran capsules need to be reduced to match adult $C_{trough,ss}$ range (Refer to section 3.3.2 for the dose reduction proposed by the review team). In contrast, the pre-titration (Visit 3) gMean $C_{trough,ss}$ values for dabigatran (b) (4) pellets were (b) (4) 20% lower than that (59.7 ng/mL) in adult patients taking capsules 150 mg BID. At Visit 3 (pre-titration), 25 among 53 patients (47%) receiving (b) (4) pellets (b) (4) had $C_{trough,ss}$ <50 ng/mL and had a dose increase. Also, the 10th percentile of gMean $C_{trough,ss}$ at Visit 3 (pre-titration) for (b) (4) and (b) (4) pellets were less than 26 ng/mL. These results suggest that the starting doses for (b) (4) (b) (4) pellets used in Studies 106 and 108 need to be increased to match adult exposure range and reasonably match clinical trial experience. The Applicant proposed to increase the doses for (b) (4) pellets by approximately (b) (4)% compared to the starting doses used in Studies 106 and 108 (b) (4)) During the review cycle, per the discussion between the FDA and Applicant, the Applicant futher increased the doses for (b) (4) pellets by (b) (4)% to ensure that dabigatran $C_{trough,ss}$ in approximately 80% of patients fall within 50 to 250 ng/mL and <10% of patients with $C_{trough,ss}$ >250 ng/mL (Refer to section 3.3.2 for the details of dose adjustment).

Table 3.3.1- 1 Comparisons of observed steady-state trough (1160.106, 1160.108, and RE-COVER) plasma total dabigatran concentrations by age groups

	0-6 months		**6 month - 2 year**		**0 - 2 year**		**2 - 12 year**		**12 - 18 year**		**Adults**
	Visit 3	All visits	Visit 3	All visits	Visit 3	All visits	Visit 3	All visits	Visit 3	All Visits	All visits
N	8	9	16	19	24	28	53	66	163	184	850

gMean	44.8	52.9	50.1	54.4	48.3	53.9	54.8	63.0	102	99.1	59.7
Median	47.9	51.8	51.4	62.6	51.4	59.5	55.3	65.8	103	98.9	58.7
Q1	31.1	41.3	29.4	43.5	30.8	42.4	42.2	55.2	71.8	78.2	38.6
Q3	68.0	60.8	77.6	78.6	70.5	78.5	74.6	83.5	131	127	94.5
P10	16.0	22.7	22.7	19.8	22.7	22.7	26.2	35.2	57.9	63.7	26.3
P90	102	108	106	110	102	108	106	109	180	152	146

Source: NDA 022512/S-041 Summary of Clinical Pharmacology Studies, Table 3.2:4; Section 5.3.3.5, Summary Tables Pooled Data 1160.106 and 1160.108, Table 1.2.6

Table 3.3.1- 2 Comparisons of observed steady-state trough (1160.106, 1160.108, and RE-COVER) plasma total dabigatran concentrations by formulations between pediatrics and adults.

	(b) (4)	(b) (4) pellets		Capsules		Adults RE-COVER
		Visit 3	All visits	Visit 3	All visits	All visits
N		53	63	177	203	850
gMean		47.5	54.7	100	97.9	59.7
Median		51.7	60.0	102	98.1	58.7
Q1		35.0	49.1	71.8	77.9	38.6
Q3		62.1	76.0	129	125	94.5
P10		20.3	25.9	57.0	63.7	26.3
P90		95.5	88.3	180	151	146

Source: Summary of Clinical Pharmacology Studies, Table 3.2:4; Section 5.3.3.5, Summary Tables Pooled Data 1160.106 and 1160.108, Table 1.2.7

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

Applicant's original proposed doses for PRADAXA capsules and (b) (4) pellets are shown in Section 2.2.1. The review team recommends adjustment to the Applicant proposed doses that are described in the following sections.

Applicant's dabigatran $C_{trough,ss}$ target range

The Applicant proposed (b) (4) to 250 ng/mL as the target range of total dabigatran $C_{trough,ss}$ to support their proposed dosing regimen for all pediatric patients. The lower bound ((b) (4) ng/mL) is the (b) (4) percentile of RE-COVER plasma total dabigatran $C_{trough,ss}$. However, due to the poor precision of the available dTT assay in estimating plasma dabigatran concentration below 50 ng/mL, the Applicant revised the lower bound to 50 ng/mL in the pediatric study plan (PSP). The upper end of 250 ng/mL is based on the exposure-response relationship for major bleeding events (MBE) in RE-COVER and RE-LY. The Applicant used a target range of 50 to 250 ng/mL to guide dosing in Studies 106 and 108, which were intended for dose finding as well as for demonstration of efficacy and safety.

FDA review team's dabigatran $C_{trough,ss}$ target range

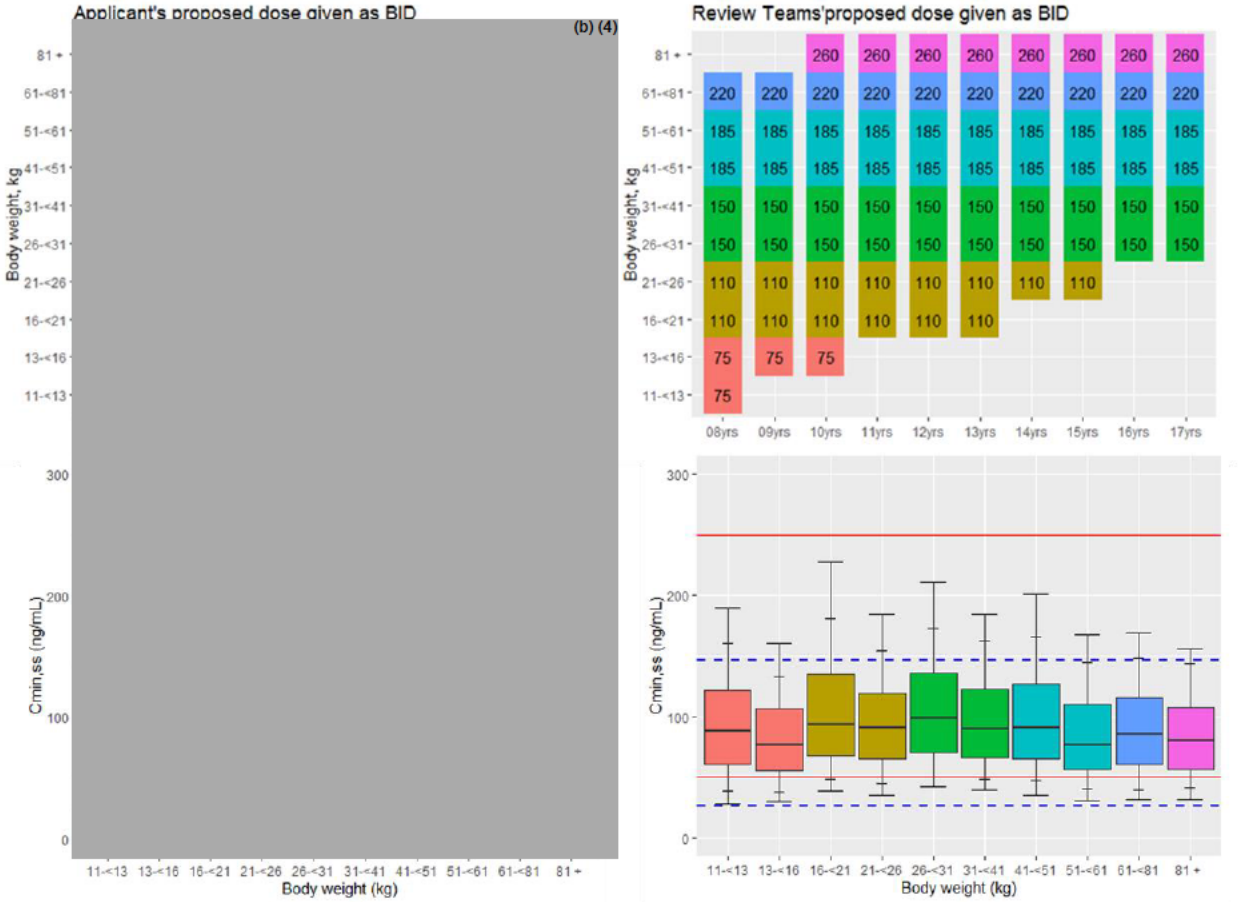
In addition to the clinical experience in pediatric patients, the review team recommends that pediatric dosing be guided by the exposure-response relationships for efficacy and safety observed in adult patients with VTE. Due to the similarity in VTE pathogensis between adolescent and adult VTE patients, the review team recommends adjustment of PRADAXA capsule doses to ensure dabigatran $C_{trough,ss}$ largely falls within (b) (4) to 146 ng/mL, which corresponds to the 10th and 90th percentiles of $C_{trough,ss}$ observed in adult VTE patients in RE-COVER. However, for PRADAXA (b) (4) pellets which are intended to be administered to patients <8 years

of age, the review team's dosing recommendations target dabigatran $C_{trough,ss}$ between 50 to 250 ng/mL. Younger pediatric patients tend to have complex medical conditions and multiple hypercoagulable risk factors that contribute to the development of VTE. As a result, younger pediatric patient with VTE are considered to be more hypercoagulable, when compared to adult patients with VTE (For more information, refer to the FDA's Information Request letter under NDA 022512 in DARRTS dated 2/25/2021). Therefore, there is greater uncertainty in assuming that dabigatran $C_{trough,ss}$ down to (b) (4) ng/mL will be efficacious. In the absence of an established exposure-response relationship in pediatric patients, the most judicious approach is to match clinical trial experience and set a more conservative lower bound $C_{trough,ss}$ of 50 ng/mL. Owing to a higher pharmacokinetic variability from PRADAXA (b) (4) pellets, the upper end of $C_{trough,ss}$ was set at 250 ng/mL, similar to the pediatric clinical trial experience.

Dose adjustments to PRADAXA capsules

Figure 3.3.2- ***1*** (top left) shows the Applicant's proposed body weight-based dosing regimen for capsules for patients ≥8 years, which is similar to the dosing algorithm used in Studies 106 and 108 with minor adjustments. As shown in **Table 3.3.1-** ***2***, patients receiving capsules had pre-titration (Visit 3) gMean $C_{trough,ss}$ of 100 ng/mL, which is 68% higher than the gMean $C_{trough,ss}$ observed in adult VTE patients (59.7 ng/mL) in RE-COVER. Furthermore, the popPK simulation shows that with the Applicant's dosing algorithm for dabigatran capsules, (b) (4) % of pediatric patients between 8 and 18 years had pre-titration $C_{trough,ss}$ higher than the 90th percentile of adult $C_{trough,ss}$ 146 ng/mL observed in RE-COVER (**Figure 3.3.2-** ***1***, bottom left). Given the known exposure-response relationship for major bleeding events in the adult trial (RE-COVER), the review team proposed between (b) (4) % reduction (depending on the weight band) of the Applicant's proposed doses as shown in **Figure 3.3.2-** ***1***. PopPK simulations showed that the review team's dosing algorithm could achieve pediatric $C_{trough,ss}$ below the 90th percentile of adult exposure (<146 ng/mL) in most patients (**Figure 3.3.2-** ***1***, bottom right). Refer to Section 4.3.3 for further details.

Figure 3.3.2- 1 A comparison of Applicant's and review team's proposed dosing tables for dabigatran capsules and simulated $C_{trough,ss}$ by body weight groups.



Source: Review team's analysis. Top figures: x-axis: age groups (in years); y-axis: body weight categories (in kg). The values represent dose (mg). Bottom figures: x- axis: body weight categories (in kg), y-axis: $C_{trough,ss}$ simulated by final popPK model. Boxplots represents 25th, median, 75th with whiskers 5th, 10th, 90th, 95th percentiles. Blue dashed lines represent 10th, 90th percentiles for adult $C_{trough,ss}$. Red solid lines represent 50 ng/mL. The simulations were conducted with virtual population (n=500) for each body weight- group.

Dose adjustments to PRADAXA (b) (4) pellets

In Studies 106 and 108, the pre-titration (Visit 3) 10th percentiles of gMean $C_{trough,ss}$ (20.3 ng/mL) for (b) (4) pellets was less than 26 ng/mL and approximately 11% of patients across several age categories had $C_{trough,ss}$ below 26 ng/mL. In the Applicant's proposed dosing algorithm (hereafter refered to as "initially proposed dosing", Section 2.2.1), the Applicant increased the doses for (b) (4) pellets in each age- and body weight-based group by approximately (b) (4)% compared to the starting doses used in Studies 106 and 108. The Applicant also made a few more adaptations to provide smoother dosing steps. The Applicant's popPK simulations showed that the proportion of patients with $C_{trough,ss}$ below (b) (4) with the initially proposed dosing table.

At the teleconference with the Applicant held on February 11, 2021, the review team conveyed its preliminary assessment of the Applicant's initially proposed dosing regimen. In particular, the team expressed concern at the proportion of patients with $C_{trough,ss}$ <50 ng/mL. The Applicant asserted that their proposed dosing regimen will result in (b) (4) percentile of $C_{trough,ss}$ just above the (b) percentile of adult exposures from RE-COVER i.e., (b) (4) ng/mL, thus preserving efficacy. However, as noted earlier, FDA expressed uncertainty with the notion of

treating younger pediatric patients (b) (4) FDA suggested that in the absence of exposure-response relationship in younger pediatric patients, a judicious approach was to mimic the clinical trial experience where younger pediatric patients were treated by targeting exposures >50 ng/mL. In this context, FDA discussed the option of titrating dabigatran doses based on dTT. FDA also noted uncertainty in the relative BA of (b) (4) pellets versus capsules in pediatric patients in derving doses for (b) (4) pellets.

In subsequent communications, to address the uncertainty in efficacy with the $C_{trough,ss}$ <50 ng/mL, the Applicant proposed a new dosing table for (b) (4) pellets (hereafter referred to as "newly proposed dosing", ***Table 3.3.2- 1***), where the doses were further increased by (b) (4) % for different body weight groups. The newly proposed dosing recommendation took into consideration the maximum daily intake for tartaric acid, one of the excipients in the (b) (4) pellets dosage form. Owing to the high within subject variability of dabigatran and the lack of PD assays to reliably estimate dabigatran plasma concentrations <50 ng/mL, the Applicant noted that titration of dabigatran doses based on a PD marker would not be feasible and in general, such an approach would not improve the precision of dosing. To address the uncertainty in age-dependent BA of (b) (4) pellets relative to capsules, the Applicant proposed to reduce the dose from (b) (4) mg BID to 260 mg BID in patients with body weigh (b) (4) kg and (b) (4) kg. In addition, the Applicant proposed to not provide dosing information for (b) (4) pellets in patients ≤3 months of age due to difficulty in swallowing (b) (4) pellets.

Table 3.3.2- 1. Applicant's newly proposed dosing table for (b) (4) pellets in the Response Letter dated March 19, 2021.

(b) (4)

Source: Applicant's Response Letter Received on 03/19/2021

Based on the submitted information on the limitations of the dTT assay and the high within subject variability of dabigatran, FDA agrees with the Applicant that titration of dabigatran doses based on a PD assay would not be feasible or practical. With the newly proposed dosing table (***Table 3.3.2- 1***), the Applicant's simulation results showed that the proportion of patients <8 years of age with $C_{trough,ss}$ <50 ng/mL was decreased from (b) (4) % (with initially proposed dosing table) to approximately (b) (4) %. The percentage of $C_{trough,ss}$ values >250 ng/mL is <9% (***Table 3.3.2- 2***). Further, based on the review team's confirmatory simulations (**Figure 3.3.2- *2***, and **Figure 3.3.2- *3***), following modifications were made to the Applicant's newly proposed dosing regimen: (1) allowing the use in patients ≥3 months and <4 months of age; (2) reducing the dose from (b) (4) mg BID to 220 mg BID for patients ⩾2 years of age and with body weight (b) (4) kg to <41 kg; and (3) reducing the dose from (b) (4) mg BID to 260 mg BID for

patients ⩾2 years of age and with body weight ⩾81 kg. These changes are further explained in the following subsections. The review team's final recommended dose table is presented in ***Table 3.3.2- 3***.

Table 3.3.2- 2. Percentage steady-state trough concentration measurements with (b) (4) pellets reaching or exceeding certain cut-offs (26 ng/ml, 50 ng/ml, 250 ng/ml) with the newly proposed dosing table

Age	% of $C_{ss,min}$ within 26 to <250 ng/mL	% of $C_{ss,min}$ within 50 to <250 ng/mL	% of $C_{ss,min}$ below < 26 ng/mL	% of $C_{ss,min}$ below < 50 ng/mL	% of $C_{ss,min}$ above > 250 ng/mL
3– <4 m	(b) (4)				
4– <5 m					
5– <6 m					
6– <7 m					
7– <8 m					
8– <9 m					
9– <10 m					
10– <11 m					
11– <12 m					
1– <1.5 y					
1.5– <2 y					
2– <2.5 y					
2.5– <3 y					
3– <4 y					
4– <5 y					
5– <6 y					
6– <7 y					
7– <8 y					
8– <9 y					
9– <10 y					
10– <11 y					
11– <12 y					

Source: Applicant's Response Letter Received on 03/19/2021

Table 3.3.2- 3. FDA review team's recommended dosing table for (b) (4) pellets

(b) (4)

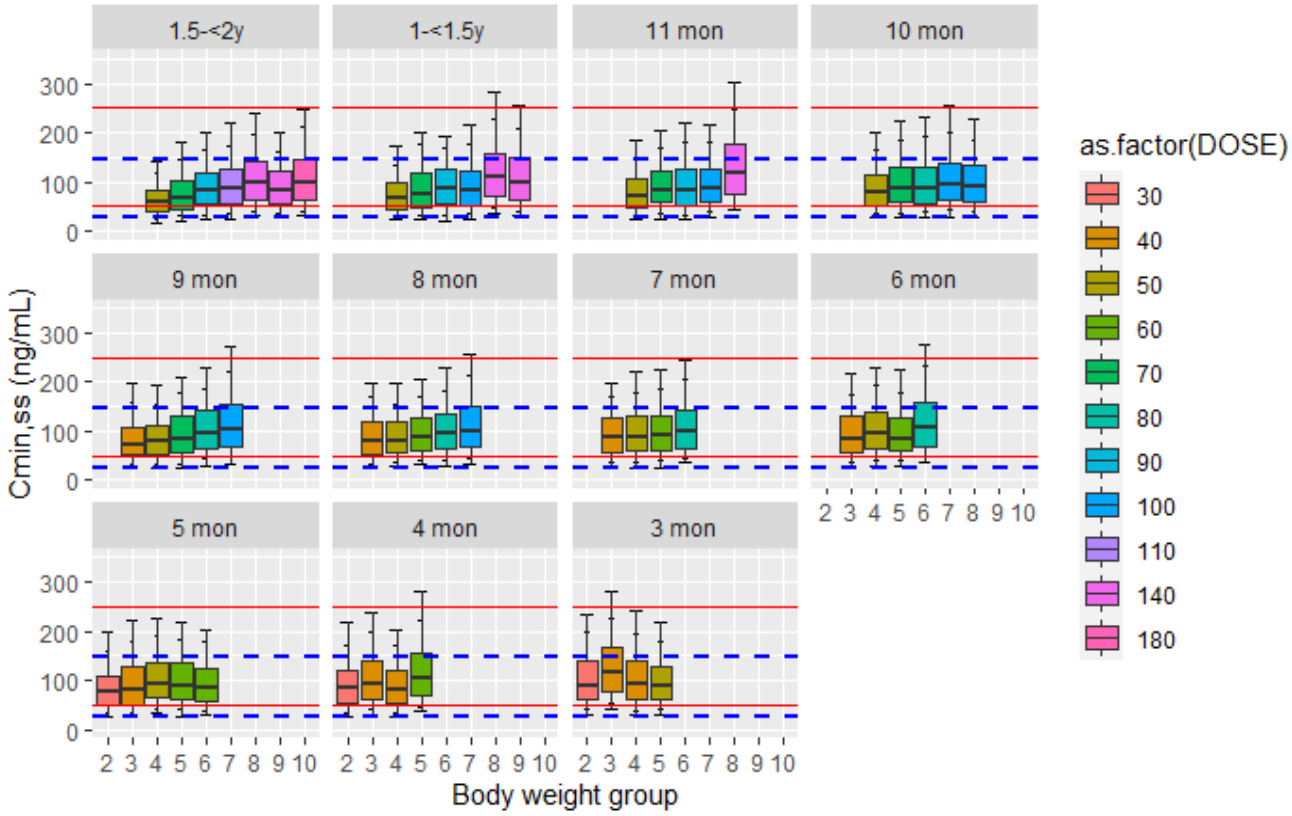
Source: Adapted from Table 4 in the Applicant's response document titled "BI Response - Dosing Table.docx",with the review team's recommended modifications (in red boxes)

Review team's dosing recommendation for (b) (4) *pellets in patients 3 months to <2 years of age*

The review team's recommended dosing regimen for patients <2 years old are based on both age and body weight (

Table 3.3.2- 3). The simulated dabigatran $C_{trough,ss}$ following the review team's recommended doses are presented by body weight groups (x-axis), and age groups (by panel) in **Figure 3.3.2- *2***. Across the age- and body-weight groups, the range (10^{th}, 90^{th} percentiles) of $C_{trough,ss}$ are largely within the range of 50 to 250 ng/mL. Note that the dose levels for certain body weight groups were not increased from those in the initially proposed dose due to the allowable daily limit of tartaric acid (equivalent to 22.2 mg/kg/day dabigatran). Therefore, the proportion of patients with $C_{trough,ss}$ <50 ng/mL is variable across body weight for a given age group. In certain age and weight group combination (e.g., 3 months old with 3 to <4 kg body weight), the simulated 90^{th} percentiles of $C_{trough,ss}$ approach the upper boundary 250 ng/mL. In general, the review team's dose selection for (b) (4) pellets in pediatric patients aged <8 years were guided to attain $C_{trough,ss}$ >50 ng/mL in as many patients as possible, provided that the 90^{th} percentiles of predicted $C_{trough,ss}$ do not exceed 250 ng/mL and the total daily dose does not exeed the daily limit of tartaric acid.

Figure 3.3.2- 2 Simulated dabigatran $C_{trough,ss}$ exposure by age and weight following the review team's recommended dosing regimen for (b) (4) pellets for pediatric patients 3 months to <2 years of age



Weight group	2	3	4	5	6	7	8	9	10
Weight (kg)	3-<4	4-<5	5-<7	7-<9	9-<11	11-<13	13-<16	16-<21	21-<26

Source: Review team's analysis. Boxplots represents 25^{th}, median, 75^{th} with whiskers 5^{th}, 10^{th}, 90^{th}, 95^{th} percentiles. Blue dashed lines represent 10^{th}, 90^{th} percentiles for adult $C_{trough,ss}$. Red solid lines represent 50 ng/mL and 250 ng/mL. The simulations were conducted with virtual population (n=300) generated by sampling for each age-, and body weight- group.

Review team's dosing recommendation for (b) (4) *pellets in patients of 2 to <12 years of age*

The review team's recommended dosing regimen for patients aged 2 to <12 years old are based on body weight only (***Table 3.3.2- 4***) which were guided 1) to increase the proportion of pediatric patients achieving $C_{trough,ss}$ >50 ng/mL and 2) to address the uncertainty in relative BA of (b) (4) pellets. The key changes made from the Applicant's initially proposed dose for age 2 to <12 years old are: 1) dose increases by (b) (4)% in certain weight groups and 2) dose reduction from (b) (4) mg BID to 260 mg BID for subjects with body weight (b) (4) kg (***Table 3.3.2- 4***).

Table 3.3.2- 4. A comparison of Applicant's initially proposed dose and the review team's recommended dose for (b) (4) pellets for age 2 to <12 years old

Body weight groups	Applicant's initially proposed dose	Review team's recommended dose	Change
7 to <9 kg	70 mg BID	70 mg BID	-
9 to <11 kg	(b) (4) mg BID	90 mg BID	+ (b) (4)%
11 to <13 kg	mg BID*) 110 mg BID	110 mg BID	(+ %) -
13 to <16 kg	140 mg BID	140 mg BID	-
16 to <21 kg	(b) (4) mg BID	170 mg BID	+ (b) (4)%
21 to <31 kg	mg BID	220 mg BID	+ %
31 to <41 kg	220 mg BID	220mg BID	-
(b) (4)			

*** The Applicant's initially proposed dose was (b) mg BID for age (b) (4) years old, and (b) mg BID for age (b) years to <12 years old.**

There was a discrepancy in the relative BA of (b) (4) pellets compared to capsules between the relative BA study (Study 194) in healthy adults and the population PK analysis performed using pediatric PK data. In healthy adults, PRADAXA (b) (4) pellets resulted in 37% higher relative BA compared to PRADAXA capsules. In contrast, the Applicant's population PK analysis estimated that the relative BA of (b) (4) pellets was 38% lower than that for capsules in the pediatric population. The reason for the discordant finding between pediatric patients and adults is not clear.

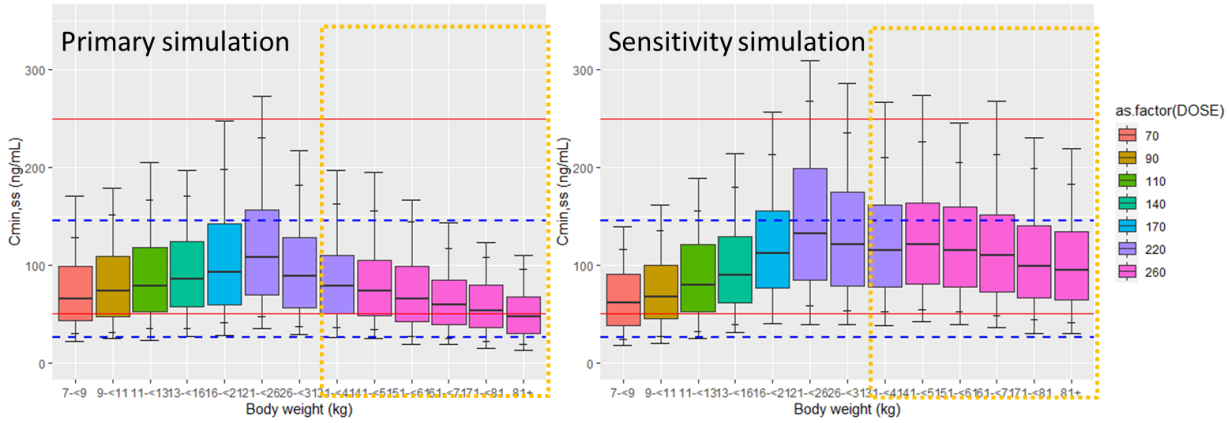
A direct BA comparison between the (b) (4) pellets and capsules in the pediatric population was not feasible because the capsule and (b) (4) pellets were used in different age groups (8 to <18 years, and 0 to <12 years, respectively) with limited PK data available from the age group (8 to <12 years) who could receive either formulation. The observed $C_{trough,ss}$ following administration of (b) (4) pellets (mean $C_{trough,ss}$ = 78.1 ng/mL, N = 6) and capsules (mean $C_{trough,ss}$ = 87.2 ng/mL, N = 19) in patients aged 8 to <12 years showed that the relative BA in this subpopulation is closer to 1.

Given the knowledge gaps and the relative BA confounded by age, the review team noted uncertainty in the projected exposures based on the population PK analysis which uses a model derived relative BA

estimate of 0.62 in pediatric patients. It cannot be ruled out that pediatric patients have a relative BA (137%) for (b) (4) pellets vs capsules similar to that observed in healthy adults. Therefore, in a worst-case scenario, (b) (4) pellets could potentially lead to higher exposures than the capsule formulation for the same dose. The review team performed a sensitivity PopPK analysis which assumed the same relative BA of (b) (4) pellets (estimate of 1.17) between pediatric patients and healthy adults (Refer to Section 4.3.3 for more information). The projected exposures using the sensitivity model are notably different from those derived using the Applicant's PopPK model especially for patients with body weight ⩾31 kg, which suggests that there is greatest uncertainty in the predicted exposures using the Applicant's PopPK model for these weight groups (i.e., ⩾31 kg). Therefore, in evaluation of the doses for patients ages 2 to <12 years, dabigatran exposures were projected using both models: Applicant's model in primary simulations, and the review team's sensitivity model in sensitivity simulations (**Figure 3.3.2- *3***).

The predicted exposures following the review team's final recommended dose are presented in **Figure 3.3.2- *3***. As patients who are eligible to receive (b) (4) pellets (<12 years of age) are not expected to weigh ⩾81 kg, the projected lower exposures in this weight group would not be of major concern. Also, capping the pellet dose to 260 mg is to ensure that the maximum recommended dose for capsules is not exceeded for the worst case scenario where the relative BA of (b) (4) pellets (vs. capsule) is greater than 1. When the exposures were projected using the sensitivity model (right panel), the 90th percentiles of $C_{trough,ss}$ in pediatric patients in body weight ⩾31 kg are expected to be below 250 ng/mL. In certain lower weight groups where the 10th percentile of $C_{trough,ss}$ is below 50 ng/mL, there is limitation to increase the dose due to the daily intake limit of tartaric acid.

Figure 3.3.2- 3 Simulated dabigatran $C_{trough,ss}$ exposure by weight following the review team's recommended dosing regimen for (b) (4) pellets for pediatric patients 2 years to <12 years of age



Source: Review team's analysis. Boxplots represents 25th, median, 75th with whiskers 5th, 10th, 90th, 95th percentiles. Blue dashed lines represent 10th, 90th percentiles for adult $C_{trough,ss}$. Red solid lines represent 50 ng/mL and 250 ng/mL. The simulations were conducted with virtual population (n=500) generated by sampling for each body weight- group.

(b) (4)

3.3.3 Is there a management strategy required for subpopulations based on intrinsic factors?

Yes, the use of PRADAXA should be avoided in pediatric patients with eGFR <50 mL/min/1.73 m^2. Age- and body weight-based dosing regimen is required for patients aged <2 years. Body weight-based dosing regimen is required for patients aged ≥2 and ≤18 years.

Intrinsic factors including body weight, sex, age, race and renal function were investigated as potential sources of variability in dabigatran PK as part of the popPK analyses of pediatric VTE patients. Body weight, age, and renal function were identified as significant factors influencing dabigatran apparent clearance (CL/F) and body weight was identified as a significant factor influencing dabigatran apparent volume of distribution (V_d/F). The apparent clearance was on average 10% lower in female pediatric subjects than in male pediatric subjects, independently of the formulation. No sex-based dose adjustment is required. The small number of African American (n=7) or Asian (n=18) subjects included in the popPK analysis precluded a meaningful conclusion on the effect of race on dabigatran PK in pediatric patients.

Body Weight:
Based on the popPK model, CL/F and V_d/F of dabigatran in pediatric patients increased with increasing body weight in accordance with allometric scaling. Body weight-based dosing regimen is required for pediatric patients.

Age:
Based on popPK simulation, the apparent clearance increased with age in patients <5 years old (independent of body weight). Half of the maturation of clearance is reached at age of 6 weeks and 90% at around age of 20 months. The Applicant proposed age- and body weight-based dosing regimen for patients aged < (b) (4) years.

Renal Impairment:
Dabigatran is eliminated primarily by renal excretion and exposure to dabigatran increases with severity of renal function impairment. PopPK simulation showed that the typical apparent clearance was 15% lower in a patient with an eGFR of 50 mL/min/1.73m^2 compared to a reference patient with eGFR of 104 mL/min/1.73m^2. For pediatric patients with eGFR >50 mL/min/1.73 m^2, no dose adjustment is required. Pediatric patients with eGFR <50 mL/min/1.73m^2 were excluded from Studies 106 and 108. Due to lack of data in pediatric patients with eGFR <50 mL/min/1.73 m^2 and the risk of increased exposure, dose recommendation cannot be provided and the use should be avoided in these patients.

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

Yes, concomitant use of P-gp inducers and PRADAXA should be avoided.

Food Effects:
A food effect study conducted in adults showed that a high-fat meal did not affect C_{max} or AUC of dabigatran but delayed T_{max} from 2 h to 4 h. The effects of food on the PK of dabigatran etexilate was not evaluated in pediatric subjects. In Studies 106 and 108, dabigatran etexilate was taken with or without food. In case of gastrointestinal symptoms, pediatric patients were instructed to take dabigatran etexilate with a meal or a proton pump inhibitor to reduce gastrointestinal symptoms.

Drug-Drug Interactions:
Dabigatran is a substrate of P-gp transporter. The concomitant use of PRADAXA with P-gp inhibitors has not been studied in pediatric patients but may increase exposure to dabigatran. The expression of intestinal P-gp mRNA in human intestinal tissues from neonates (birth to 1 month), infants (1 to 12 months), children (12 months to 17 years) and adults (>17 years) was investigated. No significant

difference in the level of expression of P-gp mRNA was found among the tissues. Concomitant use of P-gp inhibitors is allowed in adult VTE patients with eGFR >50 mL/min taking dabigatran. Consistently, concomitant use of P-gp-inhibitors is allowed in pediatric VTE patients with eGFR >50 mL/min/1.73m2. Concomitant use of PRADAXA with P-gp inducers has not been studied in pediatric patients but may decrease exposure to dabigatran. Consistent with the recommendation for adult VTE patients, concomitant use of P-gp inducers and PRADAXA should be avoided.

In Studies 106 and 108, proton pump inhibitors (PPIs) were allowed to be taken by pediatric VTE patients. PopPK analysis did not detect that concomitant use of PPIs influenced exposure of dabigatran.

3.3.5 Are the (b) (4) pellets (b) (4) bioequivalent to capsule formulation?

No, dabigatran (b) (4) pellets dosage forms are not bioequivalent to capsules. Oral absorption of dabigatran etexilate is formulation-dependent. Study 194 showed that at steady state, PRADAXA (b) (4) pellets (b) (4) resulted in 37% (b) (4) higher relative BA in healthy adult subjects, (b) (4) compared to PRADAXA capsules. Consistently, popPK analysis showed that in healthy adults receiving (b) (4) the (b) (4) pellets, the relative BA of dabigatran was (b) (4) 1.25 times that for capsules, (b) (4) A direct BA comparison of the various formulations, (b) (4) pellets, and capsules was not performed in the pediatric population. Inconsistent with the findings in healthy adults, popPK analysis showed that in children receiving the (b) (4) pellets (0 – 12 years old), the relative BA of dabigatran was (b) (4) 0.619 times that for capsules in patients aged 8 – 18 years, (b) (4) It appears that oral BA of dabigatran etexilate is both formulation- and study population-dependent. However, because no dedicated relative bioavailability study has been conducted in pediatric subjects, the magnitude of age effect on oral absorption of dabigatran is unclear and unknown.

In the response letter to the FDA's information request dated 1/15/2021, the Applicant provided a comparison of $C_{trough,ss}$ of dabigatran by formulations and age groups based on pooled PK data of Studies 106 and 108 (***Table 3.3.5- 1***). The use of (b) (4) pellets and capsules overlaps for patients between 8 and <12 years old as both formulations were tested in this age-range. The $C_{trough,ss}$ of dabigatran for (b) (4) pellets was 78.1 ng/mL (N = 6) and was 87.2 ng/mL (N = 19) for capsules in patients aged 8 to <12 years. Different from the relative BA of 1.37 (study derived) between (b) (4) pellets and capsules in adults and the model estimated relative BA of 0.62 between (b) (4) pellets in patients aged 0 to 12 years and capsules in patients aged 8 to 18 years, the limited available data of (b) (4) pellets (N = 6) showed that the relative BA between (b) (4) pellets and capsules in patients aged 8 to 12 years was approximately 1.00 (78.1/87.2 = 0.90). The mechanism of age-dependent changes in relative BA between (b) (4) (b) (4) pellets and capsules is not clear. To address the uncertainty in relative BA between (b) (4) pellets and capsules, the review team proposed dose adjustment for (b) (4) pellets, especially in patients aged 8 to 12 years weighing ≥31 kg. Refer to Section 3.3.2 and Section 4.3.3 for more information.

Table 3.3.5- 1 Steady-state trough exposure by formulations and age groups in Studies 106 and 108

	(b) (4)	(b) (4) granules 1160.106 /1160.108 Pooled (0 to < 2 y)[1]	(b) (4) granules 1160.106 /1160.108 Pooled (2 to < 8 y)[2]	(b) (4) granules 1160.106 /1160.108 Pooled (8 to < 12 y)[2]	Capsules 1160.106/ 1160.108 Pooled (8 to < 12 y)[2]	Capsules 1160.106/ 1160. 108 Pooled (12 to < 18 y)[3]	Capsules 1160.106/ 1160.108 Pooled (8 To 18, All)[3]
N		16	41	6	19	184	203
gMean [ng/mL]		53.3	52.5	78.1	87.2	99.1	97.9
gCV%		70.9	56.2	26.9	23.5	35.3	34.5
Median		61.0	57.7	76.7	88.7	98.9	98.1
Q1		41.1	48.4	67.9	71.7	78.2	77.9
Q3		78.5	65.9	78.9	103	127	125
P10		19.8	25.9	57.2	58.3	63.7	63.7
P90		110	83.5	126	125	152	151

Source: Applicant's IR response letter dated 1/15/2021, Table 8.

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.1.1 PK Assays

Five liquid chromatography–mass spectrometry (LC-MS) methods (U06-1741, U06-1743, U13-1183, n00239283, and n00238725) were developed to support analysis of plasma non-conjugated and total dabigatran as well as dabigatran etexilate and semi-prodrugs. The bioanalytical methods used in each study are summarized in **Table 4.1.1**- ***1***. Method n00239283 and Method n00238725 were used to quantify total dabigatran and non-conjugated dabigatran in human plasma in Study 105. The clinical study report for Study 105 and method validation reports for Method n00239283 and Method n00238725 were reviewed by Dr. Girish Bende. The clinical pharmacology review was uploaded to DARRTS on 8/27/2019. Dr. Bende concluded that the study report satisfactorily addressed PMR 2139-1 and fulfils the requirements of the PMR. Therefore, no further review of the clinical study report for Study 105 and method validation reports for Method n00239283 and Method n00238725 is needed. In current NDA, only the validation reports for Methods U06-1741, U06-1743, and U13-1183 are reviewed.

Table 4.1.1- 1 Bioanalytical Measurements in clinical studies of the dabigatran pediatric program

Study	Study type	Clinical study report	Plasma Matrix	Method for analysis of non-conjugated dabigatran	ISR pass rate	Method for analysis of total dabigatran	ISR pass rate	Method for analysis of dabigatran etexilate and semi-prodrugs	ISR pass rate
1160.87	Rel. BA capsules, (b) (4) granules, oral solution in adults	[U09-1839]	EDTA	[U06-1741]	46/48	[U06-1741]	48/48	n/a	
1160.88	adolescents, phase IIa (12-< 18)	[U12-3378]	EDTA	[U06-1741]	8/8#	[U06-1741]	8/8#	[U06-1743]	10/10#
1160.89	Children 2-<12 and 1-<2 years old, Phase IIa	[c09069268]	EDTA	[U06-1741]	n.d.*	[U06-1741]	n.d.*	[U06-1743]	n.d.*
1160.105	Children birth < 1 year old, Phase IIa	[c09085437]	Citrate	[n00238725]	n.d.*	[n00239283]	n.d.*	[n00238725]	n.d.*
1160.106	Phase IIb/III in children birth < 18	[c29773859]	EDTA	n/a		[U06-1741]	287/290&	n/a	
1160.108	Phase III in children, birth < 18	[c29754273]	EDTA	n/a		[U06-1741]		n/a	
1160.194	Rel. BA capsules, (b) (4) granules, oral solution in adults	[c02248557]	EDTA	[U06-1741]	189/192	[U06-1741]	190/192	n/a	

ISR = Incurred samples reproducibility.
Source: Summary of Biopharmaceutics and Associated Analytical Methods, Table 1.4: 4

Method validation parameters, including matrix stability parameters, for each method are summarized in ***Table 4.1.1- 2***. The established long-term stability (382 days at −70°C for Method U06-1741, 121 days at −20°C for Method U06-1743, and 214 days at −75°C for Method U13-1183) covered the maximum storage periods for corresponding studies. The method validation reports are adequate for measuring human plasma concentrations of non-conjugated and total dabigatran, dabigatran etexilate and semi-prodrugs.

Table 4.1.1- 2 Bioanalytical method validation parameters for quantitation of non-conjugated and total dabigatran, dabigatran etexilate and semi-prodrugs in human plasma

Method Number	**U06-1741**	**U06-1743**	**U13-1183**
Matrix	Human plasma	Human plasma	Human plasma containing idarucizumab
Analytes	Free and total dabigatran	Dabigatran etexilate (DE) and semi-prodrugs (BIBR 1087 SE and BIBR 951 BS)	Total dabigatran
LOQ (ng/mL)	1.0	1.0	5.0
Concentration range (ng/mL)	1 to 400	1 to 400	5 to 5000
Within-run accuracy (%RE)	Free: 6.6 to 12.9 Total: 6.0 to 7.0	DE: -11.5 to -4.6 BIBR 1087 SE: -9.3 to -4.4 BIBR 951 BS: -11.4 to -7.7	-6.7 to 2.4
Between-run accuracy (%RE)	Free 4.6 to 8.3 Total: 1.9 to 3.1	DE: -8.4 to -1.9 BIBR 1087 SE: -6.2 to -1.8 BIBR 951 BS: -6.9 to -6.4	-3.3 to 1.6

Within-run precision (%CV)	Free: 2.1 to 11.6 Total: 2.1 to 11.0	DE: 1.1 to 4.6 BIBR 1087 SE: 3.2 to 13.1 BIBR 951 BS: 2.6 to 9.2	2.0 to 4.9
Between-run precision (%CV)	Free: 5.5 to 10.2 Total: 4.8 to 11.2	DE: 4.9 to 6.0 BIBR 1087 SE: 5.5 to 10.8 BIBR 951 BS: 3.6 to 10.9	1.8 to 4.4
Dilution integrity **Accuracy (%RE)** **Precision (%CV)**	 Free: 14.3; Total: 10.4 Free: 4.0; Total: 3.7	 N.A.	 -5.5 to -4.7 1.4 to 1.9
Short-term stability	48 h at room temperature	DE and BIBR 1087 SE: 24 h at room temperature BIBR 951 BS: 4 h at room temperature	11days at 4 ˚C
Long-term stability	382 days at – 70 ˚C	DE and BIBR 1087 SE: 133 days at – 20 ˚C BIBR 951 BS: 121 days at – 20 ˚C	214 days at – 75 ˚C
Freeze-thaw stability	3 cycles	3 cycles	3 cycles
Clinical studies	87, 88, 89, 106, 108, and 194	88 and 89	108

CV: coefficient of variation; RE: relative error; LOQ: limit of quantitation
Source: Reviewer's summary of based on method validation reports submitted by the applicant

4.1.2. PD Assays

Blood coagulation parameters, dTT, ECT and aPTT were measured in Studies 88, 89, 105, 106 and 108. The commercially available Hemoclot® DTI assay (HYPHEN BioMed, Neuville sur Oise, France) was validated for measurement of diluted thrombin clotting time prolongation with dabigatran. Due to the direct relationship of ECT and dTT and dabigatran in plasma, both assays have been employed to investigate the reversal of dabigatran's anticoagulant effect by the dabigatran reversal agent idarucizumab. Hemoclot® DTI assays were also investigated for the exploratory calculation of dabigatran concentrations in Studies 106 and 108. Two method validation reports for Hemoclot® dTT assays were submitted. Method validation parameters are summarized in **Table 4.1.2- *1***. Method validation reports for dTT, ECT and aPTT assays are reviewed and found acceptable.

Table 4.1.2- 1 Bioanalytical method validation parameters for quantitation of dTT and dabigatran in human plasma

Method Number	**Hemoclot® dTT**	**Hemoclot® dTT with STAGO STA-R analyzer**
Matrix	Human plasma	Huamn plasma
Endpoint	dTT	dTT
LOQ	50 nM	25.5 ng/mL
Dabigatran concentration range	50 to 4000 nM	25.5 to 486 ng/mL
Dabigatran intra-assay accuracy (%)	105.6 to 113.7	84.6 to 115.8
Dabigatran intra-assay precision (%CV)	1.2 to 3.1	2.5 to 5.2
Dabigatran inter-assay accuracy (%)	N.A.	97.3 to 111.4
Dabigatran inter-assay precision (%CV)	4.0 to 10.0	3.9 to 8.7
Dilution linearity	1:8	1:4 and 1:8

Short-term stability	24 h at room temperature	N.A.
Long-term stability	12 months at – 20 ˚C	N.A.
Freeze-thaw stability	4 cycles	N.A.
Clinical studies	88, 89, 105, 106 and 108	106 and 108

Source: Reviewer's summary of based on method validation reports submitted by the applicant

4.2 Clinical BA/BE and PK/PD Assessments

As shown in **Table 4.2- *1***, two relative BA studies (Study 87 and Study 194) and three PK/PD studies (Study 88, Study 89, and Study 105) were submitted in current NDAs. The clinical study report for Study 87 submitted in NDA 022512 original submission was reviewed by Drs. Elena Mishina, Peter Hinderling, and Sudharshan Hariharan and found adequate (Clinical pharmacology review was uploaded to DARRTS under NDA 022512 on 11/30/2010). The clinical study report for Study 105 was reviewed by Dr. Girish Bende and found acceptable (Clinical pharmacology review was uploaded to DARRTS under NDA 022512 on 8/27/2019). In this review cycle, only Studies 194, 88 and 89 are reviewed.

Table 4.2- 1 Clinical studies submitted in NDA 022512/S-041, (b) (4) and NDA 214358

Type of trial	**Trial identifier**	**Objective(s) of the trial**	**Trial design and type of control**	**Test product(s); dosage regimen; route of administration**	**Number of subjects**	**Study Population**	**Duration of treatment**
BA	1160.87 [U09-1839] submitted in US eCTD sequence 0005	Relative BA	Open-label, randomized, uncontrolled, 3-way crossover	3 doses of 150 mg DE, with 1 dose per formulation (capsules, (b) (4) pellets, oral solution). Oral intake.	30	Healthy male and female adult subjects	Single dose; at least 7 days washout between treatment periods
BA	1160.194[2] [c02248557] submitted in US eCTD sequence 0378	Relative BA	Open-label, randomized, uncontrolled, 3-way crossover	5 doses of 150 mg DE (Day 1+2: bid, Day 3: single dose) per formulation (capsules, (b) (4) pellets, oral solution). Oral intake.	54	Healthy male adult subjects	Multiple dose for 3 days; at least 5 days washout between treatment periods
PK, PD, safety	1160.88 [U12-3378] submitted in US eCTD sequence 0262	PK, PD, tolerability, safety	Open-label, uncontrolled	DE capsules for 3 days bid. Weight-adjusted dose (max. 150 mg). Oral intake.	9	Male and female patients with primary VTE (aged 12 to <18 years)	3 days
PK, PD, safety	1160.89 [c09069268]	PK, PD, tolerability, safety	Open-label, uncontrolled	6 DE doses of oral (3 days bid) before global amendment 5, thereafter single dose. Age- and weight-adjusted dose, equivalent to 150 mg DE. Oral intake.	18	Male and female with VTE (aged <12 years)	3 days before amendment 5, thereafter single dose on 1 day

PK, PD, safety	1160.105 [c09085437] submitted in US eCTD sequence 0410	Appropriate-ness of dosing algorithm, safety, tolerability	Open-label, uncontrolled	Single dose of DE oral solution. Age- and weight- adjusted dose, equivalent to 150 mg DE. Oral intake.	8	Male and female patients with VTE (aged <1 year)	Single dose
PK, PD, efficac y, safety	1160.106 [c29773859]	Appropriate-ness of dosing algorithm, efficacy, safety	Active-controlled, open-label, randomized , parallel-group, non-inferiority	-Age- and weight-adjusted DE for 3 months bid (capsules, (b) (4) pellets, oral solution). Oral intake. -SoC: LMWH or fonda- parinux (subcutaneously) or VKA (oral)	267	Male and female patients with acute VTE birth to <18 years)	Up to 3 months
PK, PD, safety	1160.108 [c29754273]	Safety	Open-label, uncontrolled	Age- and weight-adjusted DE for up to 12 months bid (capsules, (b) (4) pellets, oral solution). Oral intake.	214	Male and female patients with need of secondary prevention of VTE (birth to <18 years)	Up to 12 months

4.2.1 Study 1160.194 (Multiple-dose relative BA)

Title: *Relative bioavailability of dabigatran after administration of different dosage forms of multiple doses of 150 mg dabigatran etexilate (hard capsule, pellets resolved in reconstitution solution, (b) (4) pellets on food) in healthy male volunteers (an open-label, randomized, multiple-dose, three-way crossover study)*

Objectives: The primary objective was to determine the relative bioavailability of 150 mg of dabigatran etexilate as (b) (4) pellets on food and of 150 mg of dabigatran etexilate as oral solution, both compared with 150 mg of dabigatran etexilate as hard capsule. The secondary objective was the assessment of palatability of (b) (4) pellets on food and (b) (4) pellets resolved in reconstitution solution.

Study Design: This was a randomized, open-label, 3-way crossover, multiple dose trial consisting of 3 identical treatment periods (T1; (b) (4) pellets on food, T2; (b) (4) pellets resolved in reconstitution solution, and R; hard capsules) of 3 days. Study drug was administrated twice daily on Day 1 and Day 2 and once on Day 3. Administration on Day 3 of each visit was performed following an overnight fast starting no later than 10 h before scheduled dosing. Treatment periods were separated by a washout phase of at least 5 days between last drug administration of one treatment and the first drug administration of the next treatment. A total of 54 subjects were randomly allocated to 1 of the 6 treatment sequences: T1-T2-R, T2-T1-R, R-T1-T2, R-T2-T1, T1-R-T2, or T2-R-T1.

PK Results:
The comparison of PK parameters (N, gMean, and gCV [%]) of total dabigatran by treatment is summarized in **Table 4.2.1-*1***. Compared to the hard capsule (R) formulation, the (b) (4) pellets on food (T1) had a 1.46-fold higher $C_{max,ss}$ and a 1.37-fold higher $AUC_{\tau,ss}$ for total dabigatran (**Table 4.2.1-*2***). Similarly, $C_{max,ss}$ and $AUC_{\tau,ss}$ were 1.41-fold and 1.30-fold higher, respectively, for total dabigatran following administration of the (b) (4) pellets resolved in reconstitution solution (T2) compared to the hard capsule (R) formulation (**Table 4.2.1-*3***). Steady-state pre-dose concentrations were similar for all 3 formulations. $C_{pre,ss}$ values were comparable between all 3 formulations, while trough concentration

values at 12 hours post-dose ($C_{12,ss}$) were 1.26-fold higher for (b) (4) pellets on food (T1) and 1.18-fold higher for (b) (4) pellets resolved in reconstitution solution (T2) than for the hard capsule (R) formulation.

Table 4.2.1- 1 Comparison of pharmacokinetic parameters of total dabigatran by treatment

	Hard capsule (R)			Pellets (T1)			Granules (T2)		
	N	gMean	gCV [%]	N	gMean	gCV [%]	N	gMean	gCV [%]
$C_{max,ss}$ [ng/mL]	53	131	50.8	54	191	37.4	(b) (4)		
$AUC_{\tau,ss}$ [ng·h/mL]	53	893	46.8	54	1220	34.1			
$C_{pre,ss}$ [ng/mL]	53	49.3	31.6	54	50.2	33.2			
$C_{12,ss}$ [ng/mL]	53	36.6	46.8	54	46.0	32.9			
$\lambda_{z,ss}$ [1/h]	53	0.105	20.3	54	0.113	17.1			
$t_{1/2,ss}$ [h]	53	6.59	20.3	54	6.15	17.1			
$t_{max,ss}$ [h]#	53	2.00	1.00-3.52	54	1.50	1.00-3.00			

N = number of subjects

median, minimum-maximum

Source: Study 1160.194 report, Table 11.2.2: 1

Table 4.2.1- 2 Statistical assessment of the relative bioavailability of the 150 mg (b) (4) pellets on food (T1) versus the 150 mg hard capsule (R) when dosed under fasted conditions

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	Pellets, Fasted [Test] (N = 54)	Capsule, Fasted [Reference] (N = 53)	
$AUC_{\tau,ss}$ (ng•h/mL)	1224.7	893.9	137.0 (125.8 – 149.3)
$C_{max,ss}$ (ng/mL)	190.9	130.6	146.2 (132.2 – 161.6)

Source: Study 1160.194 report, Table 11.2.2: 2

Table 4.2.1- 3 Statistical assessment of the relative bioavailability of the 150 mg (b) (4) pellets resolved in reconstitution solution (T2) versus the 150 mg hard capsule (R) when dosed under fasted conditions

Parameters	Least Squares Geometric Means		% Test/Ref Ratio (90% CI)
	Oral solution, Fasted [Test] (N = 54)	Capsule, Fasted [Reference] (N = 53)	
$AUC_{\tau,ss}$ (ng•h/mL)	(b) (4)	892.5	130.4 (119.6 – 142.2)
$C_{max,ss}$ (ng/mL)		130.5	141.1 (127.6 – 155.9)

Source: Study 1160.194 report, Table 11.2.2: 3

Reviewer's Comments:
The (b) (4) pellets/capsule $C_{trough,ss}$ ratio (1.26) and oral solution/capsule $C_{trough,ss}$ ratio ((b) (4)) are lower than corresponding relative BA between (b) (4) pellets and capsule (1.37) and between oral solution and capsule (b) (4) based on AUC ratios. This suggests that compared to AUC ratio, $C_{trough,ss}$ ratio may underestimate relative BA between two formulations. In phase 3 studies (Studies 106 and 108), only pre-dose C_{trough} PK samples were collected. Therefore, popPK analysis mainly based on C_{trough} data may underestimate the relative BA between (b) (4) pellets or oral solution and capsule.

4.2.2 Study 1160.88 (PK/PD study in patients aged 12 – 18 years)

Title: *Open-label safety and tolerability study of dabigatran etexilate given for 3 days at the end of standard anticoagulant therapy in children aged 12 years to less than 18 year*

Objectives: The objective of trial 1160.88 was to investigate tolerability and safety of dabigatran etexilate capsules in adolescents, and was to explore preliminary pharmacokinetic and pharmacodynamic parameters in adolescents.

Study Design: Dabigatran etexilate was administered twice daily for three consecutive days (total 6 doses) in eight stable adolescents (12 to <18 years) who had completed planned treatment with a low molecular weight heparin or an oral anticoagulant for primary VTE. All patients received an initial oral dose of 1.71 (± 10%) mg/kg of dabigatran etexilate (80% of the adult dose of 150 mg/70 kg adjusted for the patient's weight) capsules (**Table 4.2.2- *1***). Based on dabigatran concentrations as determined by the Hemoclot® Thrombin Inhibitors assay and clinical assessment, the dose was adjusted to the target dose of 2.14 (± 10%) mg/kg of dabigatran etexilate (100% of the adult dose adjusted for the patient's weight). No patient received more than 150 mg BID. The capsules could be taken with or without food. Peak pharmacokinetic (PK) samples were to be taken on treatment Day 1 and Day 3 two (+1) hours post dose. Trough PK samples were to be taken prior to Dose 5 on Day 3 and 12 hours after the final dose of study medication.

Table 4.2.2- 1 Dosing table for Study 1160.88

80% of adult dose (based on 150 bid for 70 kg adult: 1.71 mg/kg) (±10%)		
Weight (kg)	**Single Dose (capsules)**	**Total Dose**
32 to <40	50	50
40 to <53	75	75
53 to <66	50x2	100
≥66	75+50	125
Adult dose (based on 150 bid for 70 kg adult: 2.14 mg/kg) (±10%)		
Weight (kg)	**Single Dose (capsules)**	**Total Dose**
32 to <43	75	75
43 to <53	50x2	100
53 to <66	75+50	125
≥66	75x2	150

Note: Lower 5th percentile for 12 year old girls is about 32 kg.
Source: Study 1160.88 report, Table 9.4.1.4: 1

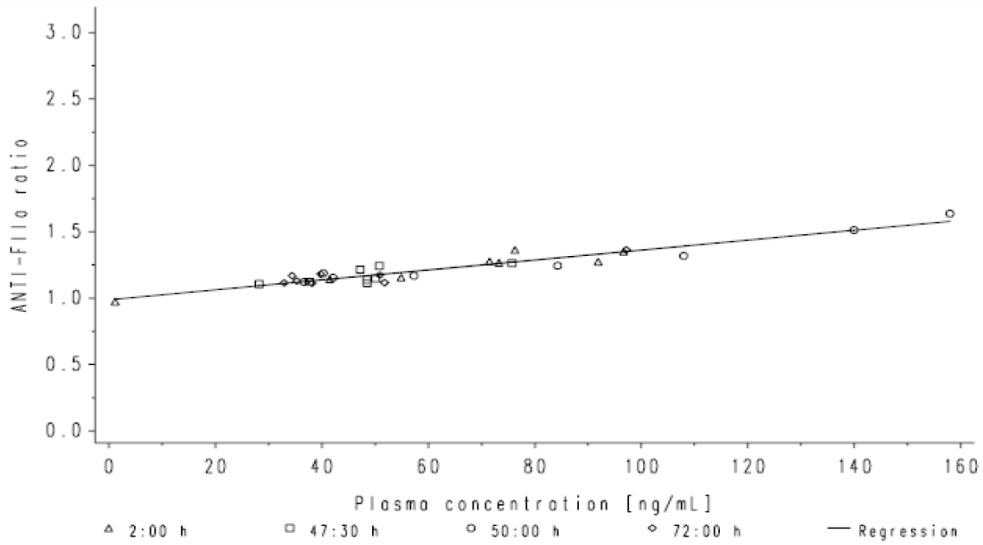
PK Results:
The individual plasma concentration-time data of total dabigatran after multiple oral doses of dabigatran etexilate are presented in **Table 4.2.2- *2***. Dabigatran etexilate and the intermediate dabigatran prodrugs taken at sampling times 2 hrs and 50 hrs were almost non-detectable. The dTT was measured using Hemoclot® assay at baseline and various time points. The dTT ratios at respective time point vs. baseline were calculated. The linear relationship between plasma concentration of total dabigatran and coagulation parameter Hemoclot® TT (Anti-FIIa) ratio was shown in **Figure 4.2.2- *1***.

Table 4.2.2- 2 Individual plasma concentrations of total dabigatran after oral administration of dabigatran etexilate (various doses, BID) in adolescent patients

		Total dabigatran plasma concentrations [ng/mL]			
		Planned times [h]			
Dose	Patient	2	47.5	50	72
75 mg then 100 mg BID	(b) (6)	BLQ	37.7	42.1	35.3
		73.3	28.2	108	32.9
		76.3	50.8	40.3	34.4
100 mg then 125 mg BID		41.5	48.5	36.7	50.9
		54.9	48.5	140	39.8
		1.17	75.7	57.3	97.2
125 mg then 150 mg BID		96.7	47.2	158	51.8
		91.9	50.1	84.3	38.2
75 mg		71.5	NOS	NOS	6.51*

BLQ below limit of quantification, NOS no observed sample, * time violation (actual sampling time: 24.05 hrs)
Source: Study 1160.88 report, Table 11.5.2: 1

Figure 4.2.2- 1 Relationship between plasma concentration of total dabigatran and coagulation parameter Hemoclot® TT (Anti-FIIa) ratio



Source: Study 1160.88 report, Figure 11.5.4: 2

Reviewer's Comments:
In this small study with sparse PK samples in eight subjects, the proposed dosing in adolescent patients provided dabigatran gMean total dabigatran $C_{trough,ss}$ at 72 hrs of 0.493 ng/mL/mg, which was slightly lower than those observed in adult VTE patients receiving 150 mg BID (0.530 ng/mL/mg in RE-COVER). Similar to adult patients with VTE, a linear PK/PD relationship was observed in adolescent patients for ECT and dTT and a non-linear PK/PD relationship was observed for aPTT.

4.2.3 Study 1160.89 (PK/PD study in patients aged 1 – 12 years)

Title: *Single dose open-label PK/PD, safety and tolerability study of dabigatran etexilate mesilate given at the end of standard anticoagulant therapy in successive groups of children aged 2 years to less than 12 years followed by 1 year to less than 2 years*

Objectives: The main objectives were: to provide pediatric PK/PD data and to investigate the tolerability and safety of the dabigatran etexilate solution in children aged 1 to <12 years who had completed planned treatment with either low molecular weight heparins or oral anticoagulation for a venous thrombotic event (VTE).

Study Design: This was an open-label, multicenter, non-randomized, uncontrolled, single arm study. Formulation was oral solution. The dose was adjusted based on age and weight and was equivalent to the adult dose of 150 mg dabigatran etexilate. A total of 18 pediatric patients were enrolled. Among 12 patients aged 2 to <12 years, 9 patients received a single dose of dabigatran etexilate and 3 patients were treated with a multiple dose of dabigatran etexilate (3 days twice daily). Six patients aged 1 to <2 years received a single dose of dabigatran etexilate.

Results:
The plasma concentrations of total dabigatran are summarized for the single dose groups in **Table 4.2.3-** ***1*** and **Table 4.2.3-** ***2***, and are listed in **Table 4.2.3-** ***3*** for the multiple dose group. The projected trough total

dabigatran plasma concentrations were in the interquartile range of data from adults with VTE. A linear PK/PD relationship was observed for dTT ratio in both patients aged 1 to <2 years (**Figure 4.2.3- *1***) and patients aged 2 to <12 years (**Figure 4.2.3- *2***).

Table 4.2.3- 1 Individual plasma concentrations of total dabigatran after a single dose of dabigatran etexilate in patients aged 1 to <2 years

Patient no.	Actual dose in [mg]	Total dabigatran plasma concentrations at time point (planned sampling time) in [ng/mL]					C_{max}	AUC_{0-tz}	t_{max}
		1 h	2 h	4 h	6 h	10 h	[ng/mL]	[ng·h/mL]	[h]
(b) (6)	62.5	-	138	81.2	49.5	26.1	138	666	1.92
	50	127	137	99.8	83.1	57.6	137	894	2.05
	43.75	102[a]	108	76.8	54.9	32.9	108	619	2.2
	43.75	48.8	129	88.8	49.8	23.2	129	603	2
	56.25	63.4	126	74.8	52.4	27.4	126	602	1.98
	50	101	141	137	105	56.1	141	1000	1.98
N		4	6	6	6	6	6	6	6
gMean		79.4	129	91	62.9	34.8	129	715	1.99[b]
gCV [%]		45.6	9.84	23	32.6	41.4	9.84	22.5	1.92-2.20[c]

[a] Excluded from descriptive statistics (sample taken outside the planned time window)
[b] Median
[c] Range

Source: Study 1160.89 report, Table 11.2.2: 1

Table 4.2.3- 2 Individual plasma concentrations of total dabigatran after a single dose of dabigatran etexilate in patients aged 2 to <12 years old

Patient no.	Actual dose in [mg]	Total dabigatran plasma concentrations at time point (planned sampling time) in [ng/mL]					C_{max}	AUC_{0-tz}	t_{max}
		1 h	2 h	4 h	6 h	10 h	[ng/mL]	[ng·h/mL]	[h]
(b) (6)	106.25	164	156	104	63.1	28.8	164	821	1.08
	106.25	118	133	109	66	33.9	133	796	2.03
	62.5	75.6	98.2	86	55.9	24.8	98.2	597	2
	106.25	140	140	80.4	50.1	19.4	140	692	1.03
	137.5	77.4	127	136	96.6	45.8	136	906	4.02
	87.5	124	138	76.5	44.9	23	138	651	2
	62.5	78	162	117	80.3	45.4	162	875	2
	125	75.4	77.6	59.4	40.1	31.3	77.6	491	2
	75	35.4	53.6	54.1	34.1	16	54.1	340	4
N		9	9	9	9	9	9	9	9
gMean		90.6	114	87.7	56.2	28.2	116	658	2[a]
gCV [%]		48.8	37.9	31.6	34.2	37	38.6	32.5	1.03-4.02[b]

[a] Median
[b] Range

Source: Study 1160.89 report, Table 11.2.2: 2

Table 4.2.3- 3 Individual plasma concentrations of total dabigatran after multiple doses of dabigatran etexilate in patients aged 2 to <12 years

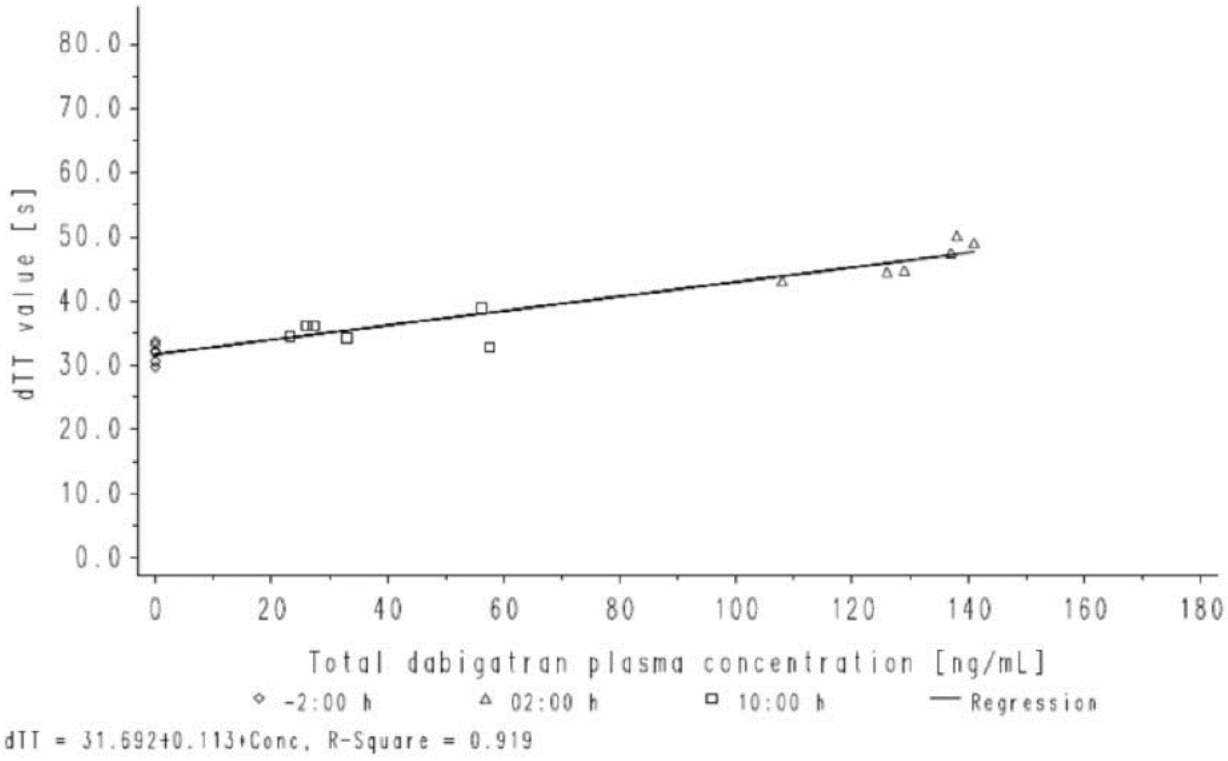
Patient no.	Actual dose (First/ subsequent dose) in [mg]	Total dabigatran plasma concentrations at time point (planned sampling time) in [ng/mL]		
		2 h	50 h[a]	72 h[b]
(b) (6)	28/35	39.0	69.9	19.9
	30/37	17.3	30.3	9.84
	31/39	13.3	46.4	8.52

[a] 50 h (2 h post-dosing after the 5th dose, peak)

[b] 72 h (12 h post-dosing after the 6th dose, trough)

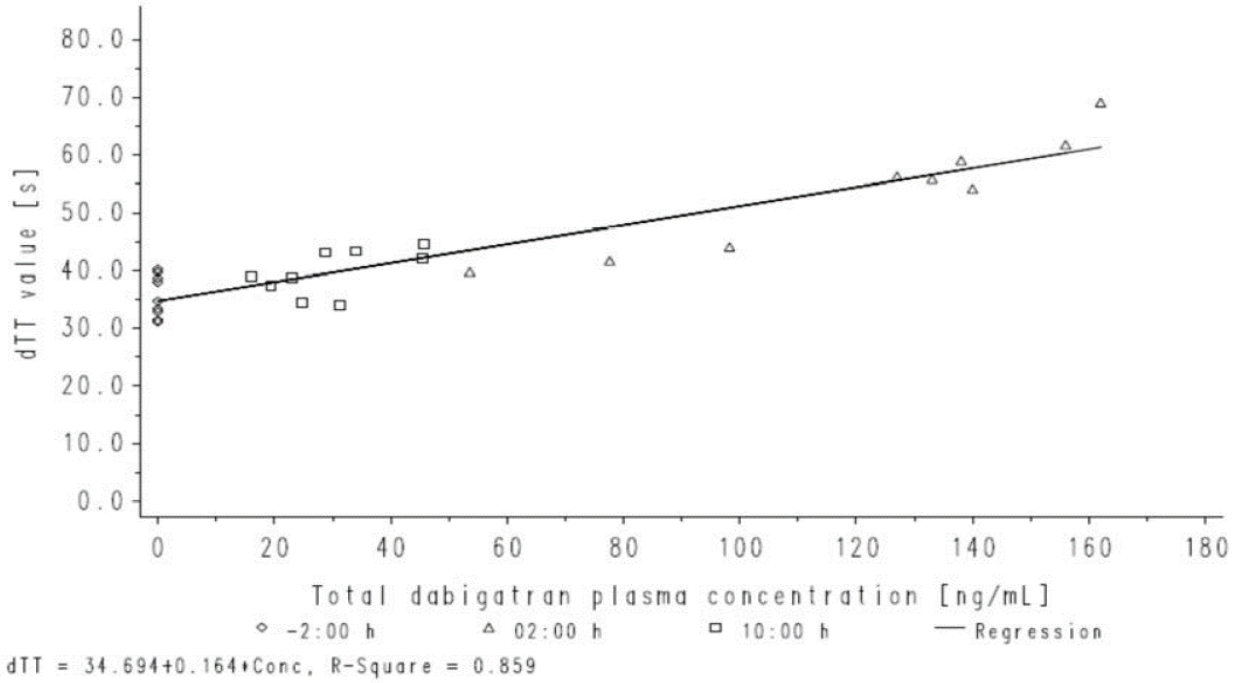
Source: Study 1160.89 report, Table 11.2.2: 3

Figure 4.2.3- 1 Relationship between the plasma concentration of total dabigatran and dTT in patients aged 1 to <2 years (single dose)



Source: Study 1160.89 report, Figure 11.2.4: 3

Figure 4.2.3- 2 Relationship between the plasma concentration of total dabigatran and dTT in patients aged 2 to <12 years (single dose group)



Source: Study 1160.89 report, Figure 11.2.4: 4

4.3 Population PK (popPK) Analyses

The following reports were reviewed by the Pharmacometrics Reviewer.

Report No.	Title	Referred to as in this section
[c31265480]	Pooled Population Pharmacokinetic Analysis of Dabigatran in Children with Venous Thromboembolism (Studies 1160.88, 1160.89, 1160.105, 1160.106, 1160.108) and Adult Healthy Subjects (Study 1160.194)	Applicant's popPK report
[c31265481]	Pooled Population Pharmacokinetic-Pharmacodynamic Analysis of Dabigatran Exposure and Blood Clotting Response in Children Treated for Venous Thromboembolism (Studies 1160.88, 1160.89, 1160.105, 1160.106 and 1160.108)	Applicant's popPK-PD report
[c31265482]	Simulations of Dabigatran Exposure Supporting the Dabigatran Etexilate Dosing Strategy in Children with Venous Thromboembolism	Applicant's PK simulation report

4.3.1 Applicant's PopPK analysis

The primary objectives of the Applicant's popPK analyses were 1) to describe the PK characteristics of dabigatran in children 0 to <18 years of age with venous thromboembolism (VTE) and quantify covariate-parameter relationships and 2) to predict dabigatran exposures following the proposed dosing regimen

Data: Data from the pediatric phase IIa studies 1160.88, 1160.89, 1160.105 and Phase IIb/III studies 1160.106 and 1160.108 (210 patients including 60 patients rolling over from study 1160.106), as well as the adult phase I study 1160.194 (32 healthy males receiving DE 150 mg twice daily both as capsules, (b) (4) pellets in sachets and oral solution) were used for the analysis. Details of baseline covariates for the analysis dataset stratified by study were presented in ***Table 4.3.1-1***.

Table 4.3.1-1. Baseline patient characteristics of PopPK dataset by study

Table 2: Baseline continuous covariate statistics for the analysis data set, stratified by study.

Covariate		1160.88	1160.89	1160.105	1160.106	1160.108	1160.194	All
Age (years)	min **median** max	13.8 **16.0** 18.0	1.15 **4.11** 11.8	0.110 **0.165** 0.460	0.0700 **14.3** 18.1	0.530 **14.6** 18.0	20.6 **27.7** 39.8	0.0700 **14.8** 39.8
	mean (SD)	16.2 (1.42)	4.82 (3.34)	0.241 (0.141)	11.7 (6.07)	13.1 (4.73)	29.1 (5.86)	13.2 (7.54)
	N	9	18	8	173	150	32	390
Body weight (kg)	min **median** max	47.0 **54.0** 84.0	9.00 **16.0** 43.0	3.80 **4.20** 7.10	3.70 **52.7** 131	6.00 **60.6** 132	70.0 **83.0** 97.0	3.70 **56.0** 132
	mean (SD)	58.9 (12.2)	19.1 (9.88)	4.75 (1.17)	47.8 (27.4)	59.6 (27.3)	83.3 (8.34)	53.3 (28.9)
	N	9	18	8	173	150	32	390
Height (cm)	min **median** max	155 **167** 189	74.0 **102** 137	48.0 **55.5** 62.0	51.0 **160** 192	64.0 **165** 195	166 **180** 190	48.0 **163** 195
	mean (SD)	167 (9.94)	104 (23.0)	55.2 (4.83)	143 (37.8)	155 (30.1)	180 (5.79)	147 (37.3)
	N	9	18	8	173	150	32	390
SCR (mg/dL)	min **median** max	0.543 **0.622** 0.882	0.200 **0.335** 0.710	0.170 **0.230** 0.470	0.150 **0.600** 1.11	0.140 **0.675** 1.22	0.730 **0.865** 1.07	0.140 **0.630** 1.22
	mean (SD)	0.669 (0.121)	0.357 (0.125)	0.268 (0.0987)	0.559 (0.219)	0.643 (0.223)	0.891 (0.0966)	0.606 (0.236)
	N	9	18	8	173	150	32	390
eGFR (mL/min/1.73m^2)	min **median** max	81.8 **106** 127	78.5 **130** 174	48.3 **92.5** 138	52.4 **107** 248	60.0 **105** 466	70.8 **85.0** 102	48.3 **104** 466
	mean (SD)	105 (13.9)	127 (24.9)	93.5 (28.7)	115 (32.3)	108 (38.2)	84.2 (9.48)	110 (34.0)
	N	9	18	8	173	150	32	390
Hb (g/dL)	min **median** max	10.5 **13.2** 16.1	10.6 **12.0** 12.9	9.20 **10.4** 14.5	7.00 **12.5** 16.9	8.40 **13.5** 17.6	14.2 **15.6** 17.7	7.00 **13.0** 17.7
	mean (SD)	12.9 (1.76)	11.9 (0.704)	10.9 (1.88)	12.4 (1.66)	13.4 (1.81)	15.5 (0.743)	13.0 (1.88)
	N	9	18	8	173	150	32	390

SCR: serum-creatinine, eGFR: estimated glomerular filtration rate using Schwartz formula, Hb: hemoglobin, SD: standard deviation. A total of 61 patients in study 1160.106 treated with dabigatran etexilate were also enrolled to study 1160.108 (60 of these patients have included PK observations in study 1160.108). In order to not count the same patient twice, statistics in this table for study 1160.108 do not include patients originally enrolled in study 1160.106.

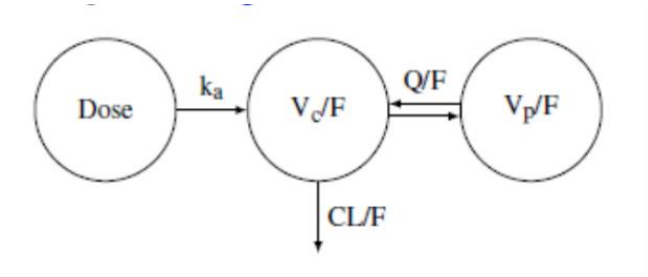
Covariate			88	89	105	106	108	194	All
Sex	Male	N	3	11	3	80	85	32	214
		Percent (%)	33.3	61.1	37.5	46.0	56.3	100.0	54.6
	Female	N	6	7	5	94	66	0	178
		Percent (%)	66.7	38.9	62.5	54.0	43.7	0.0	45.4
Race	White	N	9	14	7	161	139	32	362
		Percent (%)	100.0	77.8	87.5	92.5	92.1	100.0	92.3
	Black	N	0	0	1	1	6	0	8
		Percent (%)	0.0	0.0	12.5	0.6	4.0	0.0	2.0
	Asian	N	0	4	0	10	4	0	18
		Percent (%)	0.0	22.2	0.0	5.7	2.6	0.0	4.6
	Multiple	N	0	0	0	2	2	0	4
		Percent (%)	0.0	0.0	0.0	1.1	1.3	0.0	1.0
Formulation	Oral solution	N	0	18	8	13	0	10	49
		Percent (%)	0.0	100.0	100.0	7.5	0.0	31.2	12.5
	Capsules	N	9	0	0	119	126	11	265
		Percent (%)	100.0	0.0	0.0	68.4	83.4	34.4	67.6
	(b) (4) granules in sachets	N	0	0	0	42	25	11	78
		Percent (%)	0.0	0.0	0.0	24.1	16.6	34.4	19.9

Source: Applicant's PopPK report. Table 2 and Table 3 on pages 15-16.

The Applicant's initially developed popPK model based on phase IIa data was further updated based on a data set including interim data from phase IIb and III studies. Age and body weight were included as structural covariates on disposition parameters. The impact of formulations was assessed for absorption parameters. The potential influence of sex, race, age, hemoglobin, estimated glomerular filtration rate (eGFR) using Schwartz formula, and concomitant medication with proton pump inhibitors were evaluated using a stepwise covariate model building procedure.

Base model: The structural model is a two-compartment disposition model with first-order elimination and absorption, with a lag-time describing delayed absorption. The model accounted for growth and maturation of renal clearance by implementing a model for renal clearance that is structurally similar to that described by Rhodin et al. which uses patient age and weight as covariates.

Figure 4.3.1-1. Structural model for base model



$$CL/F = CL_{mat} \cdot f_{size} \cdot f_{PMA}$$

$$f_{size} = \left(\frac{WT}{70kg}\right)^{bCL}$$

$$f_{PMA} = \frac{PMA^{\gamma_{PMA}}}{PMA_{50}^{\gamma_{PMA}} + PMA^{\gamma_{PMA}}}$$

CLmat: the mature apparent dabigatran clearance in an adult subject with a body weight of 70 kg
fsize: an allometric model that scales apparent clearance according to a subject's body weight (WT)
bCL: an estimated power exponent
fPMA: the effect of age maturation on the apparent dabigatran clearance as a function of post menstrual age (PMA), which is the postnatal age plus 40 weeks.
PMA50: the mid-point PMA of clearance maturation or 'maturation half-time' and γ_{PMA} indicates the steepness of the PMA clearance maturation relationship.

Source: Applicant's popPK report. Figure 9 and Equations 1 to 3 on page 24.

Each formulation had separate k_a, apparent relative bioavailability (FR) and lag time (Tlag) estimated. IIV was introduced on the k_a and on FR for the different formulations. Separate FR were used for the adult and pediatric populations. Separate IIV was used on FR for the adult population receiving (b) (4) pellets in sachets. IIV was introduced on both the proportional and additive components of the combined error model. Nine strong outlier observations was identified based on model diagnostics for the starting model and were hence forward excluded from the analysis. The popPK model parameter estimates of the base model for dabigatran are presented in Applicant's popPK report, Table 5, page 30.

Covariate analysis: The covariates that were identified to be statistically significant (race, age and sex on CL/F, Hb and body weight on Vc/F and concomitant medication with proton pump inhibitors on FR) in the adult dabigatran popPK model in patients of study 1160.02 were added. Sex and race were also evaluated on the Vc/F and FR. Body weight was also evaluated on FR. In addition, the potential influence of eGFR estimated using Schwartz formula, was evaluated on CL/F.

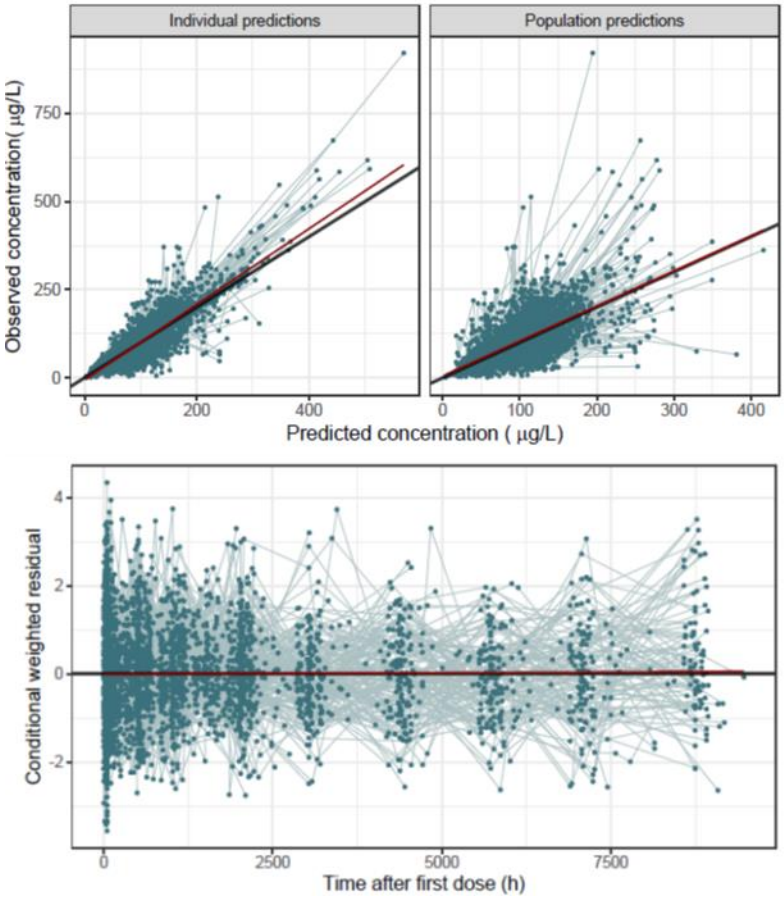
Final Model: Covariate relationships added for sex and eGFR on CL/F were added to the base model. The parameter estimates for the final covariate model are listed in **Table 4.3.1-2**. The parameter estimates are expressed for a male pediatric patient with reference body weight of 70 kg, eGFR of 100 mL/min/1.73m^2 and fully age matured CL. The goodness-of-fit plots (GOF) for the final covariate model for all data are shown in **Figure 4.3.1-2.**. The prediction corrected visual predictive check (pcVPC) plots for the final covariate model with all data are shown in **Figure 4.3.1-3.**

Table 4.3.1-3. Parameter Estimates (RSE) and Median (95% CI) for Applicant's Final Model

		Final model for dabigatran		
	Unit	Value	RSE (%)	SHR (%)
CL/F	L/h	110	2.70	
V_c/F	L	1090	5.11	
Q/F	L/h	47.8	7.93	
V_p/F	L	496	10.8	
$k_{a\,capsules}$	h^{-1}	0.939	15.3	
[redacted]			[redacted]	
$k_{a\,}$[redacted]$_{granules\ in\ sachets}$	h^{-1}	1.56	18.9	
$FR_{paediatric\ capsules}$		1.00		
[redacted]			[redacted]	
$FR_{paediatric\ }$[redacted]$_{granules\ in\ sachets}$		0.619	7.52	
$FR_{adult\ capsules}$		1.00		
[redacted]			[redacted]	
$FR_{adult\ }$[redacted]$_{granules\ in\ sachets}$		1.25	15.3	
$T_{lag\,capsules}$	h	0.431	1.96	
[redacted]			[redacted]	
$T_{lag\ }$[redacted]$_{granules\ in\ sachets}$	h	0.408	1.30	
HILLCL		2.12	22.2	
PMACL50	weeks	45.5	8.00	
WT on CL/F		0.750		
WT on Q/F		0.750		
WT on V_c/F		1.00		
WT on V_p/F		1.00		
Factor of V_c/F for adults		0.555	16.9	
eGFR on CL/F		0.223	10.3	
SEX on CL/F		-0.104	23.2	
Prop. $RUV_{capsules}$		0.0878	29.1	
Prop. RUV[redacted]$_{granules\ in\ sachets}$		0.0193	33.7	
Prop. $RUV_{capsules\ in\ study\ 106\ \&\ 108}$		0.280	2.88	
Prop. RUV[redacted]$_{granules\ in\ sachets\ in\ study\ 106\ \&\ 108}$		0.309	5.73	
Add. RUV	ug/L	6.47	4.64	
IIV CL	(CV)	0		
IIV V_c	(CV)	0.276	12.8	43.8
IIV Q	(CV)	0		
IIV V_p	(CV)	0		
IIV $k_{a\,capsules}$	(CV)	0.818	13.7	58.1
[redacted]				[redacted]
IIV $k_{\ }$[redacted]$_{granules\ in\ sachets}$	(CV)	0.605	23.8	69.2
IIV $FR_{capsules}$	(CV)	0.302	6.03	23.3
[redacted]				[redacted]
IIV FR[redacted]$_{granules\ in\ sachets}$	(CV)	0.433	9.82	62.5
IIV $FR_{adult\ }$[redacted]$_{granules\ in\ sachets}$	(CV)	0.319	16.8	71.5
IIV Prop. RUV	(CV)	1.15	27.7	73.8
IIV Prop. RUV in study 106 & 108	(CV)	0.306	8.47	31.2
IIV Add. RUV	(CV)	0.206	21.8	66.9
RUV		1.00		3.63

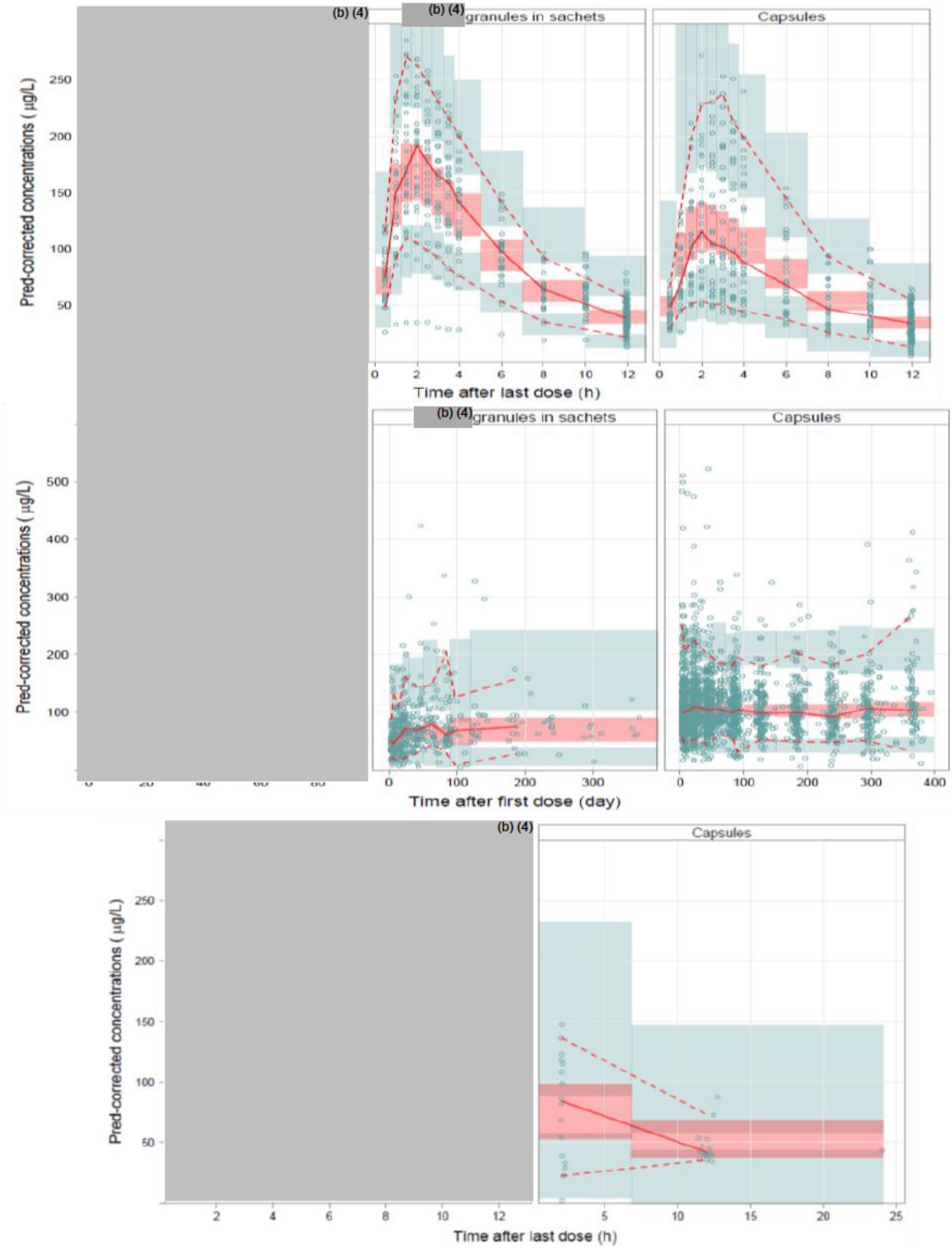
Source: Applicant popPK report. Table 7, on page 36.

Figure 4.3.1-2. Goodness-of-fit plots for the final covariate model for all data



Source: Applicant's popPK report, Figures 18-19 on page 37.

Figure 4.3.1-3. VPC plots by formulations, Study 194 (top panels), Studies 106, 108 (middle panels), and Studies 88, 89, 105 (bottom panels)



Source: Applicant's popPK report, Figures 20-22 on pages 38-40.

Conclusions:

- In infants, the apparent CL increased with increasing age (independently from body weight), with half of the full maturation occurring at 45.5 weeks and 90% occurring around 128 weeks post-menstrual age (corresponding to a postnatal age of 5.5 weeks and 20 months, respectively).
- The apparent CL decreased with decreasing renal function, as estimated by the glomerular filtration rate (Schwartz formula). The typical apparent clearance was 17% lower in a patient with an eGFR of 60 compared with a patient having an eGFR of 140 mL/min/1.73m^2. The typical apparent clearance was 15% lower in a patient with an eGFR of 50 compared with a reference patient with a median estimated glomerular filtration rate (eGFR) of 104 mL/min/1.73m^2. No additional dose adjustment seems warranted in patients with eGFR >50 mL/min/1.73m^2.
- The apparent clearance was on average 10% lower in female subjects than in male subjects, independently of the formulation. Black (n=7) or Asian (n=18) race did not have any statistically significant influence on the PK parameters, but the proportions of patients were low.
- In children receiving the oral solution and the (b) (4) pellets in sachets, the apparent relative bioavailability of dabigatran was (b) (4) and 0.619 times that for capsules, respectively. In the healthy adults receiving oral solution and the (b) (4) pellets in sachets, the apparent relative bioavailability of dabigatran was (b) (4) and 1.25 times that for capsules, respectively.
- The first-order absorption rate constant was higher after dabigatran etexilate administration as oral solution ((b) (4) h^{-1}) or (b) (4) pellets in sachets (1.56 h^{-1}), compared with capsules (0.939 h^{-1}), in both children and adults.
- The absorption lag-time was largely similar for oral solution (b) (4) (b) (4) pellets in sachets (0.408 h) and capsules (0.431 h)

4.3.2 Reviewer's Assessment of PopPK analyses

The Applicant's popPK model reasonably described the observed PK data in the pediatric studies. Parameters for CL, V, relative BA for each formulation, and their associated IIV were estimated with acceptable precisions (<30%). In general, the model diagnostics (goodness of fit [GOF] plots and prediction corrected visual predictive check [pcVPC]) did not indicate any unacceptable bias (**Figure 4.3.1-2.** and **Figure 4.3.1-3.**). The GOF plots and pcVPC stratified by studies, and formulation, did not show any unacceptable bias. As high shrinkages (>50%) were noted for most of IIV on PK parameters, using empiric Bayes estimates (EBEs) for post-hoc exposure of the studied patients is not appropriate. However, simulation-based model diagnostics (pcVPC) were generally in line with the observed data across age groups and formulations, which supports the adequacy of the model to be used to simulate exposures for the studied population.

The reviewer recognized limitations of the popPK analyses in:1) characterizing the covariate-PK relationships and 2) estimating the exposures for unstudied population in terms of age, and weight groups receiving different formulations. Due to the nature of sparse data collected from the pediatric studies in terms of key determinants for dabigatran PK (i.e., age, weight, formulations, and eGFR) that are highly correlated to each other, the popPK analyses may not be able to reasonably capture effects of each covariate separately on the dabigatran PK in pediatric patients. Also, the proposed dose regimen are age-, and weight- based nomograms for three different formulations and cover a broader range of body weight for a given age group compared to those studied in pediatric trials. Therefore, the reviewer conducted independent sensitivity analyses to verify the findings from Applicant' popPK analyses and address following issues:

Issue 1: Estimation of interindividual variability in dabigatran PK in pediatric population

The interindividual variability (IIV) in dabigatran CL was not estimated in the Applicant's model. When IIV was added on apparent CL in the Applicant's final model, IIV was estimated to be low (~1%). This may be partly because the model confined the apparent clearance (CL/F) with multiple structural components such as body weight and age dependent renal maturation as well as sex and eGFR as covariates. Instead, the inter-individual variability in PK of dabigatran in pediatric population were estimated in the IIV of relative BA. Considering the lower absolute BA (3-7% in adults) of orally formulations for dabigatran, absorption process may be another major factor impacting disposition of dabigatran especially for pediatric patients who have different physiological characteristics in GI tract from those inadults.

<u>Issue 2:</u> Discrepancy in relative bioavailability for oral solution and (b) (4) pellets relative to capsule formulations separately for pediatric patients and adult subjects

In the Applicant's popPK model, the relative BA of oral solution and (b) (4) pellet formulation relative to capsule were estimated separately for pediatric patients (0 to <18 years old) and healthy adults (Study 194). The estimated apparent relative bioavailability (BA) were (b) (4) and 0.62 for oral solution and (b) (4) pellets, respectively, in pediatric patients, compared to (b) (4) and 1.25 for adult subjects. The relative BA estimates for adult subjects were similar to those observed from the comparability BA study, where (b) (4) % and 137% were reported for oral solution and (b) (4) pellets, respectively. However, the relative BA estimated by the popPK analyses for oral solution, and (b) (4) pellets are 2-fold lower than those observed from the adult BA study.

A direct BA comparison of between the (b) (4) pellets and capsules in the pediatric population was not feasible because the capsule and (b) (4) pellets were used in different age groups (8 to <18 years, and 0 to <12 years, respectively) with limited PK data available from the age group (8 to <12 years) who could receive either formulation.

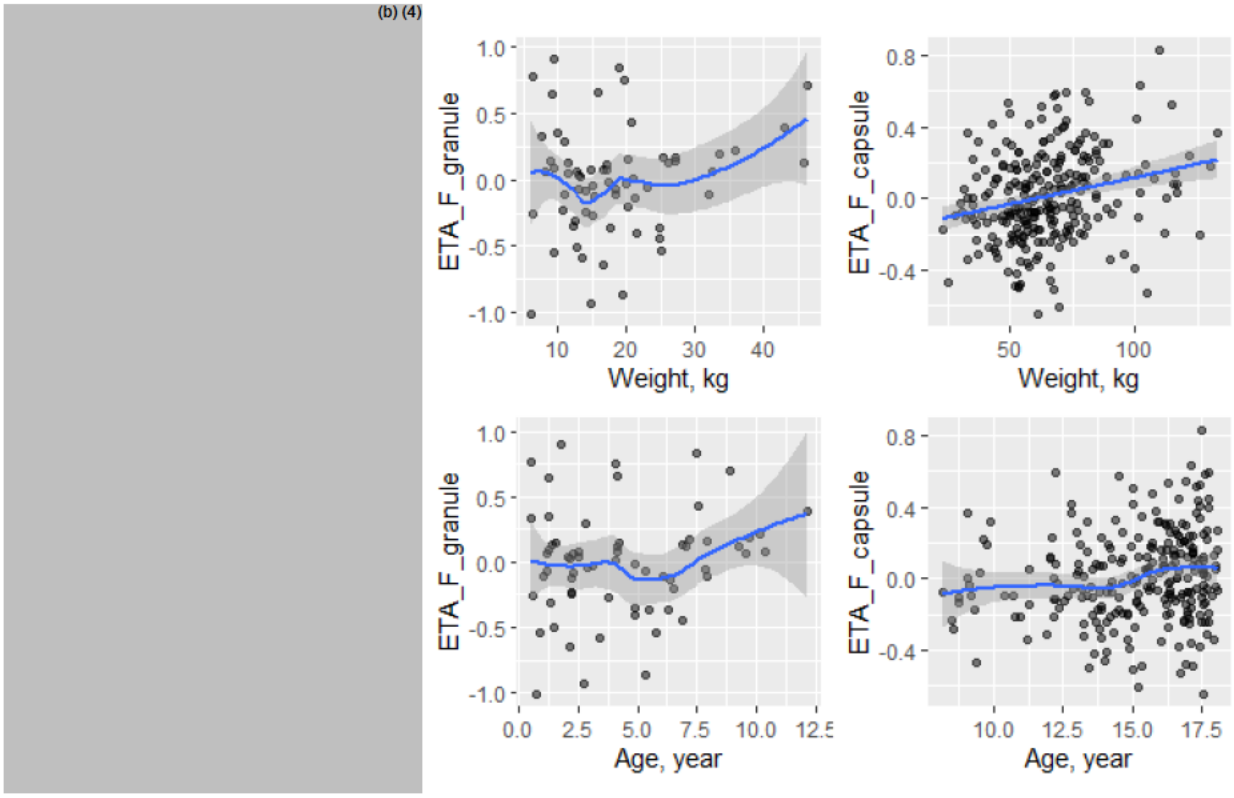
In the Applicant's popPK model, the allometric scalars on the apparent clearance (CL/F) and volumes of distribution (V/F) were fixed to the theoretical values (0.75 for clearances, 1 for volumes of distributions). While the popPK model generally well described the observed pediatric data, this considerable discrepancy in the relative BA estimation (0.62) from the observed in adults suggests uncertainty in utility of the model to simulate exposure in unstudied population in terms of the combinations of age, weight, and formulations. This discrepancy were approached by two scenarios:

1. The relative BA for (b) (4) pellets/oral solution is genuinely lower in pediatric patients (vs. adults) due to physiological/biochemical differences between adults and pediatric population.
2. The relative BA for (b) (4) pellets/oral solution is similar between adults and pediatric population. However, overall lower bioavailability in pediatric patients may be due to age-dependent absorption impacting absolute BA for both formulations rather than relative BA (between the two formulations). By fixing the allometric scaling (0.75 and 1) in pediatric patients, the Applicant's popPK model may have underestimated the apparent CL (CL/F) and volumes of distribution (V/F) in pediatric patients (mostly <12 years old), therefore, the underestimation of apparent CL may be reflected as the lower estimates for the relative BA in the popPK model.

The Applicant's popPK analyses assumed the scenario #1. In examining the ETA-covariate plots for relative BA vs. weight and age (

Figure 4.3.2-4.), Eta for the relative BA (F) tends to higher with increasing body weight for both (b) (4) pellets and capsule formulation. This suggests that the model tends to underestimate relative BA with increasing body weight, the theoretical scalars on weight effect on CL/F may not adequately capture the body weight effect on dabigatran PK.

Figure 4.3.2-4. Applicant's Final Model: Eta for Relative Bioavailability vs Weight and Age



Source: Reviewer's figures generated based on the Applicant's final PK model.
Top panels represent the relationship between ETA for apparent BA and weight. Bottom panels represent relationship between ETA for apparent BA and age. ETA_F_sol: Eta for apparent relative BA for oral solution; ETA_F_pellets: Eta for apparent relative BA for (b) (4) pellets; ETA_F_capsule: Eta for apparent relative BA for capsule.

The reviewer constructed a sensitivity model assuming the scenario #2 and the methods and results are briefly outlined below:

Methods: The original PopPK dataset was updated with the eGFR calculated using CKD-EPI equations (https://www.niddk.nih.gov/health-information/professionals/clinical-tools-patient-management/kidney-disease/laboratory-evaluation/glomerular-filtration-rate/estimating#the-ckd-epi-equation) for adult subjects from Study 194. Also, all adult subjects from Study 194 were included in the PopPK dataset.

The main difference from the Applicant's model is that the sensitivity model assumes that the relative BAs for oral solution ($FR_{oral\ solution}$), and the (b) (4) pellets ($FR_{pellets}$) are same between pediatric and adult subjects. Hence, instead of estimating different FR separately for pediatric and adult subjects, one FR was parametrized for oral solution, and (b) (4) pellets. Also, instead of fixing the allometric scalars to theoretical values, they were estimated to give more flexibility in the model to estimate the apparent CL (CL/F) accounting for the potential age-dependent absolute BA for oral formulations. The model was fitted to the modified the PK dataset.

Results: Parameter estimates from the Applicant's model and the sensitivity model were generally in agreement except for the parameters that were modified (i.e., exponents of weight effect on CL, and V2 (**Table 4.3.2-4**). In comparison of model predicted individual concentrations (IPRED) from Applicant's

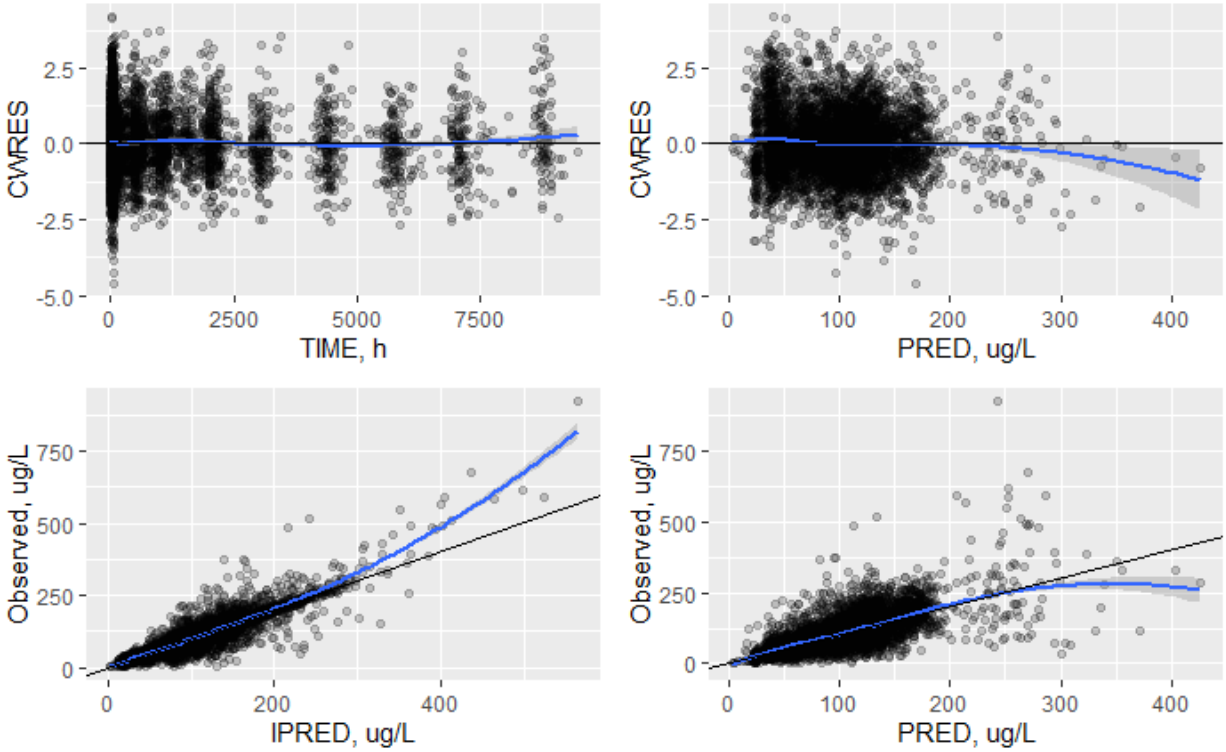
model and the sensitivity model were nearly identical. Model predicted population (PRED) from Applicant's model and sensitivity model were largely similar with the expected discordance at higher body weight groups for each formulation. Model diagnostics (**Figure 4.3.2-5.** and **Figure 4.3.2-6.**) for the sensitivity model did not show obvious bias for (b) (4) pellets and capsule formulations (b) (4) . In general, this model was considered adequate to be used as the sensitivity model for verification of the findings supported by Applicant's popPK model.

Table 4.3.2-4. Parameter estimates (Reviewer's sensitivity model)

Parameter	Estimate		RSE	IIV
01. CL/F (L/h)	106		2.70%	
02. V2/F (L)	981		5.60%	25.10%
03. Q/F (L/h)	52.7		6.20%	
04. V3/F (L)	480		7.80%	
05. Ka_capsules (/h)	0.961		12.30%	69.10%
06. (b) (4)				
07. Ka_pellets (/h)	1.73		12.90%	51.10%
08. FR_capsules	1	FIX	0%	31.10%
09. (b) (4)				
10. FR_pellets	1.17		6.10%	47.70%
11. ALAG_capsules (h)	0.417		1.40%	
12. (b) (4)				
13. ALAG_pellets (h)	0.4		1.10%	
14. HILLCL	2.76		26.30%	
15. PMACL50	43.9		8.20%	
16. WTonCL	0.444		7.30%	
17. WTonQ	0.75	FIX	0%	
18. WTonV2	0.611		6.20%	
19. WTonV3	1	FIX	0%	
20. Prop_RUV_capsules	0.0591		34.20%	
21. Prop_RUV (b) (4) /pel	0.0097		37%	
22. Add_RUV (ug/L)	7.27		3.90%	
23 Prop_RUV_capsules_study_106_108	0.278		2.90%	
24 Prop_RUV (b) (4) /pel_study_106_108	0.301		6.10%	
25 V2/F (L)_194	0.651		10.80%	
26 CLEGFR1	0.246		7.90%	
27 CLSEX1	-0.103		23.30%	

Source: Reviewer's analysis

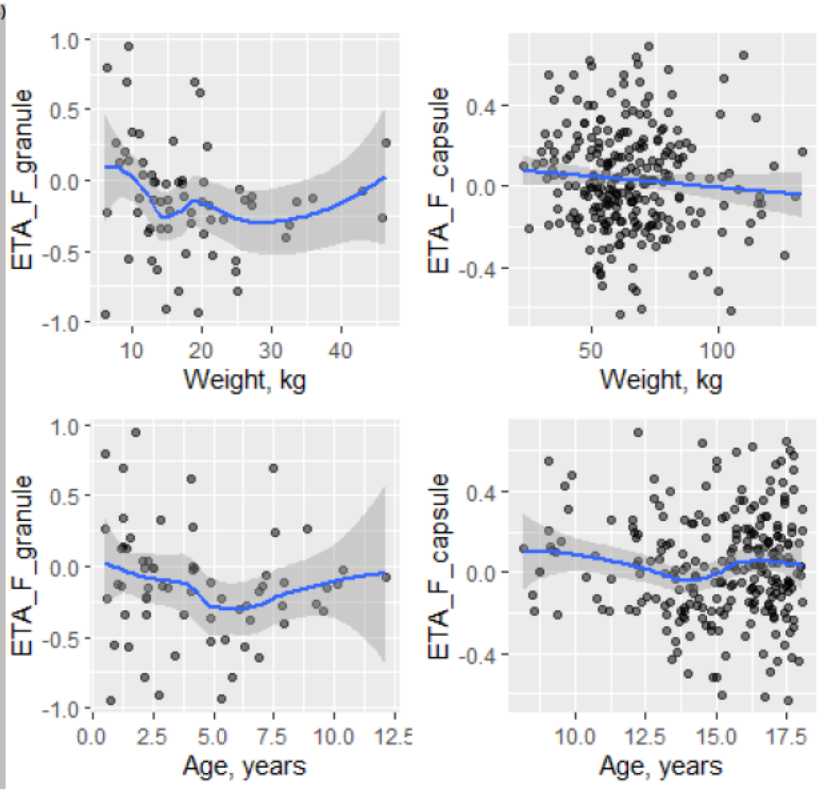
Figure 4.3.2-5. GOF plots for Sensitivity PPK model



Source: Reviewer's analysis

Figure 4.3.2-6. ETA for Relative BA vs. Weight and Age

(b) (4)



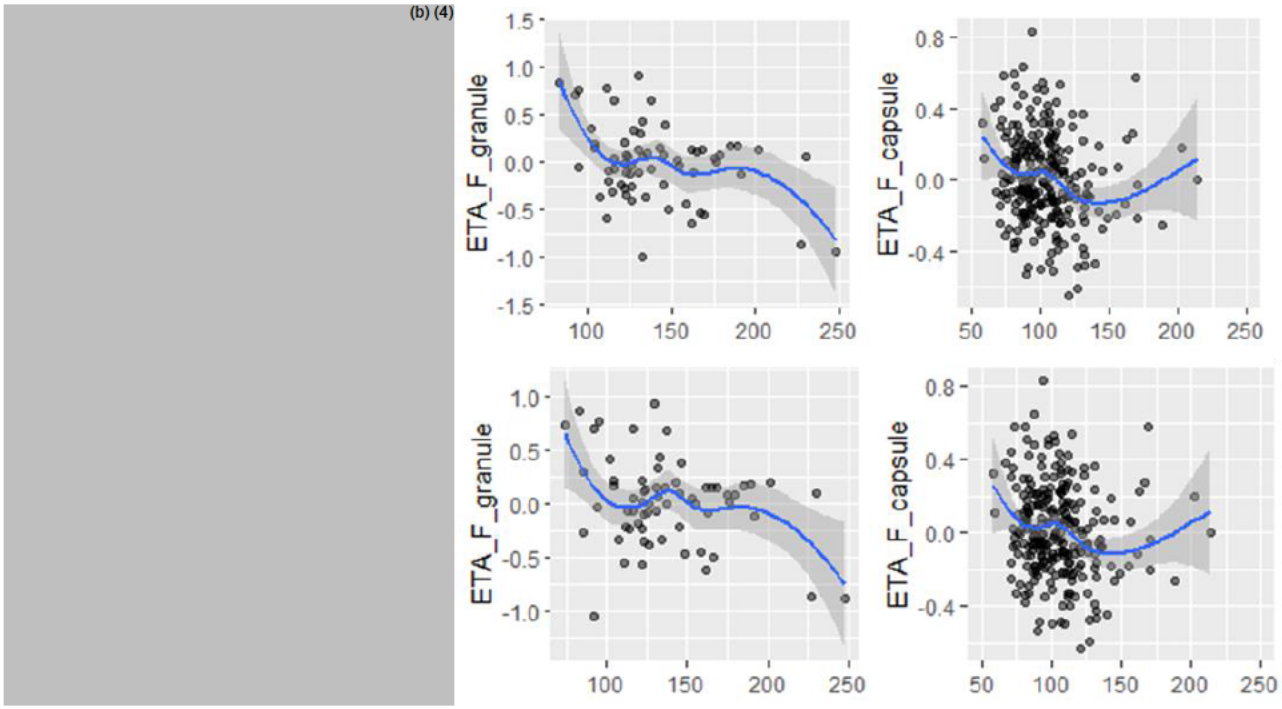
Source: Reviewer's analysis

Issue 3: Evaluation of eGFR - PK parameter relationship

The Applicant used modified (bedside) Schwartz formula (eGFR = 0.413 * Height in *cm* / Scr in *mg/dL*) to estimate eGFR for all subjects including adult subjects and infants in the popPK dataset. The modified Schwartz formula is most appropriate to estimate eGFR for children between the ages of 1 to 16 years. As for the sensitivity analysis, the reviewer calculated eGFR using CKD-EPI for the adult subjects (age >18 years old). The eGFR values for the patients younger than 1 year old were calculated using Flanders Metadata formula with an age-dependent adaptation for k (k=0.0414* ln(Age)+0.3018).

The reviewer conducted sensitivity analysis to confirm the Applicant's finding on eGFR - PK parameter relationship by re-estimation of popPK model using the updated dataset which included all adult data from Study 194 and updated eGFR calculated with different formula for adults and infants (age <1 year old). The parameter estimates using the updated dataset were close to Applicant's model estimates. Specifically, the estimate for eGFR on CL (0.25) was similar to that estimated with Applicant's original dataset (0.22). The relationship between ETA for relative BA and eGFR did not show a systemic bias for all three formulations in the Applicant's analysis (**Figure 4.3.2-7.**, top panels) and the sensitivity analysis (**Figure 4.3.2-7.**, bottom panels). The estimate for eGFR on CL shows clearance can be 20% lower in a patient with an eGFR of 60 compared to 140 mL/min/1.73m^2, suggesting that the impact of eGFR on PK parameters (i.e., CL, relative BA) is not considered significant in the observed eGFR range (50 - 250 mL/min/1.73 m^2). Therefore, the reviewer agrees that no dose adjustment based on eGFR is necessary in pediatric patients for eGFR >50 mL/min/1.73 m^2.

Figure 4.3.2-7. Relationship between ETA for Relative BA and eGFR from Sensitivity Analysis



Source: Reviewer's analysis.
Top panels were generated based on the Applicant's final PK model. Bottom panels were generated based on Reviewer's sensitivity analysis. ETA_F_sol: Eta for apparent relative BA for oral solution; ETA_F_pellets: Eta for apparent relative BA for (b) (4) pellets; ETA_F_capsule: Eta for apparent relative BA for capsule.

4.3.3 Evaluation of Proposed Dosing Algorithms

4.3.3.1 Applicant's Rationale for Dosing Algorithm for Pediatric Studies 106 and 108

The choice of formulation (capsule, (b) (4) pellets, oral solution) was based on the patient's age; the dose levels were based on the patient's age and weight as per dosing algorithm.

- Patients able to swallow capsules (aged ≥ 8 years) were assigned to DE capsules. If a patient aged ≥8 years but <12 years of age is unable to take capsules, he/she could take the (b) (4) pellets mixed with food
- Patients from birth to <8 years of age could receive DE (b) (4) pellets mixed with food
- Oral solution was used for patients who were <12 months of age. These patients could also receive DE (b) (4) pellets provided they had the minimum age/weight as per dosing algorithm and were able to swallow soft food

The Applicant used Hayton's model which expresses an allometric relationship that describes maturation and growth of the glomerular filtration rate (GFR, a renal function parameter) as a function of age and weight. And assuming proportionality between total body clearance and renal function for a drug that is predominantly eliminated by renal excretion, the Applicant calculated pediatric dose rates in reference to an adult dose rate. The final derived formula is $FRAC = W^{-0.338} (4.20 - 2.85\ e^{-0.0822*age})$, where FRAC represents a fraction of the adult refererence mg/kg dose, W denotes weight in kg, and age is the patient's age in months.

The Applicant selected a 20-year-old adult reference patient weighing 70 kg to project the pediatric dose rate. The rationale was the general pediatric population is characterized by better renal function compared to the adult population in RE-COVER trial (mean age 55.0 years). Because the reference patient is younger and has higher dabigatran clearance due to better renal function, the Applicant estimated that 300 mg dabigatran etexilate BID or 4.3 mg/kg dabigatran etexilate BID would be needed to yield similar exposure as the audlts in RE-COVER trial. The derived target doses of dabigatran etexilate, based on the Hayton calculations, are displayed below.

Figure 4.3.3-8. Target dabigatran etenxilate doses (mg) based on Hayton calculation (presented as single dose of BID dosing)

Reference Adult dose:	300 mg/70 kg = 4.3 mg/kg																		
Single Dose [mg]																			
Age [completed years]	Age [completed months]	Weight [kg]																	
		2.5	3 to <4	4 to <5	5 to <7	7 to <9	9 to <11	11 to <13	13 to <16	16 to <21	21 to <26	26 to <31	31 to <41	41 to <51	51 to <61	61 to <71	71 to <81	81 to <91	>=91
0,02083333	0,25	11,1	12,5	15,2	18,7														
0,08333333	1	12,4	14,0	17,0	20,9														
0,16666667	2	14,1	15,9	19,2	23,7														
0,25	3	15,6	17,6	21,2	26,2	32,2													
0,33333333	4	16,9	19,1	23,1	28,5	35,0													
0,41666667	5		20,6	24,9	30,7	37,7	44,1												
0,500	6			26,5	32,7	40,1	46,9												
0,583	7			28,0	34,5	42,4	49,5												
0,667	8			29,3	36,2	44,4	52,0	59,0											
0,750	9			30,6	37,7	46,3	54,2	61,5											
0,833	10				39,1	48,1	56,2	63,8	72,7										
0,917	11				40,5	49,7	58,1	66,0	75,1										
1	12				41,7	51,2	59,9	67,9	77,4	91,3									
1,5	18				47,2	57,9	67,8	76,9	87,6	103,3	121,6								
2	24					62,0	72,6	82,4	93,8	110,7	130,2								
2,5	30					64,6	75,5	85,7	97,6	115,2	135,5	154,4	180,5						
3	36					66,1	77,3	87,7	99,9	117,9	138,8	158,1	184,8						
4	48						79,1	89,8	102,2	120,6	141,9	161,7	189,0	222,9					
5	60						79,7	90,5	103,1	121,6	143,1	163,1	190,6	224,8	256,4				
6	72						80,0	90,8	103,4	122,0	143,6	163,6	191,2	225,5	257,2	287,1			
7	84							90,9	103,5	122,1	143,7	163,8	191,4	225,7	257,5	287,4	315,8		
8	96							90,9	103,5	122,2	143,8	163,8	191,5	225,8	257,6	287,6	316,0		
9	108								103,6	122,2	143,8	163,9	191,5	225,8	257,7	287,6	316,0		
10	120								103,6	122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
11	132									122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
12	144									122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
13	156									122,2	143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
14	168										143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
15	180										143,8	163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
16	192											163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8
17	204											163,9	191,5	225,9	257,7	287,6	316,0	343,2	357,8

Source: Summary of Clinical Pharmacology Studies. Table 3.1:1. Page 60.

The starting dosing algorithms provided in the clinical study for the three formulations are presented below, which refer to the total amount of dabigatran etexilate to be taken at a single time-point.

Capsule: Clinical study dosing algorithm for starting doses

Single Dose [mg]	Weight [kg]											
Age	9 to < 11	11 to < 13	13 to < 16	16 to < 21	21 to < 26	26 to < 31	31 to < 41	41 to < 51	51 to < 61	61 to < 71	71 to < 81	> 81
8– <9 years		100.00	100.00	125.00	150.00	150.00	185.00	220.00	260.00	300.00	300.00	
9– <10 years			100.00	125.00	150.00	150.00	185.00	220.00	260.00	300.00	300.00	
10– <11 years			100.00	125.00	150.00	150.00	185.00	220.00	260.00	300.00	300.00	330.00
11– <12 years				125.00	150.00	150.00	185.00	220.00	260.00	300.00	300.00	330.00
12– <13 years				125.00	150.00	150.00	185.00	220.00	260.00	300.00	300.00	330.00
13– <14 years				125.00	150.00	150.00	185.00	220.00	260.00	300.00	300.00	330.00
14– <15 years					150.00	150.00	185.00	220.00	260.00	300.00	300.00	330.00
15– <16 years					150.00	150.00	185.00	220.00	260.00	300.00	300.00	330.00
16– <17 years						150.00	185.00	220.00	260.00	300.00	300.00	330.00
17– <18 years						150.00	185.00	220.00	260.00	300.00	300.00	330.00

100	2x 50 mg capsules	150	150mg or 2x 75 mg capsules	220	2x 110 mg capsules	300	2x 150 mg or 4x 75mg capsules
125	50 mg + 75 mg capsules	185	75 + 110 mg capsules	260	110 + 150 mg or 2x 75 mg capsules	330	3x 110 mg capsules

Source: Applicant's PK simulation report. Figure 4. Page 14.

(b) (4) pellets in sachets: Clinical study dosing algorithm for starting doses

Single Dose [mg]	Weight [kg]																
Age	2.5 to < 3	3 to < 4	4 to < 5	5 to < 7	7 to < 9	9 to < 11	11 to < 13	13 to < 16	16 to < 21	21 to < 26	26 to < 31	31 to < 41	41 to < 51	51 to < 61	61 to < 71	71 to < 81	> 81
0– <1 month				20.00													
1– <2 months			20.00	20.00													
2– <3 months			20.00	20.00													
3– <4 months		20.00	20.00	30.00	30.00												
4– <5 months	20.00	20.00	20.00	30.00	40.00												
5– <6 months		20.00	20.00	30.00	40.00	40.00											
6– <7 months			30.00	30.00	40.00	50.00											
7– <8 months			30.00	30.00	40.00	50.00											
8– <9 months			30.00	40.00	40.00	50.00	60.00										
9– <10 months			30.00	40.00	50.00	50.00	60.00										
10– <11 months				40.00	50.00	50.00	70.00	70.00									
11– <12 months				40.00	50.00	60.00	70.00	80.00									
1– <1.5 years				40.00	50.00	60.00	70.00	80.00	90.00								
1.5– <2 years				50.00	50.00	70.00	80.00	90.00	90.00	110.00							
2– <2.5 years					60.00	70.00	80.00	100.00	100.00	140.00							
2.5– <3 years					60.00	70.00	90.00	100.00	110.00	140.00	150.00	160.00					
3– <4 years					60.00	70.00	90.00	100.00	110.00	140.00	150.00	160.00					
4– <5 years						80.00	90.00	100.00	110.00	140.00	150.00	160.00	220.00				
5– <6 years						80.00	90.00	100.00	110.00	140.00	150.00	160.00	220.00	260.00			
6– <7 years						80.00	90.00	100.00	110.00	140.00	150.00	160.00	220.00	260.00	300.00		
7– <8 years							90.00	100.00	110.00	150.00	150.00	160.00	220.00	260.00	300.00	300.00	
8– <9 years							90.00	100.00	110.00	150.00	150.00	160.00	220.00	260.00	300.00	300.00	
9– <10 years								100.00	110.00	150.00	150.00	160.00	220.00	260.00	300.00	300.00	
10– <11 years								100.00	110.00	150.00	150.00	160.00	220.00	260.00	300.00	300.00	330.00
11– <12 years								100.00	110.00	150.00	150.00	160.00	220.00	260.00	300.00	300.00	330.00

20	20 mg sachet	80	2x 40 mg sachet	160	110 + 50 mg sachet
30	30 mg sachet	90	40 + 50 mg sachet	220	2x 110 mg sachet
40	40 mg sachet	100	2x 50 mg sachet	260	110 + 150 mg sachet
50	50 mg sachet	110	110 mg sachet	300	150 + 150 mg sachet
60	2x 30 mg sachet	140	30 + 110 mg sachet	330	3x 110 mg sachet
70	30 + 40 mg sachet	150	150 mg sachet		

Source: Applicant's PK simulation report. Figure 3. Page 13.

Oral solution: Clinical study dosing algorithm for starting doses

Single Dose [mg]	Weight [kg]							
Age	2.5 to < 3	3 to < 4	4 to < 5	5 to < 7	7 to < 9	9 to < 11	11 to < 13	13 to < 16
0– <1 month	12.50	12.50	12.50	18.75				
1– <2 months	12.50	12.50	18.75	18.75				
2– <3 months	12.50	18.75	18.75	25.00				
3– <4 months	12.50	18.75	25.00	25.00	31.25			
4– <5 months	18.75	18.75	25.00	31.25	37.50			
5– <6 months		18.75	25.00	31.25	37.50	43.75		
6– <7 months			25.00	31.25	43.75	43.75		
7– <8 months			25.00	31.25	43.75	50.00		
8– <9 months			31.25	37.50	43.75	50.00	62.50	
9– <10 months			31.25	37.50	43.75	56.25	62.50	
10– <11 months				37.50	50.00	56.25	62.50	75.00
11– <12 months				43.75	50.00	56.25	68.75	75.00

12.5	2 mL	31.25	5 mL	50	8 mL	68.75	11 mL
18.75	3 mL	37.5	6 mL	56.25	9 mL	75	12 mL
25	4 mL	43.75	7 mL	62.5	10 mL		

Source: Applicant's PK simulation report. Figure 2. Page 13.

Reviewer's comments:

The approach of choosing a 20-year-old patient weighing 70 kg as a reference patient to project the dose fraction in pediatric patients ages is reasonable. However, requiring a high dose (b) (4) BID) for the reference patient is not adequately justified because the RE-COVER trial included patients similar to the reference patients in terms of body weight and renal funciton. In trials of 106 and 108, the age- and weight- based dose algorithm estimated from Hayton's model resulted in 1.68 fold higher exposure in the adolescents compared to mean adult exposure observed in RE-COVER trials. (Refer to Section 3.3.1 To what extent does the available clinical pharmacology information provide pivotal or supportive evidence of effectiveness?)

Also, the Hayton-estimated dose algorithms used in in trials of 106 and 108 were expected to result in a similar or higher exposures in younger patients groups (i.e., 0 to <12 years old) who received oral solution/ (b) (4) pellets compared to older pediatric groups (8 to <18 years old) who received the capsule formulation. This is because the adult BA study (194) showed that the relative BA for oral solution/ (b) (4) granlues compare to capsule formulation is greater than 1 and the trial dose algorithms did not account for this different BA among the formulations. However, in trials 106 and 108, the younger patients (i.e., 0 to <12 years old) had nearly 2-fold lower exposures compared to the adolescents who received capsule formulation.

4.3.3.2 Applicant's Proposed Dose Algorithms

Applicant's initially proposed doses

The Applicant proposed a dosing regimen which were further updated from the dose algorithms utilized in pediatric trials of 106 and 108. Key changes were:

- (b) (4)

Applicant's newly proposed dose for (b) (4) pellets

During labeling negotiation for (b) (4) pellets (NDA 214358), the Applicant proposed to universally increase the doses for (b) (4) pellets to address FDA review team's concern regarding the uncertainty of efficacy in the dabigatran exposure ($C_{min,ss}$) below 50 ng/mL. The newly porposed doses were based on consideration of daily limit of tartaric acid, exclusion of patients ≤3 months of age, and adjust dose for patients with weight of (b) (4) kg to address the uncertainty of the relative BA of (b) (4) pellets. Per the Applicant, with the newly proposed final dosages, the percentage of $C_{min,ss}$ below 50 ng/mL is reduced from approximately (b) (4) (with the initially proposed dose) to approximately 10 to 17%%, and the percentage of $C_{min,ss}$ greater than 250 ng/ml at trough remains below 10%.

Applicant's Table 1: Applicant's newly proposed dose for (b) (4) pellets with consideration of limit of tartaric acid, exclusion of patients <3 months of age, and adjust dose for patients with weight of (b) (4) kg

(b) (4)

Source: Applicant response letter titiled "BI response – Dosing Table.docx" received on 3/12/2021, Table 4.

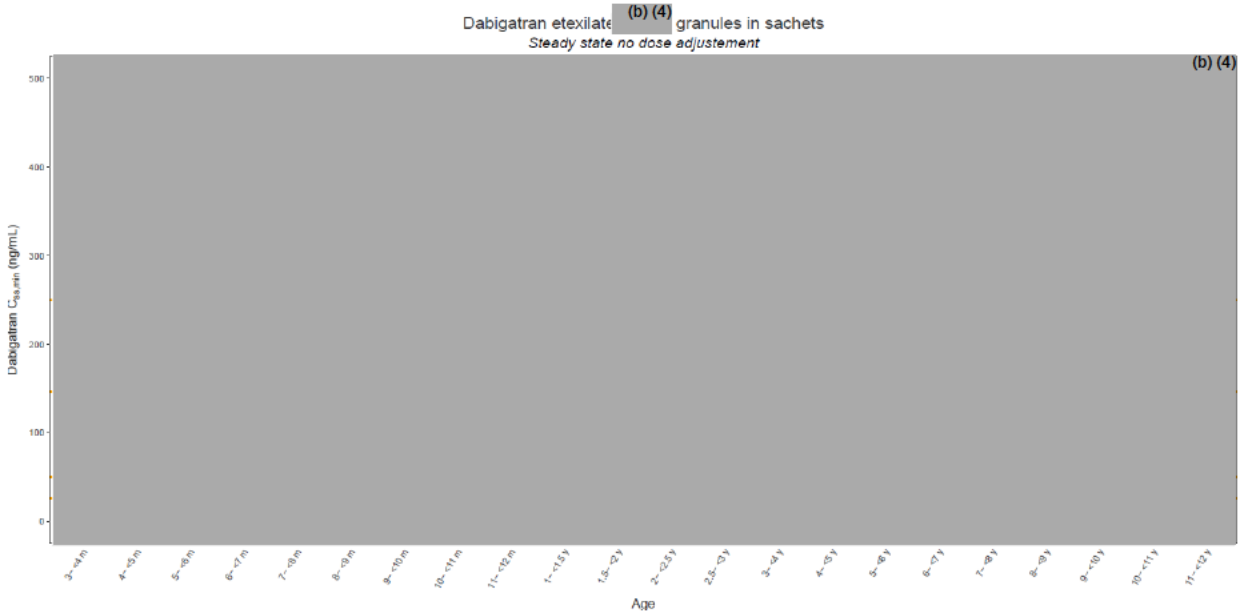
Applicant's Table 2: Proportion (%) of $C_{min,ss}$ reaching or exceeding the cut-offs following the Applicant's newly proposed doses for (b) (4) pellets

Dabigatran etexilate (b) (4) granules in sachets

Age	% of $C_{ss,min}$ within 26 to <250 ng/mL	% of $C_{ss,min}$ within 50 to <250 ng/mL	% of $C_{ss,min}$ below < 26 ng/mL	% of $C_{ss,min}$ below < 50 ng/mL	% of $C_{ss,min}$ above > 250 ng/mL
3– <4 m	(b) (4)				
4– <5 m					
5– <6 m					
6– <7 m					
7– <8 m					
8– <9 m					
9– <10 m					
10– <11 m					
11– <12 m					
1– <1.5 y					
1.5– <2 y					
2– <2.5 y					
2.5– <3 y					
3– <4 y					
4– <5 y					
5– <6 y					
6– <7 y					
7– <8 y					
8– <9 y					
9– <10 y					
10– <11 y					
11– <12 y					

Source: Applicant response letter titiled "BI response – Dosing Table.docx" received on 3/12/2021, Table 5.

Applicant's Figure 1. Distribution of $C_{min,ss}$ on by age following the Applicant's newly proposed dose



Source: Applicant response letter titiled "BI response – Dosing Table.docx" received on 3/12/2021, page 7.

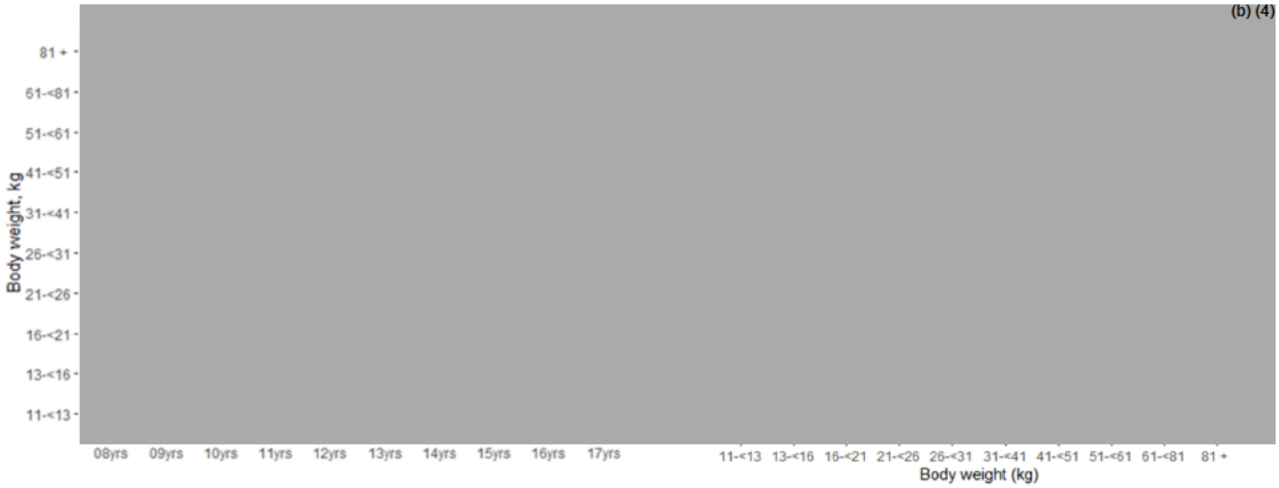
4.3.3.3 Reviewer's Assessment of Applicant's Proposed Dosing Algorithms

Each dose tables (b) (4) formulations was evaluated by the reviewer's independent analyses based on Monte Carlo simulations. The primary simulations were those conducted using the Applicant's popPK model. When assessing the dose tables for (b) (4) pellets, sensitivity simulations were conducted using the reviewer's sensitivity model.

1) Capsule (NDA 021222-S41)

The Applicant's proposed dose which is to be administered as BID are presented in **Figure 4.3.3-9.** (left panel) and the simulated dabigatran $C_{min,ss}$ were presented in **Figure 4.3.3-9.** (right panel). Similar to the observed $C_{min,ss}$ in the trials 106, and 108, the median with the proposed dose is estimated to be 107 ng/mL compared the gMean of the adult $C_{min,ss}$ (59.7 ng/mL) from RE-COVER trial. Approximately, >25% subjects in certain weight groups were projected to have a higher $C_{min,ss}$ than adult's 90th percentile of $C_{min,ss}$ observed in RE-COVER trial.

Figure 4.3.3-9. Applicant's proposed dose (mg) for capsule (to be administered as BID) and the predicted $C_{min,ss}$ (right)



Source: Reviewer's analysis. In the right box plot, the whiskers represent 10th- 90th percentile (inner, narrow whiskers), and 5th – 95th percentile (outer, wide whiskers).

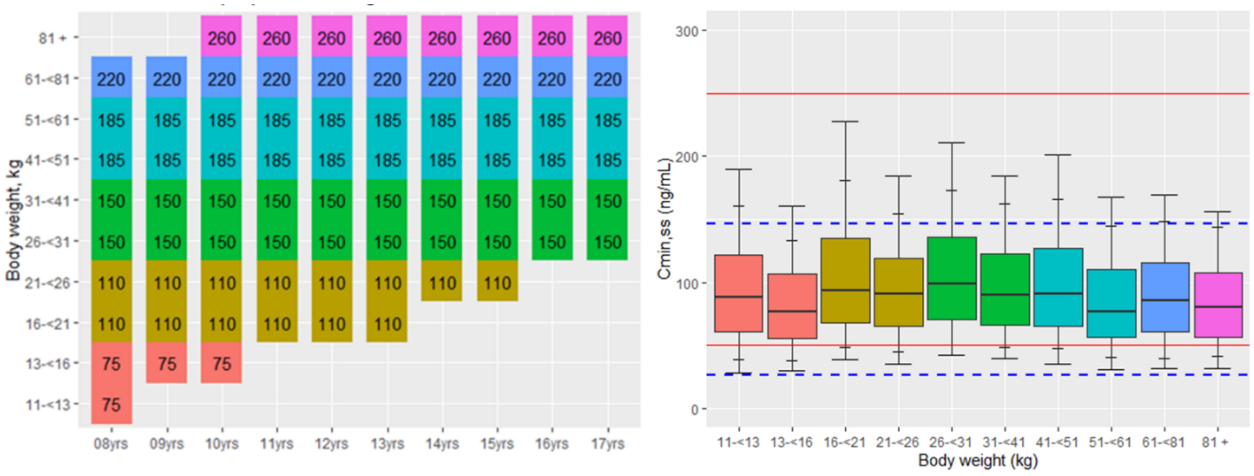
While the body weight-based dose significantly reduces the variability in dabigatran exposures, the mean $C_{min,ss}$ values in the pediatric patients are expected to be higher by up to 2 folds compared to those in adults (mean $C_{min,ss}$ of 59.7 ng/mL). Because of the small event rate for the primary safety endpoint (major bleeding event [MBEs]) in the pediatric trials, it was not feasible to conduct a formal exposure-response analysis. While no signal was noted between the dabigatran $C_{min,ss}$ and MBEs in the trials 106 and 108, the potential relationship might have not been detected due to the small event rate and the small sample size of these pediatric studies. FDA review team concluded that the benefit risk profile in the intended age group (8 to <18 years) supports the recommendation of dose reduction for capsule formulation.

Review Team's Recommendations for Dosing Regimen for Capsule Formulation

The review team's recommended dose for capsule formulation is presented in Figure 4.3.3-10. (left panel). The recommended dose were selected by targeting the simulated $C_{min,ss}$ range of 10th to 90th percentiles that lay within the adult exposure range while maintaining most of the patients above the trial

titration steady-state concentration bound of 50 ng/mL. The predicted $C_{min,ss}$ following the review team's recommended dose are presented in Figure 4.3.3-10. (right panel)

Figure 4.3.3-10. Review team's recommended dose (mg) for capsule (to be administered BID) and the predicted $C_{min,ss}$ (right)



Source: Reviewer's analysis. In the right box plot, the whiskers represent 10th- 90th percentile (inner, narrow whiskers), and 5th – 95th percentile (outer, wide whiskers).

2) (b) (4) Pellets (NDA 214358)

The proposed dose nomograms for (b) (4) pellets were evaluated based on both the primary simulations using Applicant's final PopPK model and the sensitivity simulations using the reviewer's sensitivity PPK model.

Applicant's initially proposed dose for (b) (4) pellets

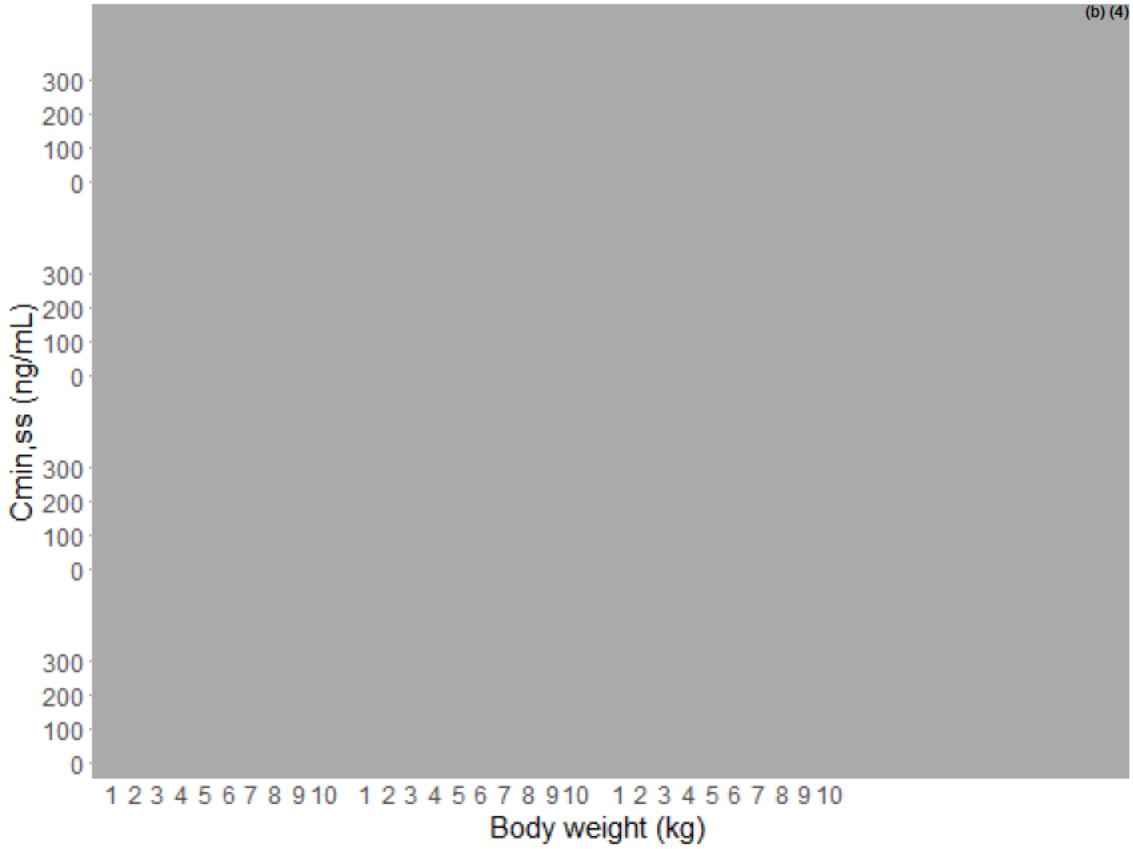
Applicant's initially prosed dosing nomogram were based on both age and body weight for patients ages (b) (4)

Figure 4.3.3-11. Applicant's initially proposed dose (mg) for pediatric patients ages birth to <12 years (to be administered as BID)

Source: Applicant's simulation report.

The popPK analyses estimated that a half of the full maturation in renal function is reached at a postnatal age of 5.5 weeks, and 90% of the full maturation is reached around 20 months. This indicates that the age effect on apparent CL is independent of the body weight effect on CL in the age groups younger than (b) (4) years old ((b) (4) months). Therefore, to evaluate the dosing for the age group 0 to < (b) (4) years old, the simulations were conducted with virtual population generated by sampling for each age-, and body weight- group (n=300 for each cell in the dose nomogram) and the simulations were performed based on weight groups by sampling (n=500) for each body weight category for the age group (b) (4) years <12 years old. The simulated dabigatran $C_{min,ss}$ following the Applicant's initially proposed dose table summarized by subgroups of body weight groups (x-axis), and age groups (each panel) in the figures below.

Figure 4.3.3-12. Simulated Cmin,ss for patients age birth to <(b) (4) years (age-, weight- based dose) following Applicant's initially proposed dose for (b) (4) pellets



Source: Reviewer's analysis. In the right box plot, the whiskers represent 10th- 90th percentile (inner, narrow whiskers), and 5th – 95th percentile (outer, wide whiskers). Weight groups represents following:

Weight group	1	2	3	4	5	6	7	8	9	10
Weight (kg)	2.5-<3	3-<4	4-<5	5-<7	7-<9	9-<11	11-<13	13-<16	16-<21	21-<26

Figure 4.3.3-13. Simulated Cmin,ss for patients ages(b) (4) to <12 years following Applicant's initially proposed dose for (b) (4) pellets

Source: Reviewer's analysis.

The simulated exposures with the Applicant's initially proposed dose fall within the adult reference range in general, across age groups and body weight range with primary simulations using the Applicant's popPK model. However, there is a obvious discrepancy in the projected exposures when comparing results from the primary and sensitivity simulations, which is most pronounced in patients with body weight (b) (4) kg who will receive the highest doses (b) (4) mg) of (b) (4) pellets. It should be noted that this discrepancy reflects the uncertainty of the model predictions in this weight groups (unstudied population).

Assessment of Applicant's <u>newly proposed dose</u> for (b) (4) pellets

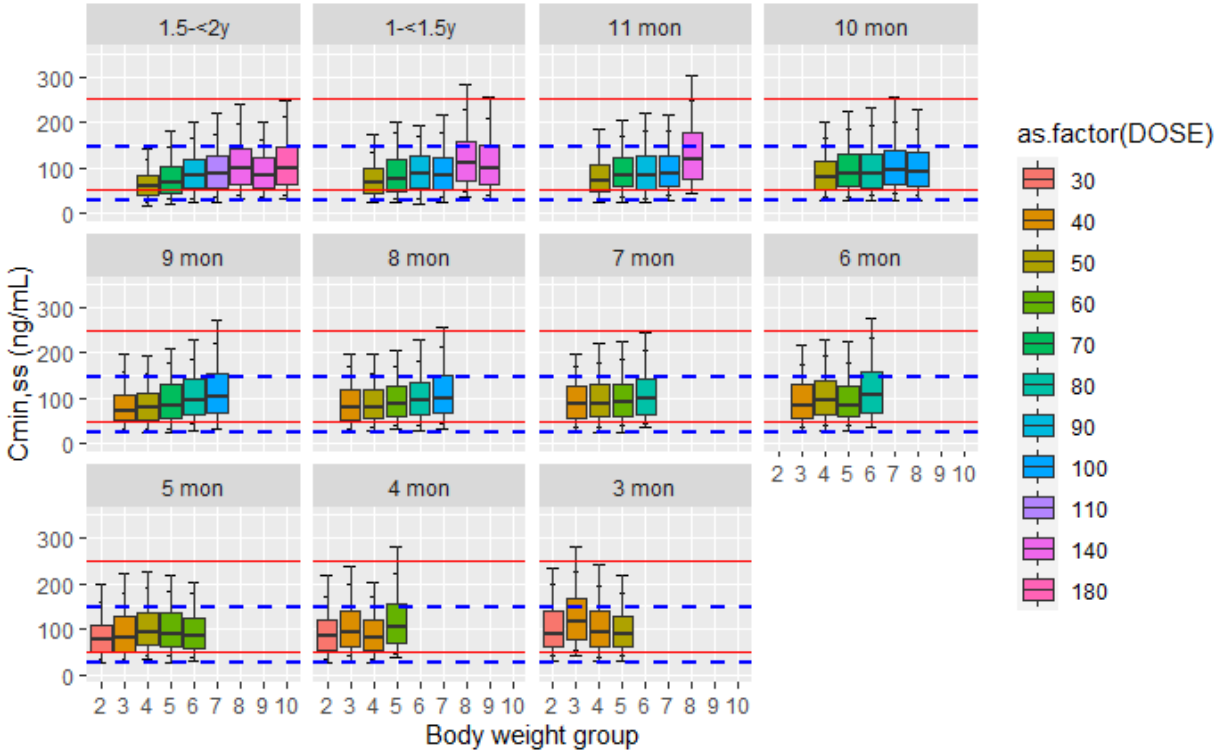
Based on the Applicant's popPK simulations and the reviewer's confimatory simulations, the review teams agreed that the Applicant's newly proposed doses for (b) (4) pellets would generally increase the proportion of patients age <12 years with dabigatran exposures above 50 ng/mL. However, the following modifications to the Applicant's further revised dose are recommended:

- <u>Inclusion of the dosing recommendation for 3 months to <4 months old</u> as following:
  - 3 to <4 kg: 30 mg
  - 4 to <5 kg: 40 mg
  - 5 to <7kg: 40 mg
  - 7 to <9 kg: 50 mg
- <u>A dose reduction from (b) (4) mg to 220 mg for age ≥2 years and body weight ≥31 to <41 kg</u>: The reviewer's sensitivity simulations showed that with a dose of (b) (4) mg, more than 10% of patients exceed 250 ng/mL but with a dose reduction to 220 mg, only the 95th percentile of trough exposure is just outside of 250 ng/mL. With primary simulations, a dose of 220 mg (b) (4) mg does not affect the lower end of trough exposures significantly.
- <u>A dose reduction from (b) (4) mg to 260 mg for Age ≥2 years and body weight 81 kg and above</u>: Patients who are eligible to receive (b) (4) pellets (<12 years of age) are not expected to weight heavier than 81 kg. This is also to not exceed the maximum recommended dose for capsules.

Review team's final recommended doses (mg) for pediatric patients ages 3 months to <12 years (to be administered as BID)

Source: Adapted from Table 4 in the Applicant's response document titled "BI Response - Dosing Table.docx",with the review team's recommended modification (in red boxes)

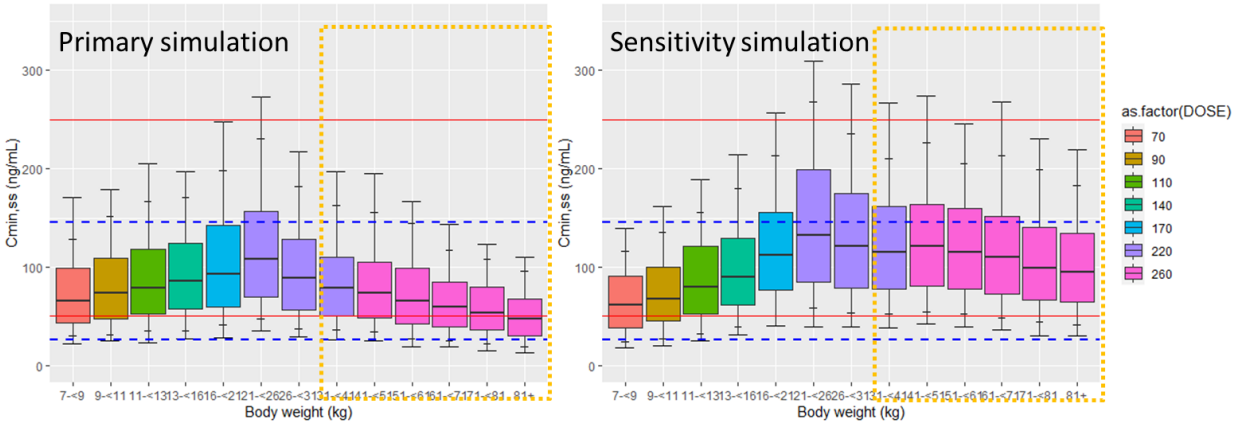
Simulated Cmin,ss for patients ages 3 months to <12 years old following the review team's recommended dose



Source: Reviewer's analysis. In the right box plot, the whiskers represent 10th- 90th percentile (inner, narrow whiskers), and 5th – 95th percentile (outer, wide whiskers). Weight groups represents following:

Weight group	2	3	4	5	6	7	8	9	10
Weight (kg)	3-<4	4-<5	5-<7	7-<9	9-<11	11-<13	13-<16	16-<21	21-<26

Simulated Cmin,ss for patients ages 2 years to <12 years old following the review team's recommended dose



Source: Reviewer's analysis.

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4.3.4. PopPK-PD Analysis

Summary of Applicant's Population PK-PD Analysis

Objectives:

- To characterize the relationship between dabigatran plasma concentrations and clotting time variables: activated partial thrombin time (aPTT), diluted thrombin time (dTT), and ecarin clotting time (ECT) in the pediatric venous thromboembolims (VTE) patient population
- To compare the PK-PD relationships with those in adult populations.

Data: Data from the pediatric phase IIa studies 1160.88 (9 patients, aged 13-18 years), 1160.89 (18 patients, aged 1-<12 years), 1160.105 (8 patients, aged 0-<1 years) as well as the phase IIb/III studies 1160.106 (171 patients, aged 0-18 years) and 1160.108 (155 patients, aged 0-18 years), receiving age and weight based dabigatran etexilate dosing) were used for the analysis.

Methods: The observed pediatric data was graphically compared to observed data from adult patients and model predictions for healthy adult subjects. Separate population PK-PD models were developed to characterize the dabigatran PKPD relationship for each of the clotting time variables, using non-linear mixed effects modelling. The previously developed phase IIa and interim phase IIb/III population PK-PD models were used as a starting point. Covariates (sex and age) were assessed on baseline and drug effect parameters, using a stepwise covariate model (SCM) building procedure.

Results and Conclusions

1. *Activated partial thrombin time (aPTT)*

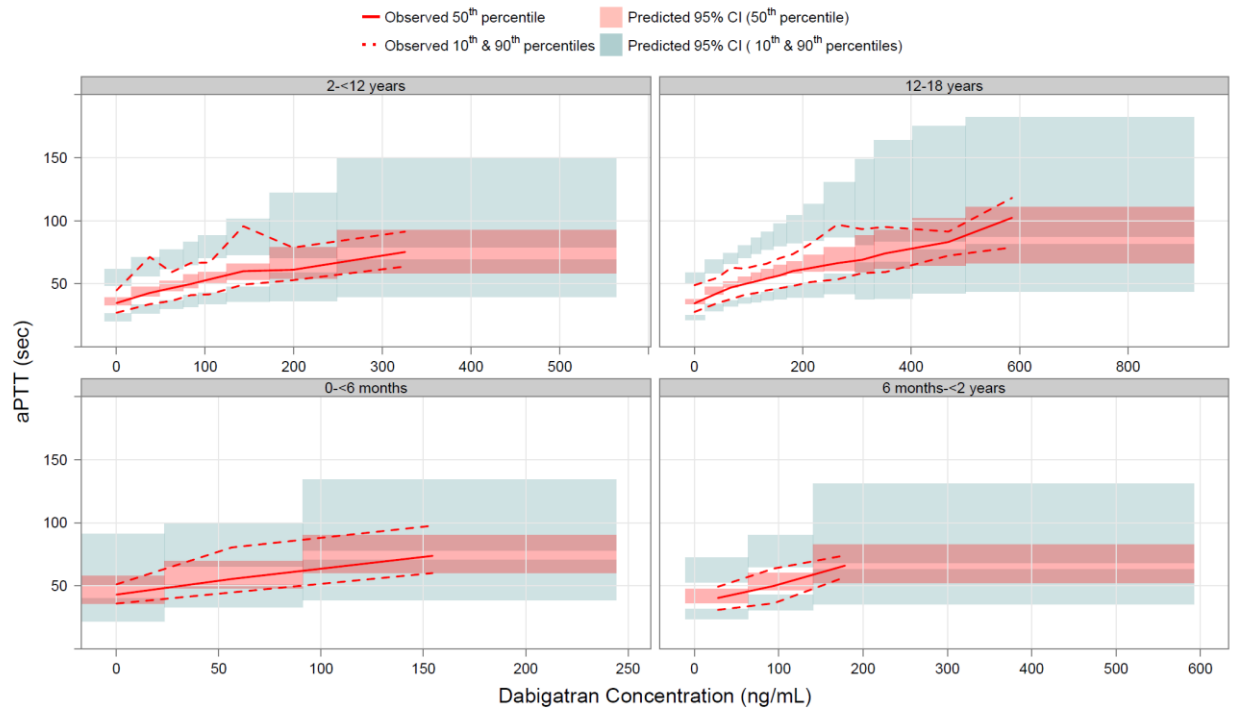
In the base model for aPTT, the increase in aPTT from baseline with increasing dabigatran concentration was described with a non-linear Emax function. The final model included age-effect on baseline by estimating a separate baseline in children below or above 5.8 months old. An additional age-effect on Emax was evaluated but was not statistically significant. The parameter estimates of the final aPTT model and VPC plots are presented in ***Table 4.3.4- 1*** and ***Figure 4.3.4-16.***, respectively. The final model adequately described the aPTT data across all age groups, although IIV was slightly overestimated for children 12-18 years (***Figure 4.3.4-16.***).

Table 4.3.4- 1. Parameter estimates of the final aPTT model

		Final aPTT model	
	Unit	**Value**	**RSE (%)**
Baseline	sec	36.1	1.64
Baseline <5.8 months	sec	44.8	6.85
Age on baseline	months	5.80	
EC50	ng/mL	368	16.1
Emax		2.02	12.7
IIV Baseline	(CV)	0.285	13.7
IIV Emax	(CV)	0.749	17.4
corr Baseline-Emax		-0.722	20.5
Prop. RUV	(CV)	0.178	5.25

Source: Applicant's pop PK-PD report. Table 13. Page 39. The RSE for IIV and RUV parameters are reported on the approximate SD scale; Emax: maximum response (fold increase from baseline); EC50: dabigatran concentration where half the maximum response is achieved; CV: coefficient of variation; IIV: interindividual variability; RSE: relative standard error; RUV: residual unexplained variability.

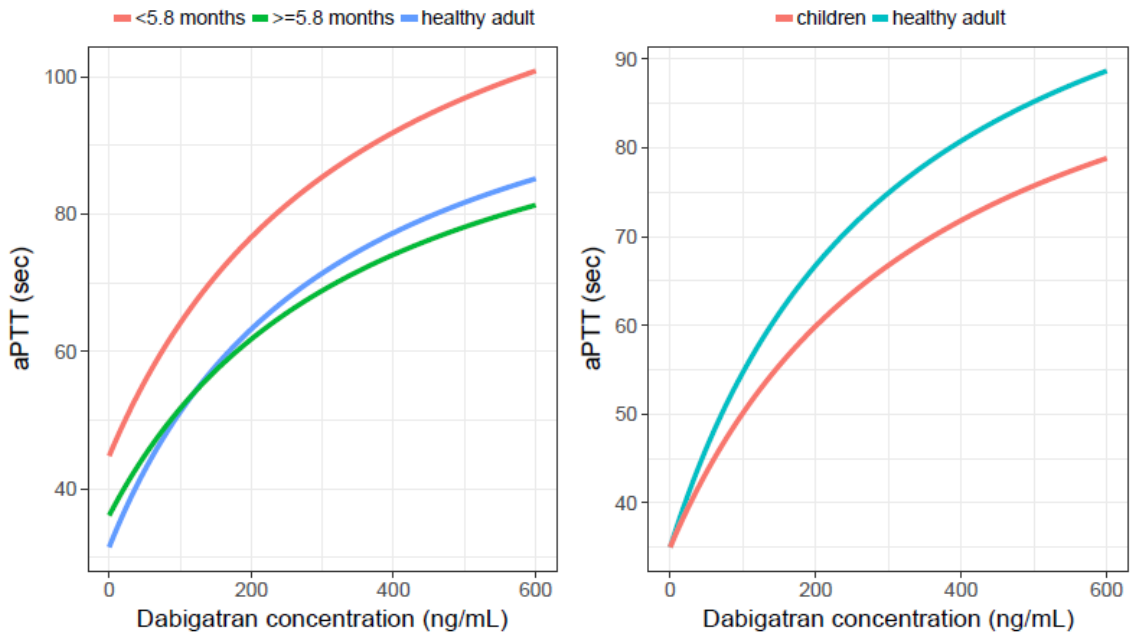
Figure 4.3.4-16. Visual predictive check of aPTT versus dabigatran plasma concentrations for the final aPTT model



Source: Applicant's pop PK-PD report. Figure 22. Page 40.

A comparison of the resulting PK-PD curves with the final aPTT model in typical pediatric and healthy adult subjects is shown in ***Figure 4.3.4-17.***. The PK-PD relationships are similar between the children and the healthy adults. Much of the difference appears to be related to the difference in baseline. Generally, when correcting for baseline differences, children achieve a lower response to dabigatran than what was seen in healthy adults.

Figure 4.3.4-17. Typical population model predictions for the final aPTT model by age group



Source: Applicant's pop PK-PD report. Figure 23. Page 40. The left plot includes the observed baseline differences. In the right plot a baseline of 35 seconds was assumed for both groups.

2. *Diluted thrombin time (dTT)*

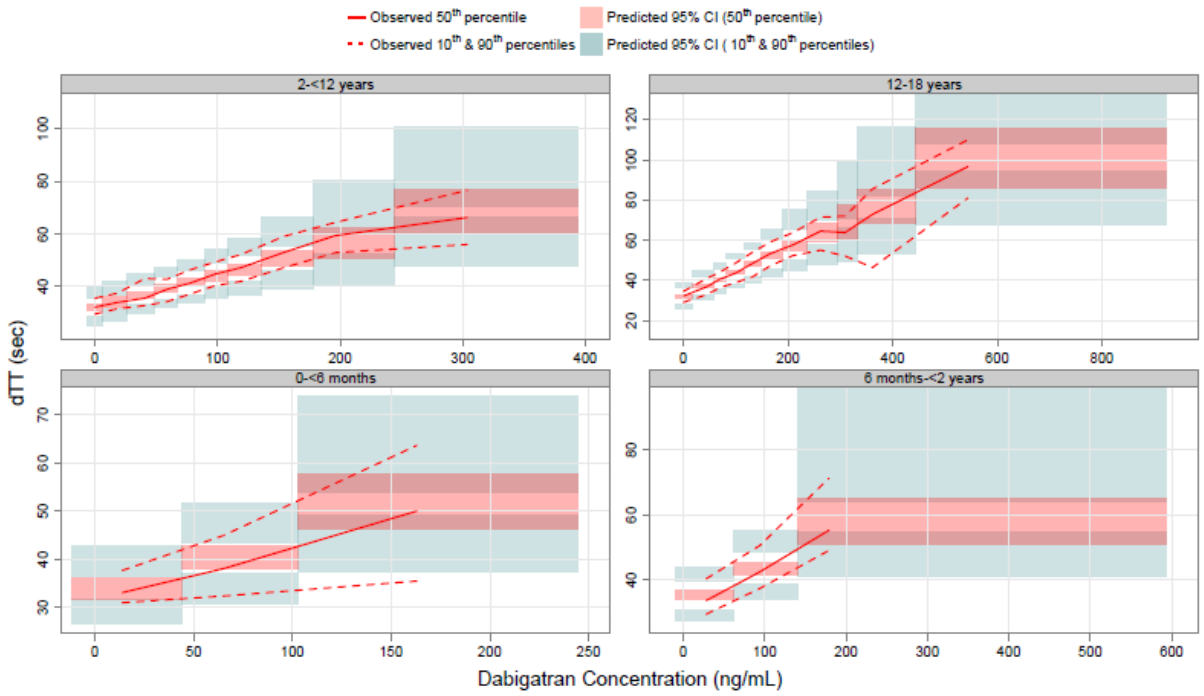
In the base model for dTT, the increase in dTT from baseline with increasing dabigatran concentration was described with a linear function. No covariates were identified. Baseline was similar for the adults and children (31.9 in adults and 32.1 in children). Therefore, the base model is the final model. The parameter estimates of the base model for dTT are presented in ***Table 4.3.4- 2***. The final model adequately described the data across the studied dabigatran plasma concentration range as indicated by the VPC (***Figure 4.3.4-18.***) and standard goodness-of-fit plots (Refer to Applicant's pop PK-PD report. Page 42-43)

Table 4.3.4- 2 Parameter estimates of the final dTT model

		Base dTT model	
	Unit	**Value**	**RSE (%)**
Baseline	sec	32.1	0.600
Slope	/ng/mL	0.00373	2.46
IIV Baseline	(CV)	0.0670	14.9
IIV Slope	(CV)	0.301	15.5
corr Baseline-Slope		-0.646	20.6
Prop. RUV	(CV)	0.107	5.71

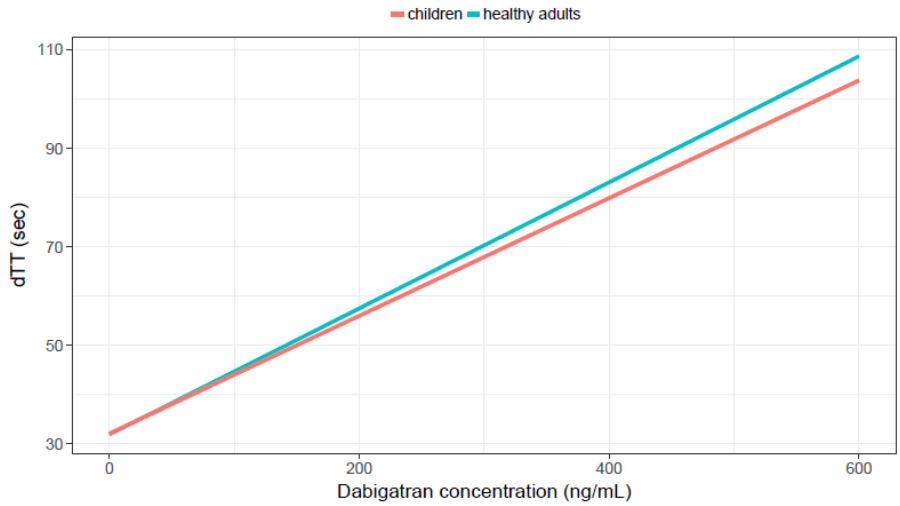
Source: Applicant's pop PK-PD report. The RSE for IIV and RUV parameters are reported on the approximate SD scale. corr: correlation between IIV parameters described by omega block; CV: coefficient of variation; IIV: interindividual variability; RSE: relative standard error; RUV: residual unexplained variability.

Figure 4.3.4-18. Visual predictive check of dTT versus dabigatran plasma concentrations for the final dTT model stratified by age group



Source: Applicant's pop PK-PD report. Figure 28. Page 44.

Figure 4.3.4-19. Typical population model predictions for the final dTT model



Source: Applicant's pop PK-PD report. Figure 29. Page 45.

3. Ecarin clotting time (ECT)

In the base model for ECT, the increase in ECT from baseline with increasing dabigatran concentration was described with a linear function. The final model included the covariate model for age on the slope parameter and estimated a separate baseline in children below or above 5.8 months which resulted in the

model all parameters were precisely estimated. The parameter estimates and VPC plots of the final ECT model are presented in ***Table 4.3.4- 3*** and
Figure 4.3.4-20., respectively.

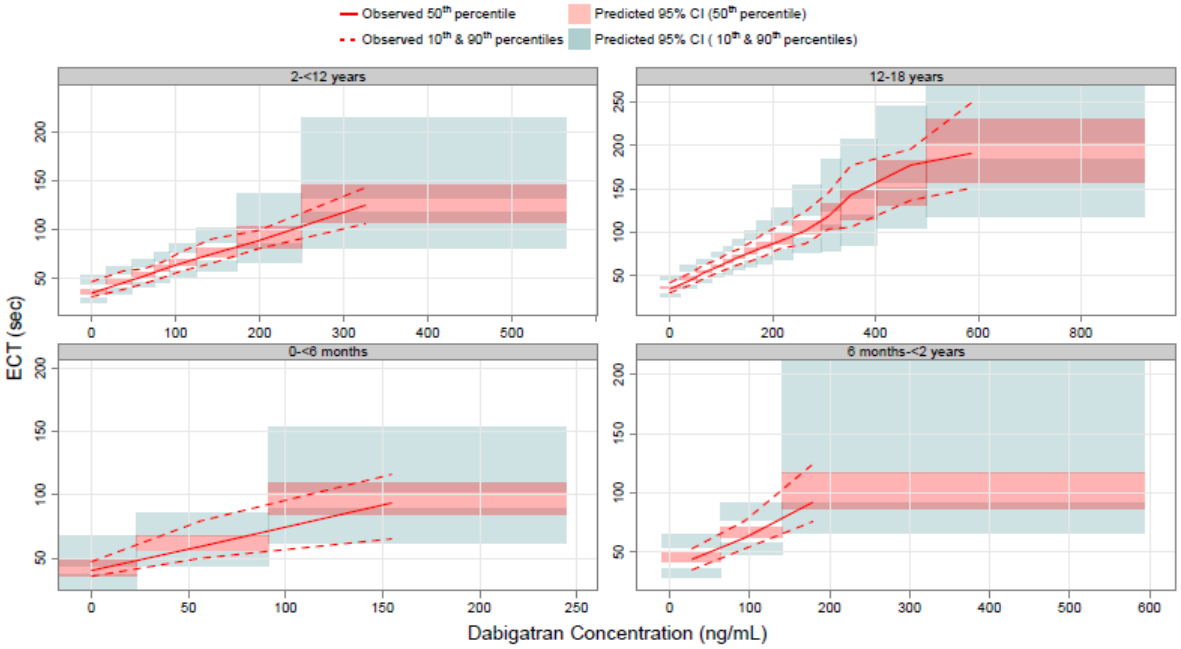
With the final model, the decrease in slope with age on average translated into a slope of 0.0084 per ng/mL in a 1-year old child and 0.0070 per ng/mL in an 18-year-old. At a dabigatran concentration of 50 ng/mL the increase from baseline ranged between 42 and 35% in a 1-year and 18-year-old, respectively. At a concentration of 250 ng/mL the increase from baseline ranged between 210 and 175% in a 1-year and 18-year-old, respectively.

Table 4.3.4- 3 Parameter estimates of the final ECT model

		Final ECT model	
	Unit	**Value**	**RSE (%)**
Baseline	sec	36.4	1.13
Baseline <5.8 months	sec	39.9	3.90
Age on baseline	months	5.80	
Slope	/ng/mL	0.00732	3.01
Slope-age effect		-0.0633	26.1
IIV Baseline	(CV)	0.199	11.2
IIV Slope	(CV)	0.450	15.7
corr Baseline-Slope		-0.888	13.7
Prop. RUV	(CV)	0.114	6.26

Source: Applicant's pop PK-PD report. Table 19. Page 48. The slope parameter describes the drug effect in a 9-yearold reference patient. The RSE for IIV and RUV parameters are reported on the approximate SD scale; CV: coefficient of variation; IIV: interindividual variability; RSE: relative standard error; RUV: residual unexplained variability.

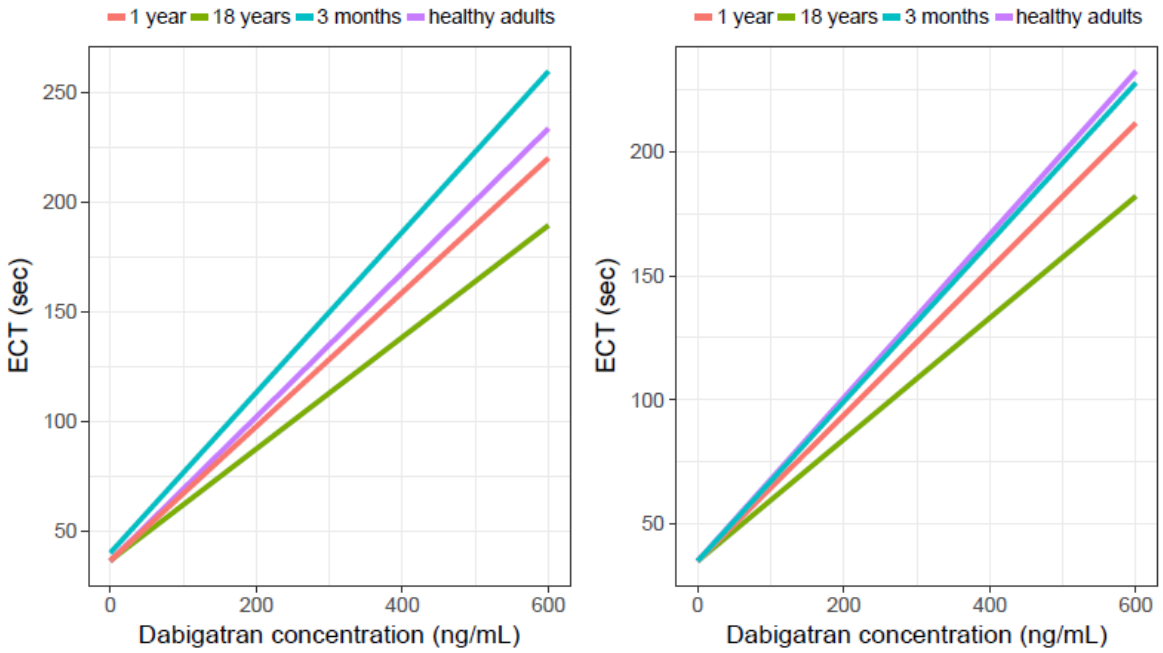
Figure 4.3.4-20. Visual predictive check of ECT versus dabigatran plasma concentrations for the final ECT model, stratified by age group



Source: Applicant's pop PK-PD report. Figure 35. Page 49.

A comparison of the resulting PK-PD curves with the final ECT model in typical pediatric and adult healthy subjects is shown in **Figure 4.3.4-21.**. The PK-PD relationships are similar between the children and the healthy adults. Much of the difference appear to be related to the difference in baseline. Generally, when correcting for baseline differences, children achieve a slightly lower response to dabigatran, gradually decreasing with age, than what was seen in a typical healthy adult.

Figure 4.3.4-21. Typical population model predictions for the final ECT model by age group



Source: Applicant's pop PK-PD report. Figure 35. Page 49. The left plot includes the observed baseline differences. In the right plot a baseline of 35 seconds was assumed for all groups.

Reviewer's Assessment:

Population PK-PD analyses for aPTT, dTT and ECT were conducted using the pediatric patients data by Applicant. The PK-PD analyses were adequately performed with acceptable precision (with RSE less than 20%) for the structural parameters (i.e., Emax and EC50 for aPTT model, and slope and baselines for dTT and ECT models). PK-PD modeling suggests that patient's age was a significant covariate for baseline aPTT levels and baseline ECT, while there were no age-related differences for baseline dTT. The mean baseline aPTT value was higher in pediatric patients aged younger than 5.8 months than in the rest of pediatric patients (45 versus 36 seconds). The mean baseline for ECT was estimated higher in pediatric patients younger than 5.8 months of age than the those older than 5.8 months (40 versus 36 seconds). Also, the age was a significant covariate for the slope of linear relationships between ECT and dabigatran concentration. For a typical 18-year old subject, ECT change is less sensitive to dabigatran concentration compared to 1 year old subjects.

The interindividual variability (IIV) for aPTT was high for the Emax (CV 75%) and modest for baseline aPTT level (CV 29%). IIV for dTT was low for baseline dTT (CV 7%) and modest for the linear slope (CV 30%). IIV for ECT was modest for baseline ECT (CV 20%) and slope (CV 45%). Examining VPC plots for each PK-PD model, the variabilities in the observed clotting times were generally captured by the models.

Population PK-PD analyses conducted in pediatric patients were compared to the model-derived relationship from healthy adults.

- aPTT: In comparisons between patients aged <5.8 months, those aged >5.8 months, and healthy adults, in general, the shape of the relationship for aPTT appears similar among these groups. However, when correcting for baseline differences for aPTT, pediatric patients achieved a less degree of response in aPTT change at the same dabigatran concentrations compared to healthy

adults. This separation is more pronounced at the higher exposure (dabigatran concentration >200 ng/mL).

- dTT: In comparisons between pediatric patients and healthy adults, the baseline of dTT and the slope of the correlation (dTT-dabigatran concentrations) are similar.
- ECT: In comparisons of typical population of different ages (3-month-old, 1-year-old, 18-year-old patient, and healthy adults, the 18-year-old patient was estimated to have the flatter slope than the rest. Similar to aPTT model, this flatter response is more pronounced at high concentrations (>200 ng/mL). Within the therapeutic range of dabigatran concentration, the PK-PD relationships are considered similar.

Overall, the Applicant's analyses (graphical exploration and population PK-PD analyses) suggest that the PK-PD relationships for three clotting time variables (aPTT, dTT, ECT) are similar between adults and pediatric VTE patients across the pediatric age range 26 days to <18 years old.

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